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Biochemistry

● Sheet ○ Slides

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Title: Reactions of Fatty Acid Synthesis

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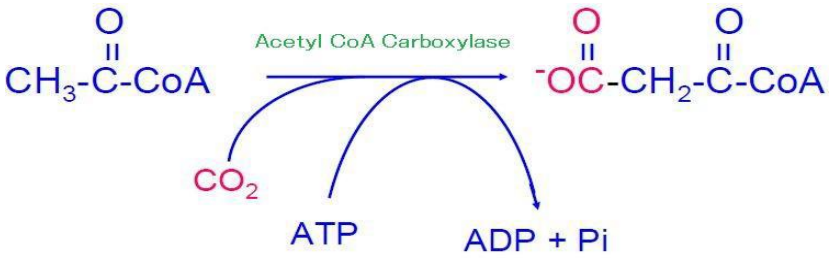
Fatty acids synthesis

The synthesis start from Acetyl COA the first step requires ATP + reducing power NADPH! even though the oxidation and synthesis are different pathways but from chemical part of view they are almost opposite to each other.

In fatty acids oxidation first step is oxidation followed by hydration then oxidation and finally the thiolytic cleavage, this is repeated again and again until the fatty acid is Completely Converted to Acetyl COA.

In the case of synthesis, the first step is Condensation followed by reduction then dehydration and another reduction.

The Converging of Acetyl COA to Malonyl COA is the first step and it is the rate limiting step, it is require reduction power and energy, this carboxylation reduction reaction catalyzed by ACC (Acetyl COA carboxylase enzyme),



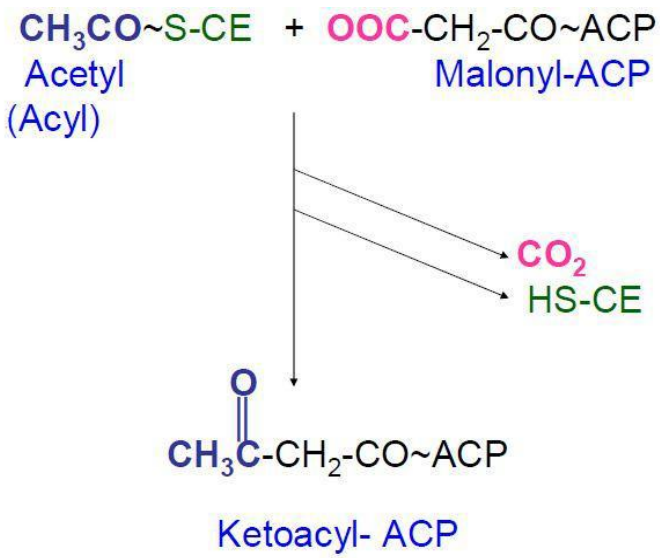
And the fatty acid synthase is catalyzed the remaining steps.

Fatty acid synthase is multifunctional enzyme Complex (the same protein "enzyme" catalyzed 7 reactions), It is a dimer of two identical chains (the dimer is the active form) have 7 catalytic activity, one of this enzymes activity is the Condensing enzyme portion, and one domain is linked to phosphopantetheine which is a part of Co enzyme with reactive –SH group ,this domain carries the Acyl intermediates such as Acetyl and Malonyl groups during synthesis, it is known as Acyl carrier protein (ACP).
the synthesis occurs in the cytosol whereas the degradation occurs in the mitochondria!

The Acyl carrier protein carries an Acetyl group and transfer it to the Condensing enzyme of fatty acid synthase following the carboxylation of another Acetyl COA to Malonyl COA by Acetyl COA carboxylase then the

Malonyl COA is transferred to the Acyl carrier protein of fatty acid synthase which already has an Acetyl group linked to its Condensing enzyme portion.

Now both the Acetyl COA and Malonyl COA are attached to different portions of the same fatty acid synthase enzyme Complex then the Condensation take place by Combination → the Acetyl group with only 2 of the 3 carbons of Malonyl COA to produce ketoacyl - ACP and CO2 is release (it is the same CO2 that added to Malonyl COA from carboxylation of Acetyl COA).



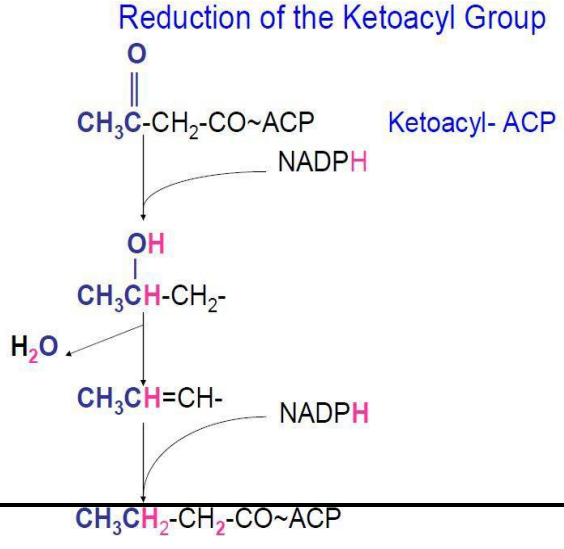
**The Condensation reaction is proceeding favorable so what drive the reaction in forward direction??

1- that It is release CO2 " all the decarboxylation reaction favorable and have negative delta G " SO NO NEED OF ENERGY.2-we have cleaved a high energy bond.

The Ketoacyl COA which it has 4 carbons unit attached to Acyl carrier protein in the fatty acid synthase and undergoes 3 reactions:

1-Reduction by NADPH →it reduces the keto group to hydroxyl group so keton reduces to 2ry alcohol.

2-Dehydration (removal of H2Oor HOH from beta carbon and a double bond is forming).



3-another reduction reaction by NADPH to reduce the double bond to a single bond .

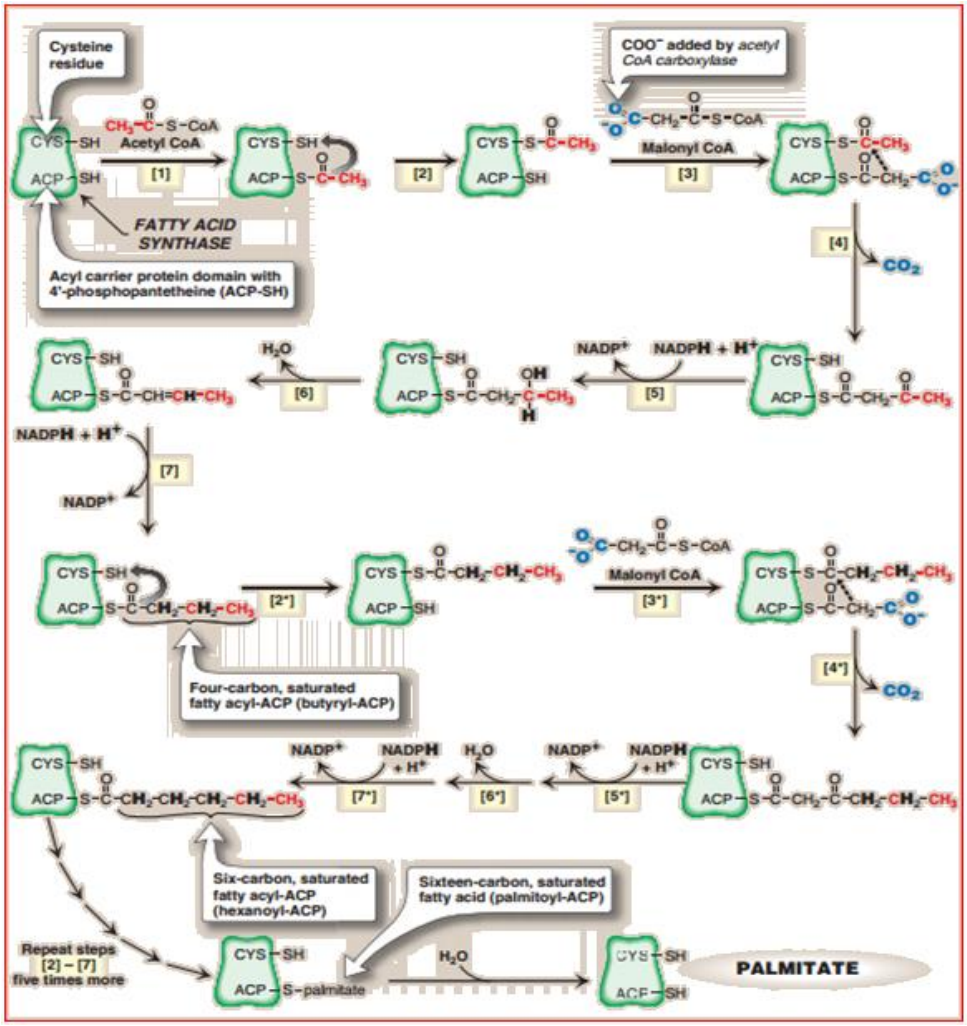
Result in butyric acid; a 4 carbons and this acid is transferred to the Condensing enzyme of the fatty acid synthase and the

Acyl carrier protein is now empty and so it takes a new Malonyl COA group and the whole process of Condensation take place again .

So the cycle of "**Condensation – Reduction – Dehydration –Reduction**" will be repeated again and again, until a fatty acid with 16 carbons is formed (palmitate) .

**By the way the fatty acid synthase enzyme which is a large protein that catalyzed the fatty acid synthesis is found in the mammals cells whereas bacterial cells have the 7 enzyme separated which facilitate the study of mechanisms of each step which is applicable in humans.

The next picture is taken from the book it has more details…you can see the fatty acid synthase Contain the Condensing enzyme that have –SH group (to form thioester bond which is high energy bond) and the ACP (Acyl carrier protein) is free, at first the Acetyl COA is add to ACP then it is transferred to Condensing enzyme and now in the Condensation with Malonyl COA it will be added to ACP by that the enzyme Contain Acetyl and Malonyl group and after the Condensation the product transferred to ACP and so on….



***So we need 7 cycle, 7 Malonyl COA, only one Acetyl COA, 14 NADPH because we have 2 reduction reaction in each cycle .

Production of cytosolic Acetyl COA for fatty acid synthesis:

Pyruvate dehydrogenase Convert the pyruvate to Acetyl COA ,but "The Acetyl COA that producing by beta oxidation shouldn't be use for fatty acids synthesis" the F.A synthesis occurs in the cytoplasm but Acetyl COA synthesized in the mitochondria **so how it will be released??**

Oxaloacetate + Acetyl COA→→ citrate

This is the first reaction in TCA cycle, so if the cells are requiring energy the citrate Continues in TCA cycle but if the energy level is already high, the isocitrate dehydrogenase is inhibited , so citrate starts to Accumulate and transport through the inner mitochondrial membrane and then the citrate in cytosol, the it's cleavaged to oxaloacetate and Acetyl COA.

**And remember it is not the reverse reaction because of the following:

1-**Different enzymes** "citrate synthase, citrate lyase"

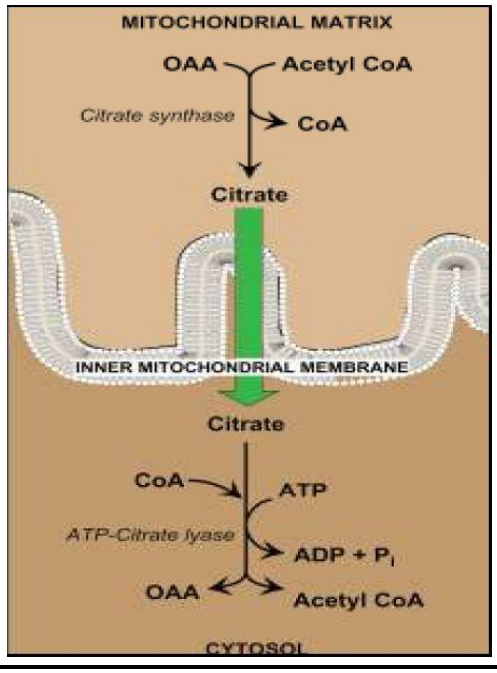
2- **The delta G** for the first reaction is negative but the second one is positive so it requires ATP (and for the second reaction According to one of the products which is Acetyl COA a high energy Compound that needs energy to synthesizes it)

3- **The places** "the first in mitochondria, and the second in the cytosol"

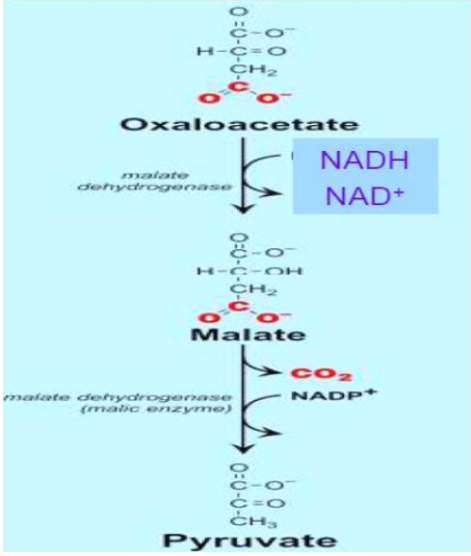
**And the oxaloacetate will return back by malate shuttle

"Oxaloacetate →malate→pyruvate" so malate undergoes oxidative decarboxylation to give pyruvate. CO2 is removed and NADP is reduced to NADPH, the enzyme for this reaction is malate dehydrogenase or Malic enzyme.

** during the oxidative decarboxylation reaction NADP is reduced to NADPH that is needed in fatty



acids synthesis so 8 out of 14 of NADPH that required during fatty acid synthesis of paltimate is obtain by this way when 8 Acetyl COA leave the mitochondria .and within the mitochondria pyruvate Convert to oxaloacetate " this reaction require ATP " ……



**This photo taken by the dr from the 2nd edition of the book it has mistake!!!

** The mistake was during reduction of oxaloacetate to malate we convert NADH to NAD+.

Remember that we reducing the NAD+ to NADH.

The regulation of fatty acids synthesis and oxidation

**oxidation and synthesis shouldn't occur at the same time and at the same place, if they occurred at the same time we will get nothing just waste of energy (ATP is used for carboxylation reaction).

--- Regulation of synthesis by 3 mechanisms:

1-Acetyl COA carboxylase activity.

2-Covalent modification.

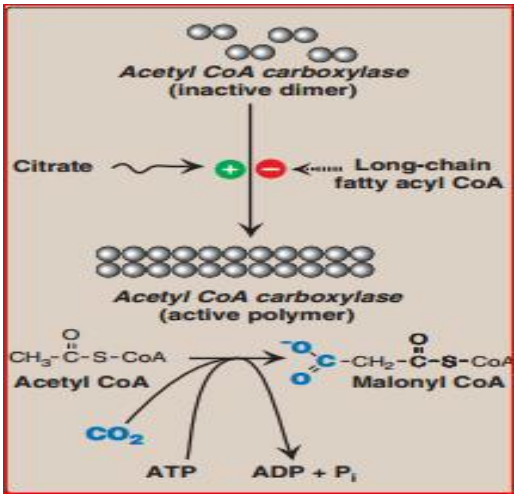
3- Regulation the amount of enzymes.

**The first regulation is through the ACC that catalyzed Committed step "because Malonyl COA is used only for F.A synthesis" by Allosteric regulation.

** The allosteric is the reversible binding of small molecule to allosteric site of the enzyme leading to more activation or less activation .

In this case the **citrate** can bind to ACC enzyme and Convert it to the active form whereas **the long chain fatty Acyl COA** can inhibit the enzyme.

** Why the citrate is the activator?? Because high level of citrate indicate a high level of energy so the building block is adequate so let's do F.A synthesis. .



And the allosteric regulation is very rapid it can happen during a fraction of seconds in the presence of citrate that stimulate the enzyme .

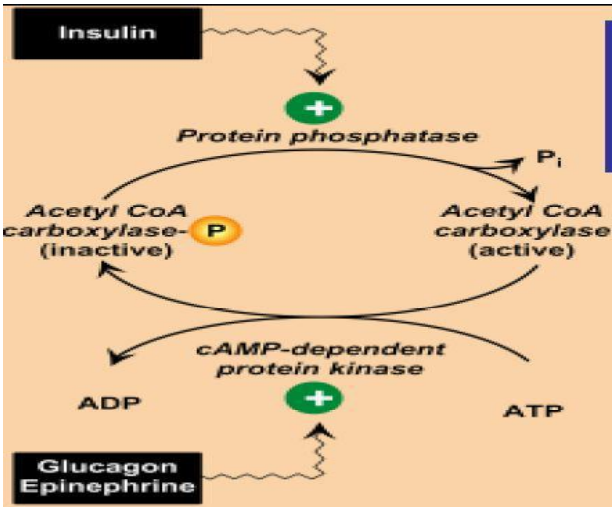
**The second regulation is by covalent modification that is mediated by hormones:

"Glucagon and epinephrine" stimulate the cAMP dependent protein kinase that add phosphate group to Acyl COA carboxylase and this phosphorelated form is inactive..

What is the significant of that??

Low blood glucose level mean it is not the suitable time to Convert glucose to F.A synthesis so the enzyme that is making the Committed step for fatty synthesis is inhibited when the blood glucose level is low.

But when we eat food the insulin level will raised and it activates the protein phosphatase that removes the phosphate group from ACC so it's back to active form and this is so similar to glycogen synthesis + degradation. " Always addition of phosphate group to enzyme mean a message to spare (keep)



the glucose from using to anything else""

**The 3rd regulator is the amount of enzymes: if we keep eating most of the time we are in the well fed state , the amount of enzymes that are involved in F.A synthesis is increasing "adequate amount of enzymes".

In the other hand during fasting just eating one snake or a half one, so we don't require F.A synthesis so the amount of enzymes is greatly reduced. This thing is important to understand for the glucose tolerance test this test is used to see how the body responds to the amount of glucose given.

For example u give your patient 75 g of glucose and every half - hour , you measure the blood glucose level, the patient should handle this amount of glucose and the blood glucose level should not elevate so much.

**And remember if u doing this tests u should let the patient eat freely for three days before the test because we need high amount of the enzymes for F.A synthesis .

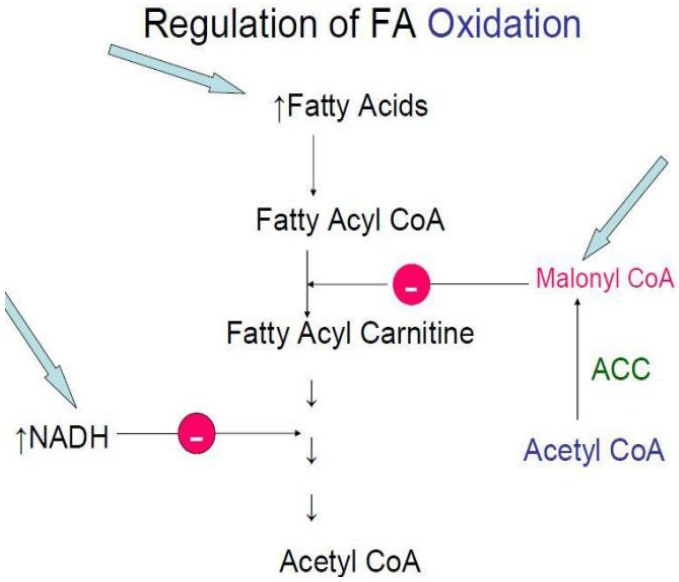
Regulation of oxidation of fatty acids

**The oxidation is regulated by:
1-supply of fatty acids 'substrate'.
2- Availability of NAD
3- Entry into the mitochondria

**The first regulator→ if the level of glucagon is high, that leads to high mobilization of F.A from adipose tissue,"The hydrolysis of triacylglycerol in response to glucagon "After releasing of F.A from adipose tissue, they are transported to muscles and liver binding to albumin and by that whether fatty acids are available or not (how much their Concentration) and high availability leads to high rate of oxidation.
** The second regulator is by the amount of NADH and NAD+. High level of NADH means that the cells have adequate level of energy, so decreasing the oxidation process. and high level of

NADH → low level of NAD+ that's required for oxidation process

**the third method of regulation is by the entry of F.A groups into mitochondria require carnitine shuttle and it is inhibited by Malonyl COA because it inhibits transport of fatty Acyl intermediate into mitochondria " because malony COA is needed during synthesis so the oxidation should be inhibited" – at time of synthesis, oxidation is inhibited-!



** Now one of our problems these days is the obesity, it is a worldwide problem in developing and developed Countries. if we discover a drug that can act as inhibitor for F.A synthesis so we will decrease the obesity.

**Note: the drugs act by inhibited of enzyme or receptor there is no drug can stimulate enzyme because the enzyme is already designed to be acting in their maximum activity "to be stimulated"….

**Now which step we look for to inhibit it??? Inhibition of the ACC enzyme leads to enter of F.A to mitochondria and increase the level of oxidation.

Then the doctor read an article about this discovery ……

Elongation of fatty acids

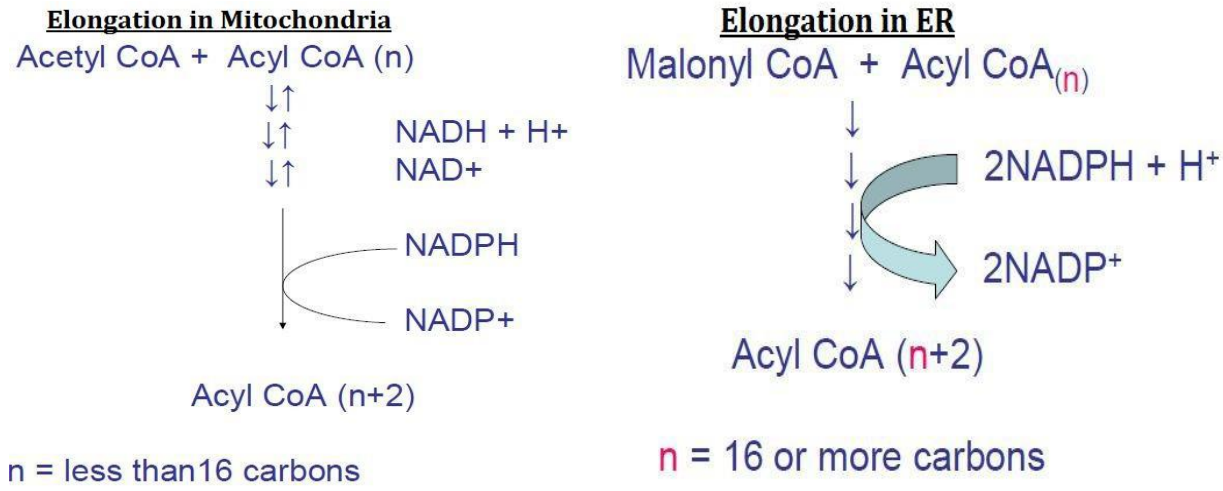
The end product of F.A synthesis is 16 c what about 18c , 20c how we can make these F.A ??

The elongation process occurs in the endoplasmic reticulum (ER) why?? Because the F.A is insoluble in water so always the water insoluble substances react in ER

It involves a similar sequence of reactions but with different enzymes this is because the specificity of fatty acid synthase enzyme stops at 16 c.

The elongation can take places in the mitochondria.

If elongation takes place in the mitochondria , fatty acids with less than 16 Carbons are used. Those are obtained from the food we eat ex. 6 Carbon fatty acid and In order to store these short fatty acids in the body, they must be elongated in fatty acid Synthase. This involves similar sequence of steps but with modification.



Desaturation of fatty acids

(Mean introducing of double bond in F.A)

Synthesis of monounsaturated fatty acid "has just one double bond usually at carbon 9 ".

The most Common ones are the oleic acid and palmitoleic acid .

It occurs in ER ……..

We can't introduce a double bond after carbon 9 in human and mammals yet the fatty acids that have a double bond after carbon 9 are important for us (essential fatty acids)

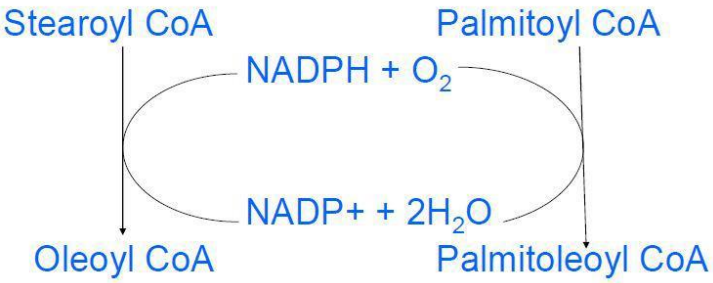
How to introduce the double bonds??

*****introduction of double bond dose not occur by dehydration "removal of 2H" it occurs by hydroxylation followed by dehydration.

Side chain ->hydroxylation at carbon 9 ->alcohol ->dehydration -> alkenes

Example: the Conversion of: 1-stearoyl COA to oleoyl COA by introduction of double bond at carbon 9

2-palmitoyl COA to palmitoleoyl CoA.



Δ^9 Desaturase; Cytochrome b_5

The enzyme that is involved:** **delta 9 desaturase** which transfer electron from NADH to one oxygen atom to convert it to H2O the other oxygen atom become so reactive so it is added to hydrocarbon chain of fatty acids at carbon 9.

((one oxygen is removed from O2 -> reduced to H2O

The other one is introduced at carbon 9 -> once carbon 9 is hydroxylated you can dehydrate this molecule to make double bond))

What do we need for this process in addition to desaturase enzyme??

Cytochrome b5 to move electron from NADPH to desaturase enzyme Complex that carries both hydroxylation and reduction of the other oxygen

Formation and modification of "PUFA" polyunsaturated fatty acids

We can't synthesis PUFA but we can modify them by elongation and desaturation.

*This is done by addition of double bond at carbon 4, 5, 6 but not after carbon 9

Additional double bonds can be introduced by:

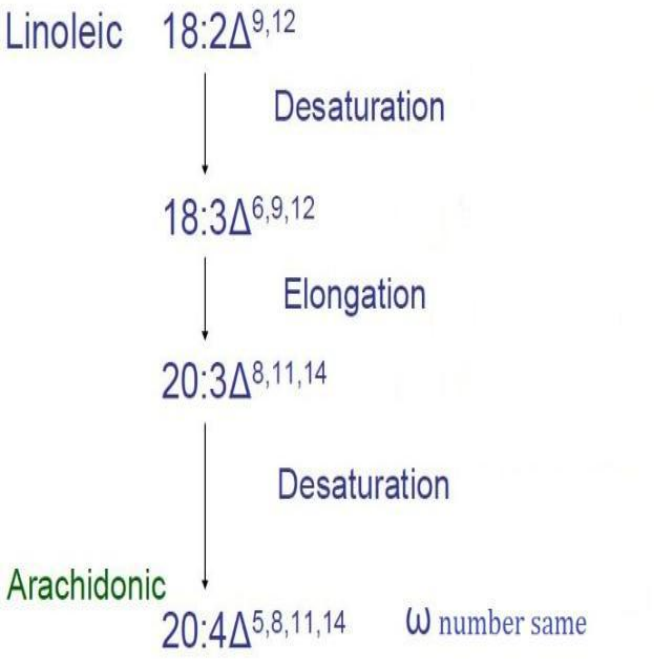
Δ^4 Desaturase

Δ^5 Desaturase

Δ^6 Desaturase

**Note: several desaturases differ by their specifity to which carbon they add the OH group and to decide which desaturase will act is where the double bond is found
When we add new double bond it should be separated from original double bond by methylene (ch2)

The last example :::



Linoleic Acid (18:2) has 2 double bonds at Carbon 9 and 12. If we want to add a double bond, the double bond is introduced at Carbon number 6 not 7 or 5 because the difference between double bonds must be 3 carbons. Desaturase enzyme adds double bonds at 6,9,12.
-if it elongated, it becomes a 20 carbon fatty acid, each double bond pushed by 2 C's.
Thus it is now (20:3 Δ 8, 11, 14).
The omega classification is still the same ω6.
- Another desaturation at carbon 5 takes place now, not at 6 since 8-3=5.
The fatty acid becomes (20:4 Δ 5, 8, 11, 14) which is Arachidonic acid.

Note: The Omega classification does not change upon modification, because modification does not take place from the omega side. Thus, fatty acids are divided into omega classification families such as the ω 3 family, the ω 6 family, and the ω 9 family.