9

BIOCHEMISTRY

faculty of medicine - JU2017

◉ Sheet ○ Slides

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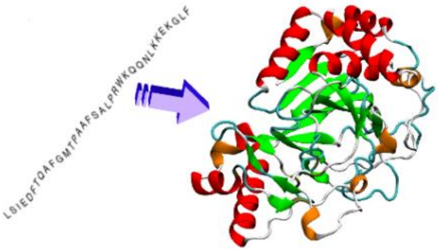
Proteoglycans and glycoproteins have been previously discussed and the differences between them have been noted.

Protein glycosylation (protein-linked sugars; a process by which a carbohydrate is covalently attached to a target macromolecule, typically proteins) promotes the solubility of proteins and allows them to function as membrane proteins.

Now what's the importance of the presence of sugar on a protein or lipid (What is the significance of protein-linked sugars)?

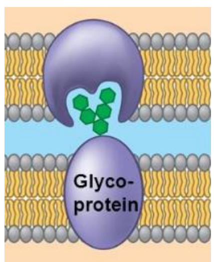


1. Protein folding: The first step during protein synthesis occurs as an amino acid sequence is formed into a chain. This chain will then start to fold in order to form the final structure of the protein leading to its special function. Thus, the way of folding and the final structure of the protein depends on multiple factors, one of which is the presence of sugar molecules on the protein.

2. Protein targeting: During protein synthesis, the cell adds sugar molecules to the protein in the rough ER or the Golgi. Depending on the type of sugar added, this protein will either go to the lysosome or to the cell membrane or to the outside of the cell. Hence, acting like a label on the protein.

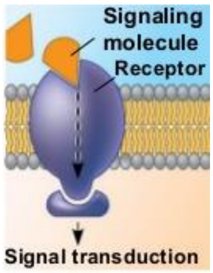
3. Prolonging protein half-life: Every protein has its own half-life, so the cell that synthesized this protein after a period of time will degrade this protein and produce new one. (Half-life: is the time it takes for a substance to lose one-half of its pharmacologic, physiologic, or radiological activity.) One of the plasma membrane proteins has a half-life of 19 days when it's glycosylated (with sugar on it), while it has a half-life of 1 and a half hours when it's un-glycosylated (without sugar on it).

4. Cell to cell communication: In the environment between tissues there are different cells (which have various proteins with sugars attached to them). The cells will interact and therefore communicate with one another by the glycoproteins present on the plasma membranes.



5. Cell recognition: Our immune cells recognize their own self-cells and their different types through the attached sugar molecules (These sugars act as cell markers).

6. Signaling: Any ligand (a molecule that binds to a receptor specifically, e.g. A growth hormone) binds to its receptor through the attachment of a sugar molecule on this protein (receptor).



The importance of the linkage of sugar molecules onto proteins is evident in **Blood Typing**:

* We have 4 blood types (groups): A, B, AB, O.

What determines the type of the blood?

* 2 terminal sugar molecules (found at the end of a sugar chain on a glycolipid)

The whole structure of the antigen is a glycolipid, so it's a lipid molecule (sphingolipid) which has a chain of monosaccharides (sugar residues).

* Consequently, there are three different structures: A, B, and O.

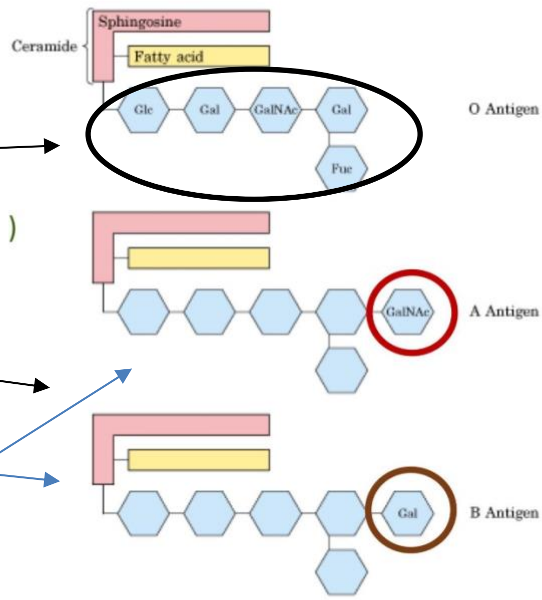
- The difference: N-acetylgalactosamine (for A), Galactose (for B), None (for O)

Type O: Just the sugar chain.

Type A: Chain + GalNAc.

Type B: Chain + Gal.

Type AB: B (Chain + Gal) + A (Chain + GalNAc). (So, it's a combination of both type A and B antigens but NOT one chain with both Gal and GalNAc connected to it).

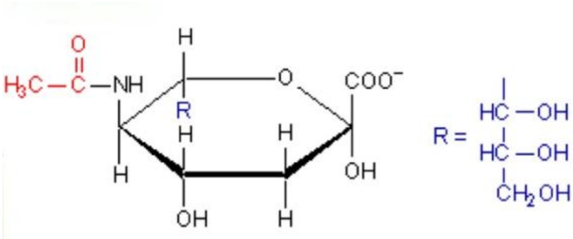


For that reason, an O type person may donate to all blood types because all blood types have the same chain and is therefore universally recognized. An AB type person may take from all types simply because it has all 3 components.

An O type person can't take from A or B or AB because Gal and Gal N-aceytl are considered foreign to its cell, so it's attacked by immune cells.

Sialic acid:

N-acetylneuraminate



N-acetylneuraminate (sialic acid)

* Neura: neuron (it's abundant in the nervous system).

* Precursor: the amino sugar, neuraminic acid

* Location: a terminal residue of oligosaccharide chains of glycoproteins and glycolipids.

It's terminal in glycolipids and glycoproteins (terminal to the sugar chain), so nothing can be added after it.

* It's negatively charged.

Lipids

Carbohydrates, proteins and nucleic acids are homogeneous. (consisting of parts all of the same kind)

Carbohydrates -> chains of sugar residues.

Proteins -> amino acids have almost the same structure but differ slightly.

Nucleic acids -> nucleotides have almost the same structure but differ slightly.

ON THE OTHER HAND, ... **lipids are heterogeneous** in terms of structure (they have nothing common in structure except that they're all hydrophobic/ fat soluble or soluble in organic solvents (ether, chloroform, benzene, acetone)/ water insoluble.

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

* They are **Amphipathic** in nature. (having both hydrophilic and hydrophobic parts)

* They are widely distributed in plants & animals.

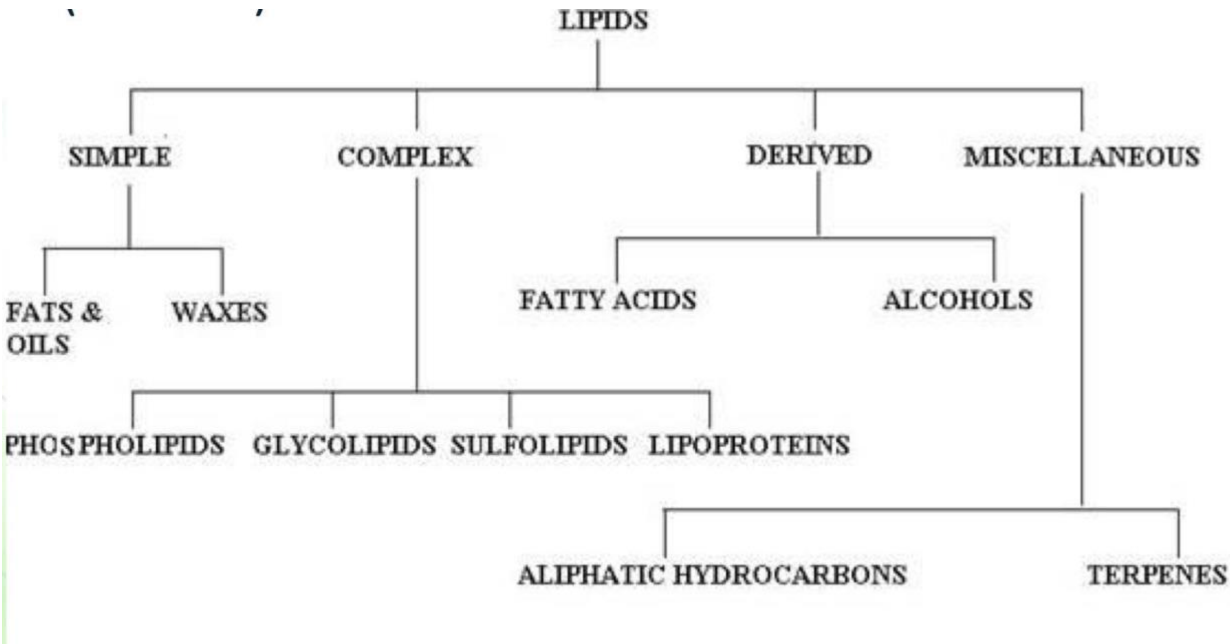
Classes:

1. Simple lipids (fats, oils, and waxes).

2. Complex lipids (glycerides, glycerophospholipids, sphingolipids, glycolipids, lipoproteins).

3. Derived lipids (fatty acids, alcohols, eicosanoids).

4. Cyclic lipids (steroids).



Functions of Lipids:

*** Lipids include:**

- Storage lipids: are lipids stored in our bodies. When the body needs energy, it metabolizes these lipids to produce ATP.

- Structural lipids in membranes.

- Lipids as signals, cofactors (enzymatic reactions) & pigments (providing color for different structures)

* They are a major source of energy.

- They are storable to an unlimited amount (vs. carbohydrates)

Note: Excess carbohydrate intake by the body is converted into lipids(fat).

- They provide a considerable amount of energy for the body (25% of body needs) & serve a high-energy value (more energy per gram vs. carbohydrates & proteins). They produce double the amount of energy compared to carbohydrates per gram. So, 1 gram of sugar produces 4kcal, while 1 gram of lipid produces 9kcal.

* Structural components (cell membranes)

* Precursors of hormone and vitamins

* Shock absorbers /thermal insulators: internal organs are surrounded by fats (fatty sheet).

Fatty acids:

* **<u>Aliphatic</u>** mono-carboxylic acids (Aliphatic: chain of carbon (it's the backbone of the molecule)).

* **Formula:** R-(CH_2)n -COOH

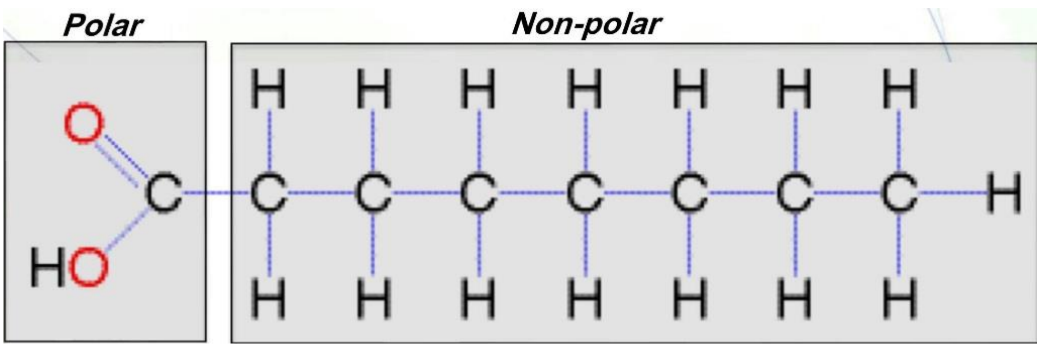
* **Lengths:**

- Physiological (12-24)
- Abundant (16 and 18)

* **Degree of unsaturation** (Unsaturated = double bonds / saturated = no double bonds)

* **<u>Amphipathic</u> molecules:** it means one can draw a line through the molecule and say a part is hydrophobic and a part is hydrophilic.

* Fatty acids can't be branched.



Functions:

* Building blocks of other lipids.

* Modification of many proteins (lipoproteins).

* Important fuel molecules.

* Derivatives of important cellular molecules.

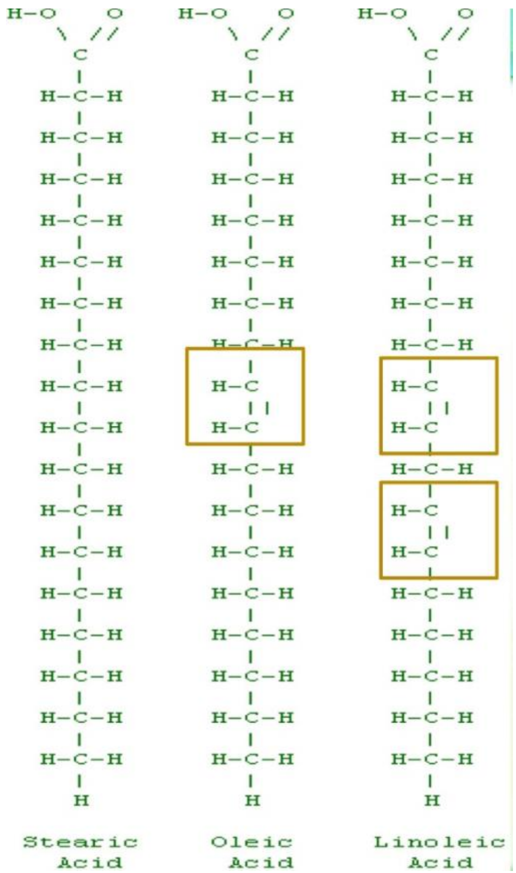
Types of fatty acids:

* **Saturated fatty acids** are those with all C-C bonds being single. (e.g. Stearic acid: fully saturated, 18 carbon fatty acid).

* **Unsaturated fatty acids** are those with one or more double bonds between carbons.

- Monounsaturated fatty acid: a fatty acid containing one double bond. (e.g. Oleic acid that's found in olive oil).

- Polyunsaturated fatty acids contain two or more double bonds. (e.g. Linoleic acid has 2 double bonds).

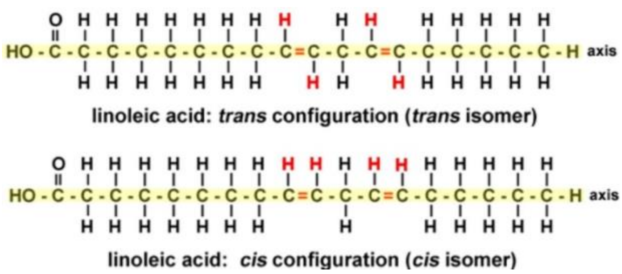


Double bonds have different configurations/orientations (they can be cis or trans).

This image is a simple structure (not realistic).

Cis: Hydrogen on double bond oriented in the same direction.

Trans: Hydrogen on double bond oriented in different (opposite) directions around the same double bond.



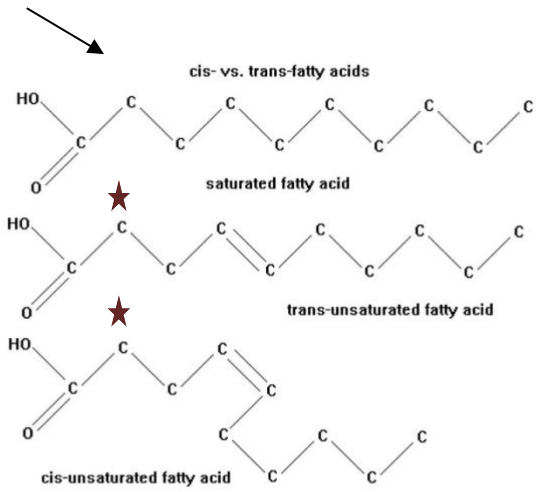
Realistically:

For example, start counting from the starred carbon.

Trans: Bonds are up-down-up-down-up (even if it's a double bond).

Cis: Bonds are up-down-up-down-down-down (this causes a kink in the fatty acid).

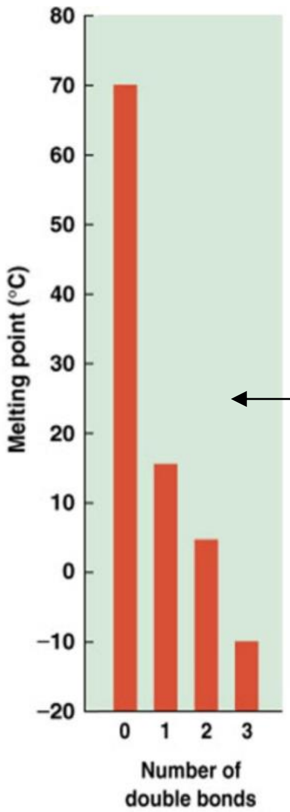
- This has physiological and pathological implications.



Physical properties of fatty acids:

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

So... what's the importance of the number of carbons and the number of double bonds on the physical properties of fatty acids?



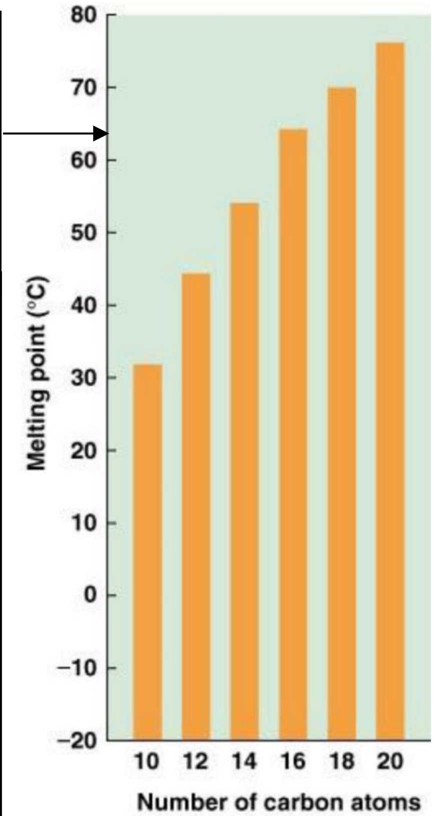
*** The longer the chain (number of carbons), the higher the melting point.**

e.g. margarine which has high melting point because it's composed of a long carbon chain.

*** The more the number of double bonds, the lower the melting point.**

e.g. on 0 double bonds is oleic acid (olive oil), at room temperature it's liquid but when we put it in the refrigerator it solidifies.

Because it's stable when it's saturated (due to Van Der Waals interactions) and therefore it needs higher energy to make it liquid like (unstable) and when there are more double bonds it's less stable and therefore it needs less energy to make it liquid like.



We can classify fatty acids into different groups according to the length of the carbons:

Short chain F.A.	Medium-chain F.A.	Long chain F.A.
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

Short: e.g. acetic acid (vinegar) CH_3COOH / butyric acid (butter).

Medium: e.g. caprylic acid (capri: goat, so it's found in goat milk). It's important for people who have long chain fatty acid metabolism problems, so a nutritionist tells them to depend on medium chains instead of long chains.

Long: e.g. stearic acid in nutmeg.



Naming of fatty acids:

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-		

There are 3 ways of naming:

The first way depends on the number of carbons of alkane or alkene that makes the fatty acid. Say we have an 18 carbons alkane, its name would be Octadecane and the fatty acid that's produced when adding carboxyl group would be called Octadecanoic acid.

One double bond = Octadecenoic acid.

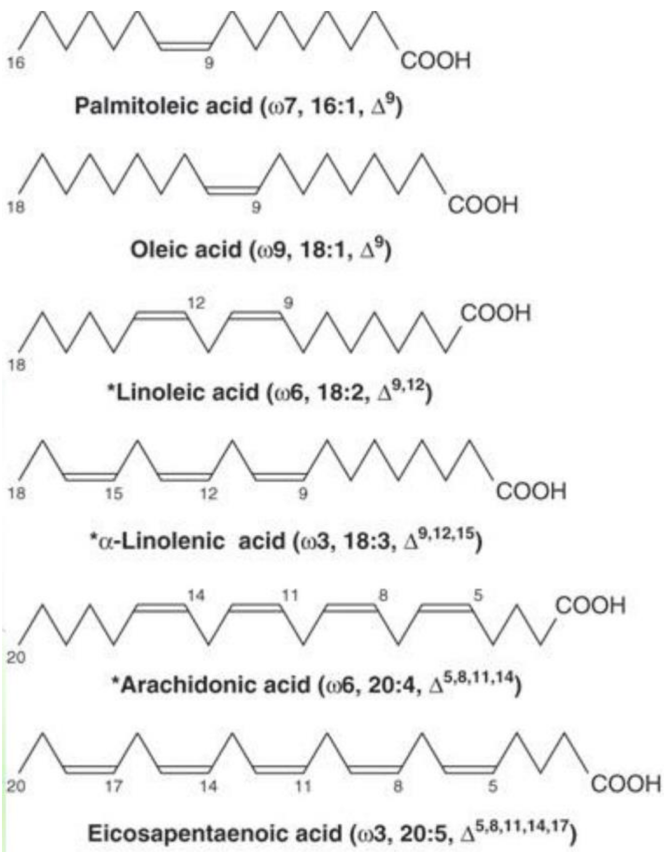
Two double bonds = Octadecadienoic acid.

Three double bonds = Octadecatrienoic acid.

Saturated: Prefix (number) + anoic acid

Unsaturated: Prefix (number) + (di/ tri/ …) enoic acid.

In the second way of naming we start numbering from the carboxylic carbon.



<u>**Designation of carbons and bonds**</u>

18:0 = a C18 fatty acid with no double bonds

e.g. on 0 double bonds: stearic acid (18:0); palmitic acid (16:0)

18:2 = two double bonds (linoleic acid)

<u>**Designation of location of bonds**</u>

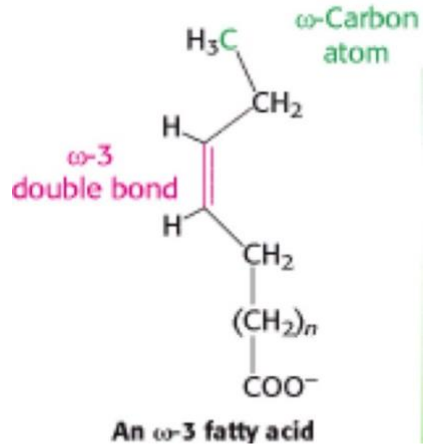
Δ^n: The position of a double bond

e.g. cis-Δ^9: a cis double bond between C 9 and 10

trans-Δ^2: a trans double bond between C 2 and 3

Number of carbons	Number of double bonds	Common name	Systematic name	Formula
14	0	Myristate	n-Tetradecanoate	$CH_3(CH_2)_{12}COO^-$
16	0	Palmitate	n-Hexadecanoate	$CH_3\,(CH_2)\,_{14}COO$-
18	0	Stearate	n-Octadecanoate	CH_3(CH2) $_{16}COO$-
18	1	Oleate	cis-Δ^9-Octadecenoate	$CH_3(CH_2)\,_7CH{=}CH(CH_2)\,_7COO$-
18	2	Linoleate	cis,cis-Δ^9,Δ^{12}-Octadecadienoate	$CH_3(CH_2)\,_2(CH{=}CHCH_2)\,_2(CH_2)\,_6COO$-
18	3	Linolenate	all-cis-Δ^9,Δ^{12},Δ^{15}-Octadecatrienoate	$CH_3CH_2(CH{=}CHCH_2)\,_3(CH_2)\,_6COO$-
20	4	Arachidonate	all-cis-Δ^5,Δ^8,Δ^{11},Δ^{14}-Eicosatetraenoate	$CH_3\,(CH_2)\,_4(CH{=}CHCH_2)\,_4(CH_2)\,_2COO$-

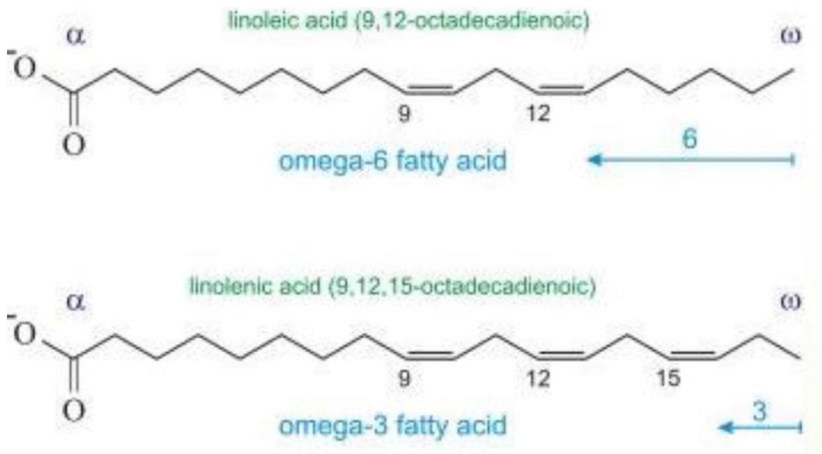
((You have to know all the information in this table (if you know the systematic name, the other information can be known easily)))



In the third way of naming we start numbering from the last carbon which is a methyl group

(ω)-C: distal methyl C as #1, (omega carbon = last carbon, because omega is the last Greek alphabet).

This way of naming depends on the location of the double bond relative to the omega carbon not the carboxylic carbon.



Note: This naming system isn't detailed enough to tell the number of double bonds, so 2 omega 3 fatty acids can have different number of double bonds, therefore omega 3 fatty acid is a group not just one molecule.

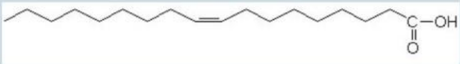
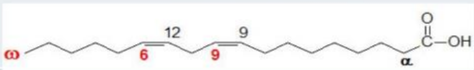
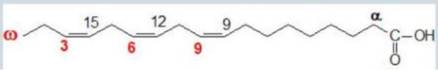
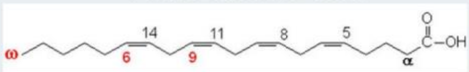
So… Omega 3, 6, 9 are also fatty acids but differ in the naming method.

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

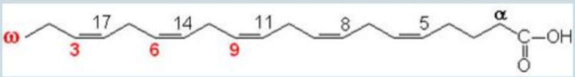
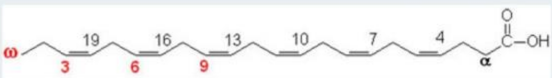
Omega 3 is good for memory and can be found in salmon, tuna, sardine, almond, and pecans.

Omega 9 can be found in olive oil.

All these fatty acids are important to our bodies and are components of the plasma membrane of nerve cells.

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

((You've to know the names of the first 4 fatty acids, but the last 2 just know the abbreviation.))

$20:5^{\Delta 5,8,11,14,17}$	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 Acids:

Eicosanoids

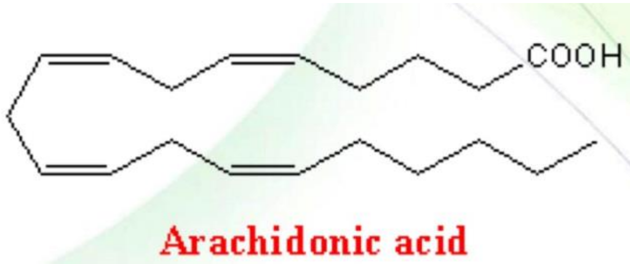
From fatty acids one can synthesize other important molecules such as eicosanoids.

(Eico = 20) so we're talking about 20 carbon fatty acid.

all cis-Δ^5, Δ^8, Δ^11, Δ^14 -eicosatetraenoate,

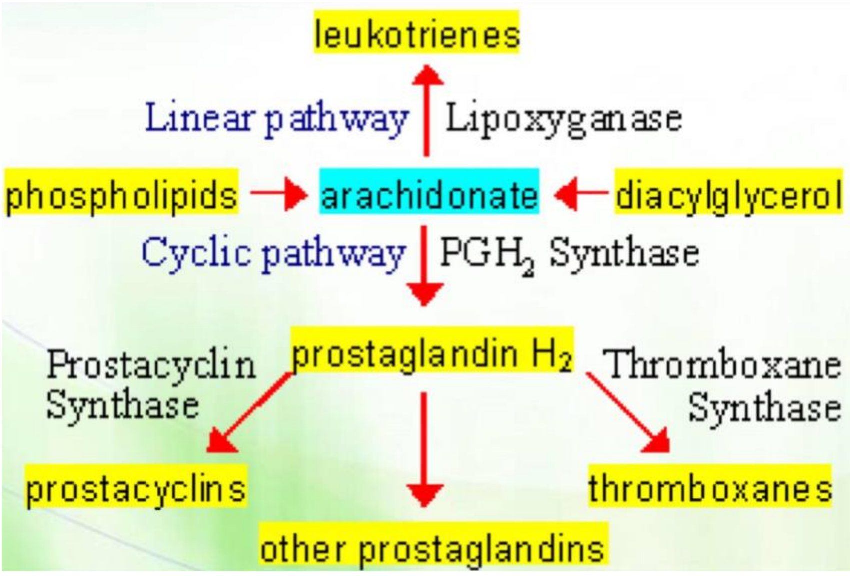
CH3 (CH2)4 (CH=CHCH2)4 (CH2)2COO-

the most important one in our bodies is Arachidonic acid (20 carbons, 4 double bonds).



Synthesized from arachidonic acid are other molecules such as Prostaglandins, Diacylglycerol, Leukotrienes, Thromboxane, Prostacyclin. (these are all eicosanoids derived from arachidonic acid).

These eicosanoids are important because they're signaling molecules and therefore affect the cell's function.



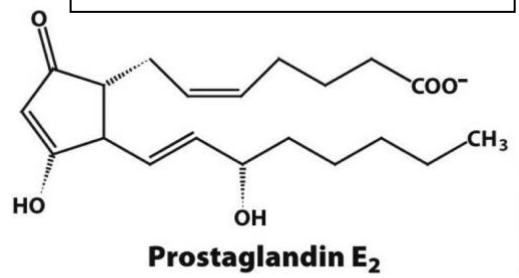
Prostaglandins:

Don't memorize these structures.

First found in the prostate gland but then discovered that it's synthesized by other cells.

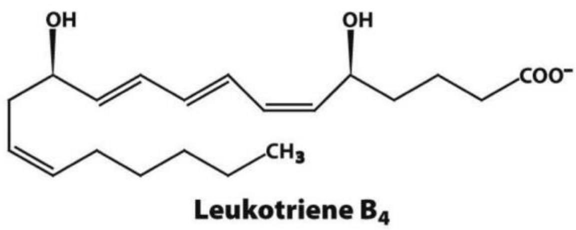
<u>* Inhibition of platelet aggregation</u> ↓

<u>* Blood clotting</u>



Leukotrienes:

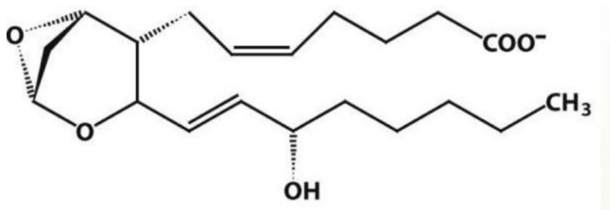
First discovered in leukocytes (a type of immune cells). It contains 4 **double** bonds, 3 of these double bonds are conjugated, that’s why it's called leuko**tri**e**nes**.



<u>* Constriction of smooth muscles</u>

<u>* Asthma:</u> blood vessels are constricted so blood flow is slow, and one can't take enough oxygen. It's caused by over synthesis of leukotrienes.

Thromboxane:



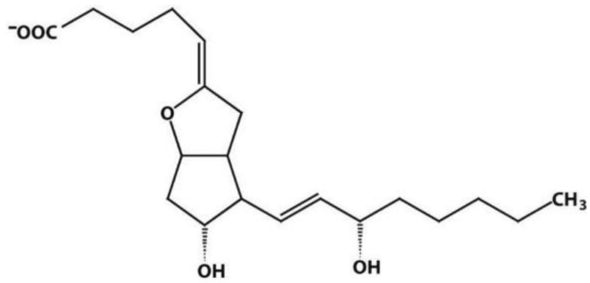
Thromboxane A_2 (TXA_2)

Thrombo-: Blood clot.

<u>* Constriction of smooth muscles</u>

<u>* Induces platelet aggregation</u> ↑

Prostacyclin:



Prostacyclin (PGI_2)

<u>* An inhibitor of platelet aggregation</u> ↓

<u>* A vasodilator</u>

[(Notice that different eicosanoids have different functions, the same eicosanoid (prostaglandins for example) also can have two opposite functions. That's because:

1) there are different types of prostaglandins

2) it also depends on the amount of prostaglandins secreted and where they're being secreted. -> we're talking about homeostasis (keeping a balance)]