SHEET NO. 16

METABOLISM

DOCTOR 2019 | MEDICINE | JU

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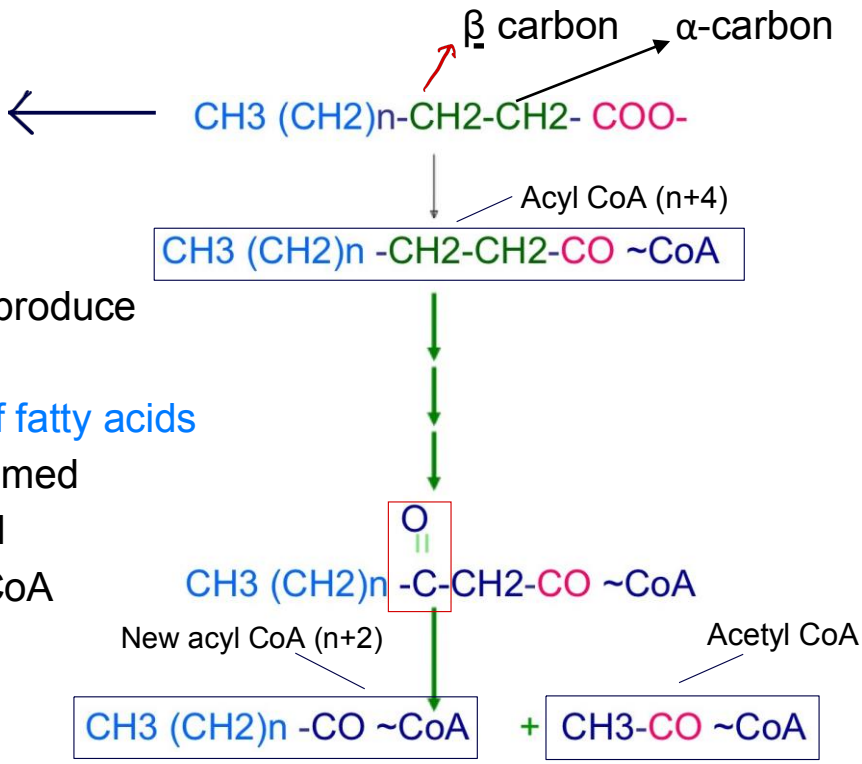
Oxidation of Fatty Acids (Quick revision)

1) β Oxidation of Fatty Acids

• the first step is joining the Fatty acid with CoA

- they are joined by a thioester bond (high energy bond)
- note : breaking this bond will produce about 7.5 kcal/mol
- this step is called activation of fatty acids
- two ATP molecules are consumed in order to CoA to the fatty acid
- CoA + fatty acid = fatty acyl CoA



• fatty acyl CoA then enters the mitochondria , and by a sequence of three reactions (oxidation reactions), the β carbon CH_2 is converted to ketone group (Losing 2 Hydrogen atoms and obtaining 1 oxygen atom)

• then , two carbon atoms are cleaved and released as acetyl CoA .

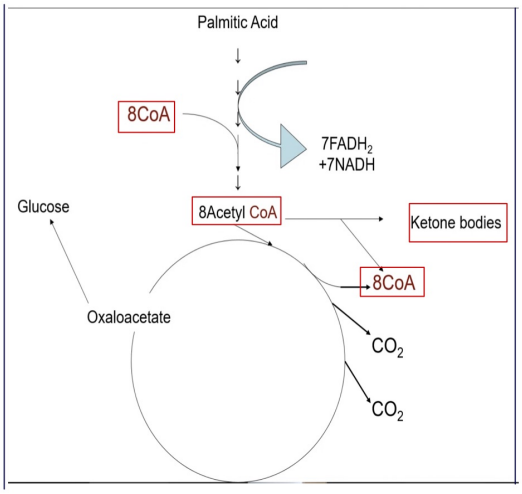
- the remaining fatty acid now is a new acyl CoA and it is shorter than the original one by two carbon atoms .

• note : this process is repeated again and again, until the fatty acid is completely converted to acetyl CoA .

- for example: fatty acid with 16 carbons requires 7 cycles and produces 8 acetyl CoA molecules.

2) production of ketone bodies

- in order for fatty acid oxidation to continue, a constant supply of CoA molecules is required.
- when the krebs cycle is activated, CoA is released, then can be reused in fatty acid oxidation.
- But in the fasting state, oxaloacetate is used to synthesize glucose , so the level of oxaloacetate is greatly decreased and the cycle can no longer operate at the same rate.



- Liver can synthesize ketone bodies from acetyl CoA, and release CoA as a solution.

Note: ketone bodies are not used as source of energy in the liver , but they are used in other tissue cells .

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Fatty Acid Synthesis

• occurs mainly in the liver, also it occurs in the lactating mammary glands.

• requires carbon source: acetyl CoA

- the starting material for fatty acid synthesis is acetyl CoA

• requires Reducing Power: NADPH

$8\ CH_3COO \rightarrow C_{15}H_{33}COO$

Acetyl group → Palmitic acid

- the end product is much more reduced, so we need a high energy reducing substance, which is NADPH.

Note : the main source of fatty acid synthesis is the excess carbohydrates from the diet .

- Fatty acid synthesis and oxidation are opposite processes, so they can't occur at the same time.

• requires energy input: ATP , why ??

Synthesis of fatty acid from acetyl CoA is endergonic reaction. → So in order to drive it in the forward direction, we need to couple it with ATP hydrolysis.

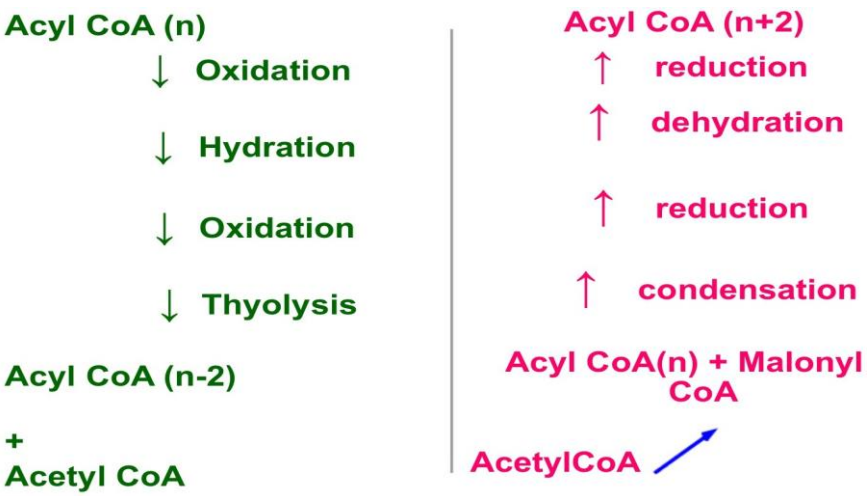
Acetyl CoA
↓
↓
↓
↓
Fatty Acid

ΔGo : +ve

Acetyl CoA + n(ATP)
↓
↓
↓
↓
Fatty Acid + n(ADP)

ΔG^{o} : -ve

• comparison between FA Degradation and Synthesis .

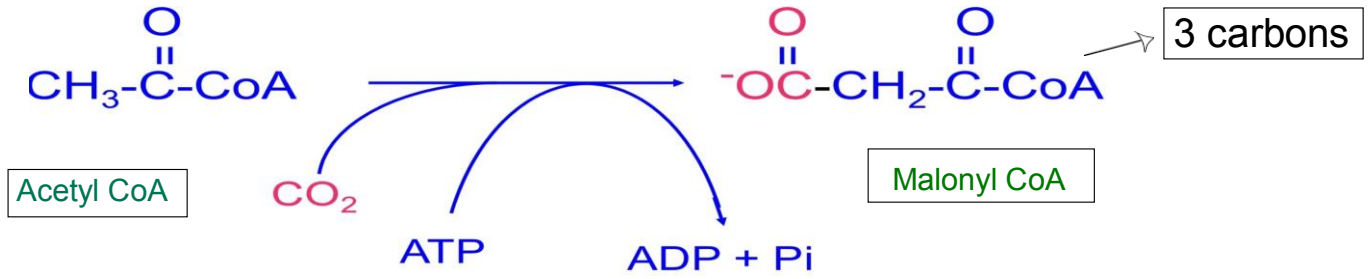


• fatty acid degradation and synthesis share many common intermediates .

- seems one of them is reversible to the other, but actually they are not .

Steps of fatty acid synthesis

1- Carboxylation of Acetyl CoA Produces Malonyl CoA



- malonyl CoA have more ability to condense with acyl CoA .
- malonyl CoA has two carboxyl groups (dicarboxylic acid)
- reaction: carboxylation reaction (requires ATP)
- enzyme: Acetyl CoA Carboxylase .
- coenzyme: biotin (vitamin B7)
- we get the CO_2 from bicarbonate(HCO_3^-)

2- Fatty Acid Synthase Catalyzes the remaining steps

⊛ fatty acid synthase

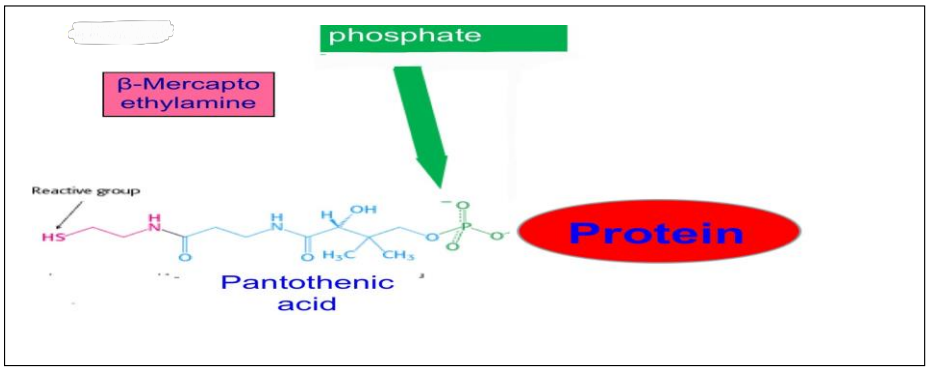
1- Multifunctional Enzyme Complex

2- Dimer of two Identical Chains

- if these chains are separated, it is no longer active.
- Each chain has Seven Catalytic Activities (One activity is Condensing Enzyme with –SH) ⟶ We call it condensing enzyme (CE)

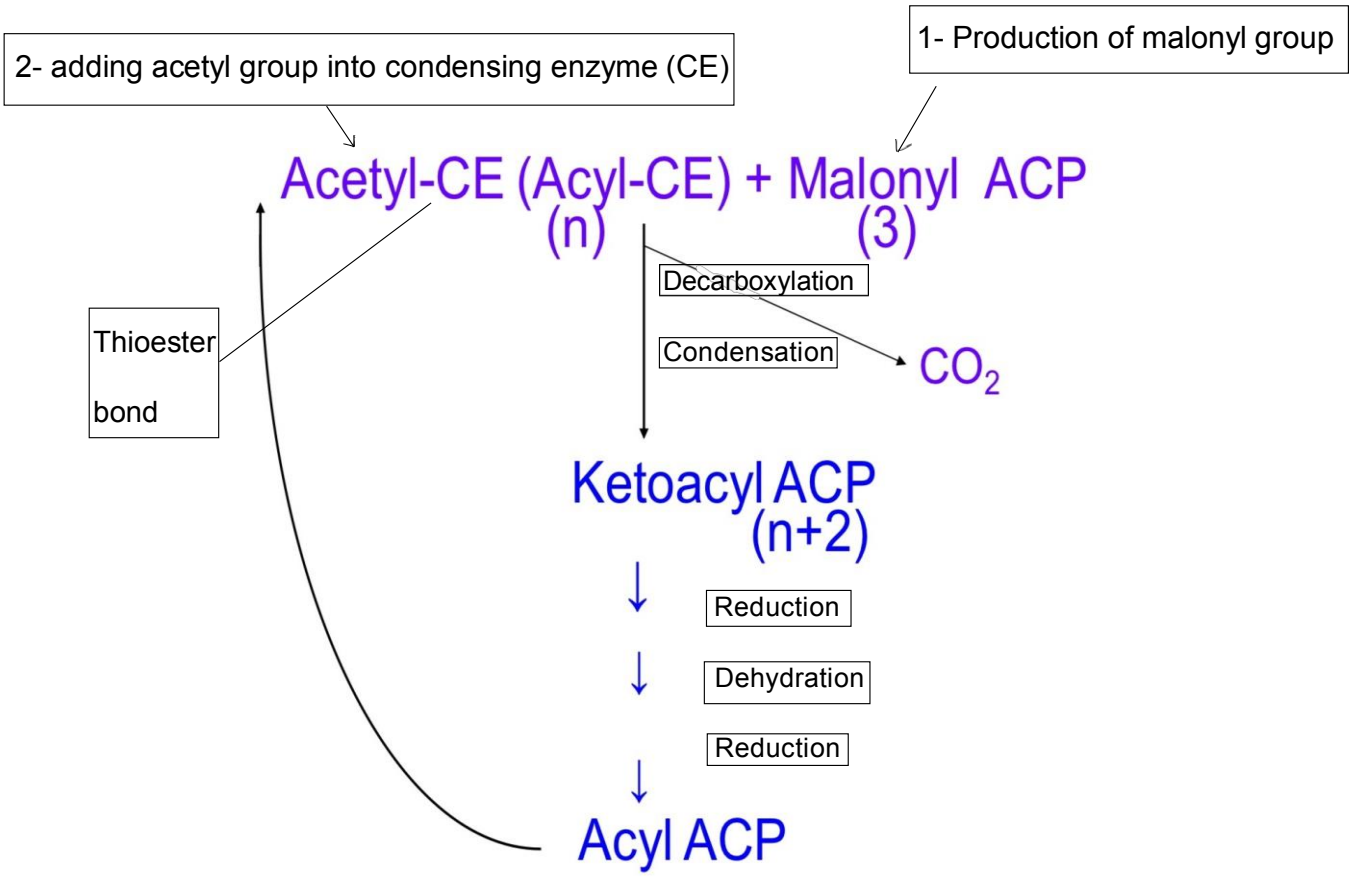
• One Domain is known as Acyl Carrier Protein (ACP)

• acyl carrier protein: A protein joined to Phosphopantheine group (contains reactive SH group)



Acyl carrier protein

Fatty Acid Synthesis (Overview)



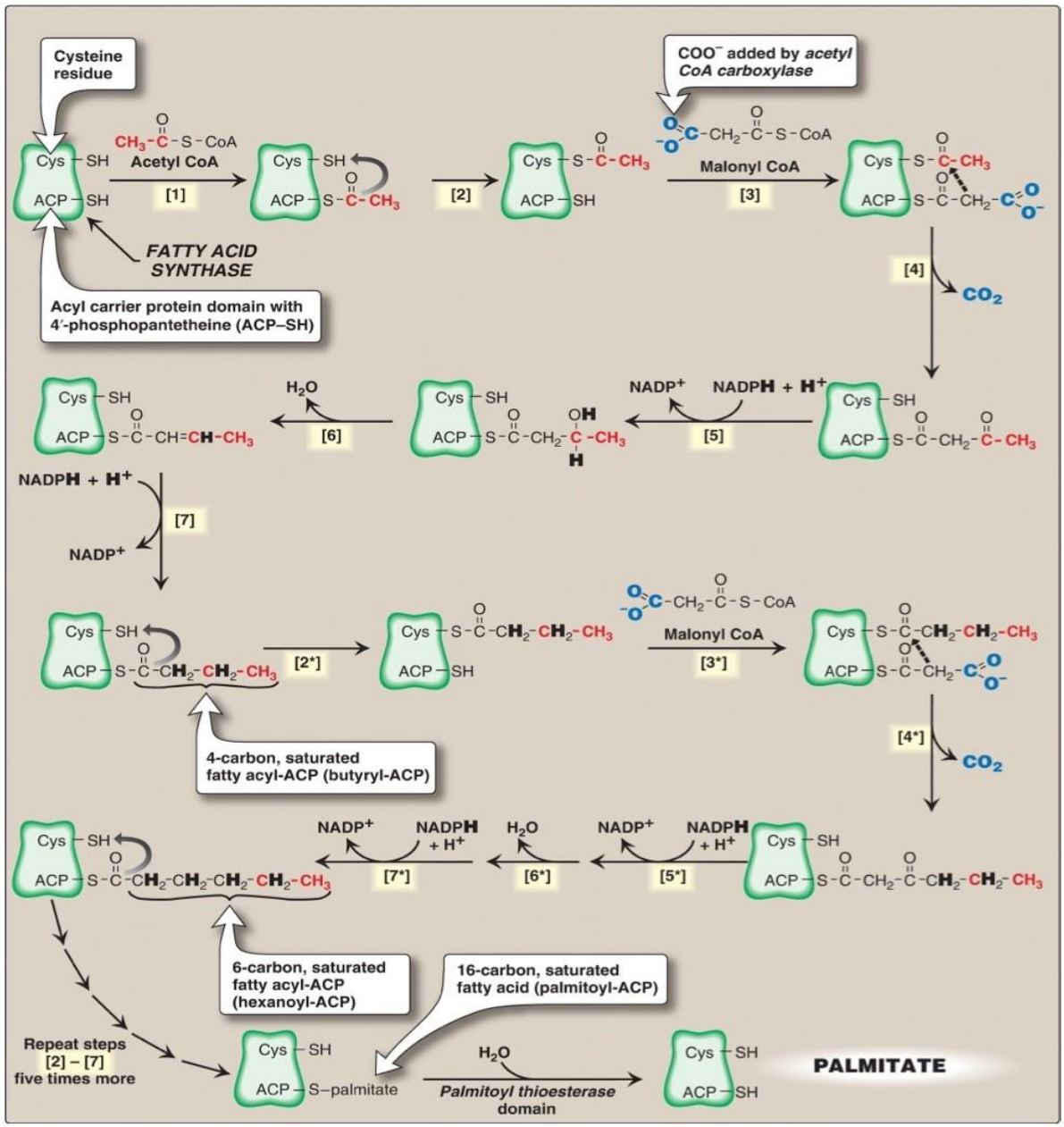
• what drives the above reaction in the forward direction??

1- decarboxylation

- because it is an exergonic reaction

2- breaking the high energy bond that joins the acetyl group with the condensing enzyme.

Synthesis of Palmitate by Fatty Acid Synthase



1- acetyl CoA is added to Acyl carrier protein.
2- transfer of acetyl group from ACP to condensing enzyme
3- adding malonyl group into acyl carrier protein.
4- condensation ——»producing ketoacyl group.
5- reduction, where ketone group is reduced to hydroxyl group.
6- dehydration, where double bond is introduced.
7- reduction, producing saturated fatty acyl.

. the process is repeated again and again, until we reach a 16 carbons fatty acid

• What is the advantage of having all these enzyme activities in one enzyme?
- this makes the reaction more efficient.

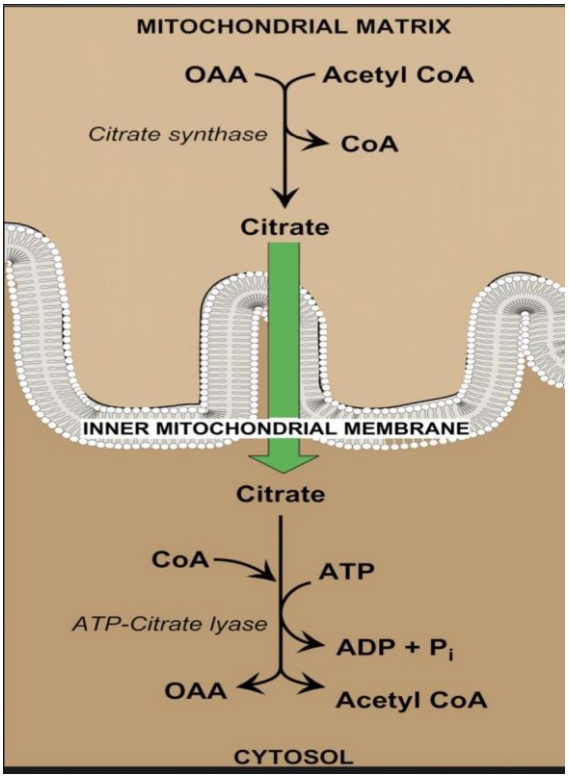
Synthesis of Palmitate (net reaction)

How many cycles of synthesis (Condensation)? ——»7
How many Malonyl CoA?——» 7 (remember: the first step is between acetyl CoA and malonyl CoA , not malonyl and malonyl)
How many Acetyl CoA? ——» 1
How Many NADPH?——» 14 (each cycle has two reduction steps, each reduction step requires 1NADPH
? remember: the pathway that provides NADPH is the pentose phosphate pathway.

- Production of Cytosolic Acetyl CoA for FA Synthesis

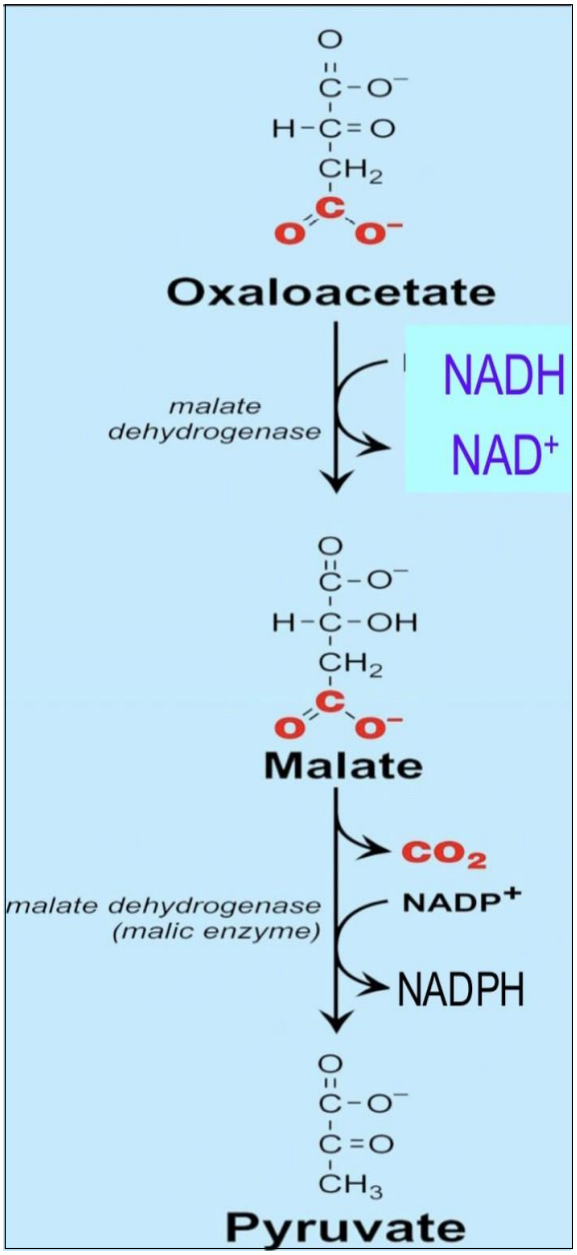
- fatty acid synthesis starts from acetyl CoA .
- where is the acetyl CoA prduced ?
- it is produced from pyruvate by pyruvate dehydrogenase complex in the mitochondrial matrix .
- to use it for fatty acid synthesis, we need to get it out of the mitochondria to the cytosol, where fatty acid synthesis happens.
- the inner mitochondrial membrane is immpermiable to acetyl CoA and there is no transporter for it .
- to overcome this problem, acetyl CoA binds to oxaloacetate to form citrate (there is citrate transporter)

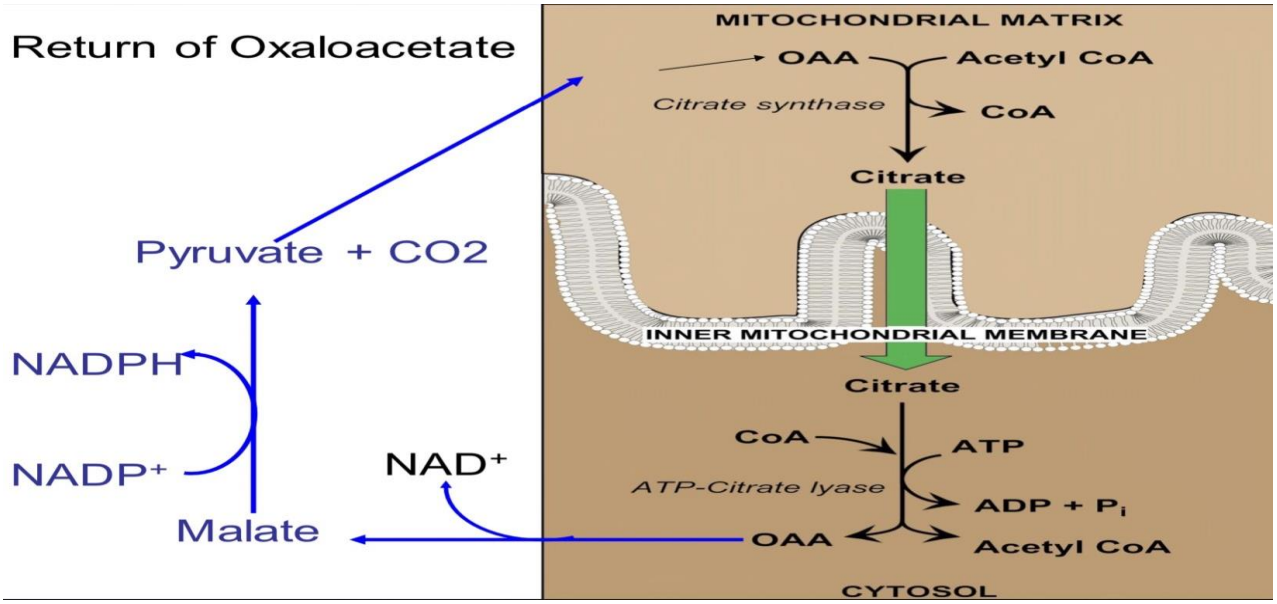
- citrate diffusion through the mitochondrial membrane is facilitated diffusion (it depends on the abundance of citrate in the matrix)
- in the cytosol, citrate is converted again to oxaloacetate and acetyl CoA by ATP-Citrate lyase .



- now , acetyl CoA and oxaloacetate is outside the mitochondria, we can use acetyl CoA for fatty acid synthesis, but oxaloacetate has to return to the mitochondria.
- it cannot return directly, so it is converted to pyruvate in a reaction that produces NADPH .
- for one oxaloacetate, one NADPH is produced.
- pyruvate can get into the mitochondria.

O for palmitic acid synthesis, 8 acetyl CoA is used, 8 oxaloacetate molecules is converted to pyruvate,and 8 NADPH molecules is produced (more than half the amount that we need to synthesize palmitic acid.





• Regulation of FA Oxidation & Synthesis

- they should not occur at the same time (oxidation is not directly producing ATP whereas synthesis consumes ATP , so it is just a waste of energy)
- oxidation occurs in the mitochondria whereas synthesis occurs in the cytosol , this helps regulating these processes, so they don't occur at the same time .

- Regulation of FA Synthesis

• *Regulation of AcCoA Carboxylase*

- it catalyzes the first step which is acetyl CoA carboxylation .
- Regulated by
- Allosteric Mechanism
- Phosphorylation

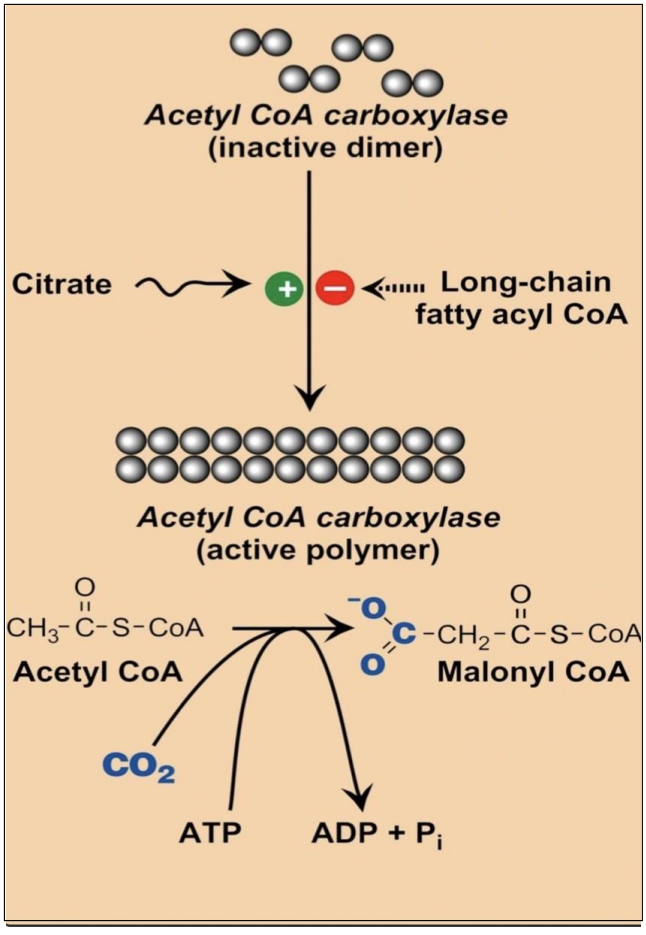
But , why this enzyme??

- because acetyl CoA carboxylation is the rate limiting step , malonyl is used only for FA synthesis , so production of malonyl CoA is a committed step (the product is committed to the fatty acid synthesis)

• Amounts of Enzymes also regulate FA synthesis.

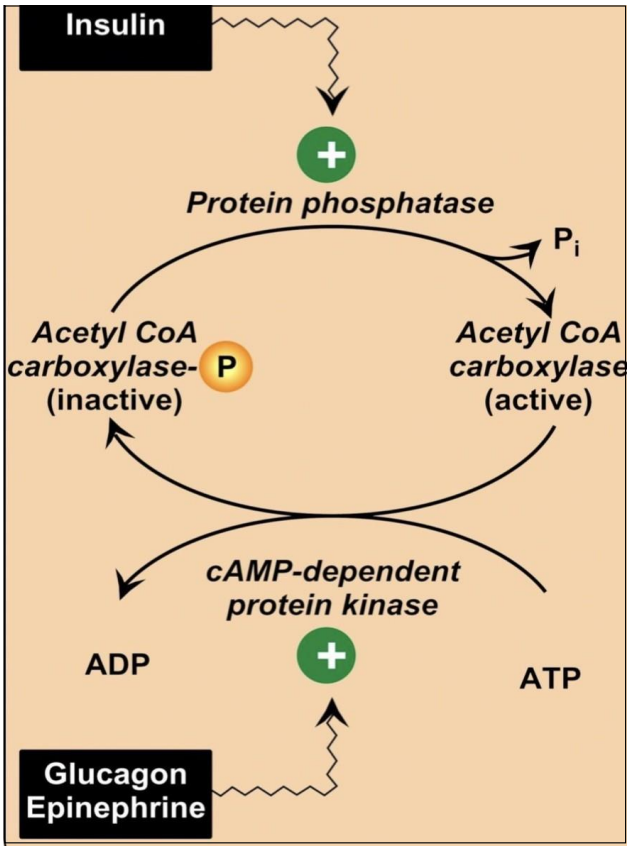
• Allosteric Regulation of Acetyl CoA Carboxylase

- Acetyl CoA Carboxylase is found as inactive dimer , when it is activated, it is converted to active polymer.
- citrate stimulates the enzyme
- citrate reflects that the amount of energy in the cell is high.
- long-chain fatty acyl CoA inhibits the enzyme (it is an end product so we call it *negative feedback*)



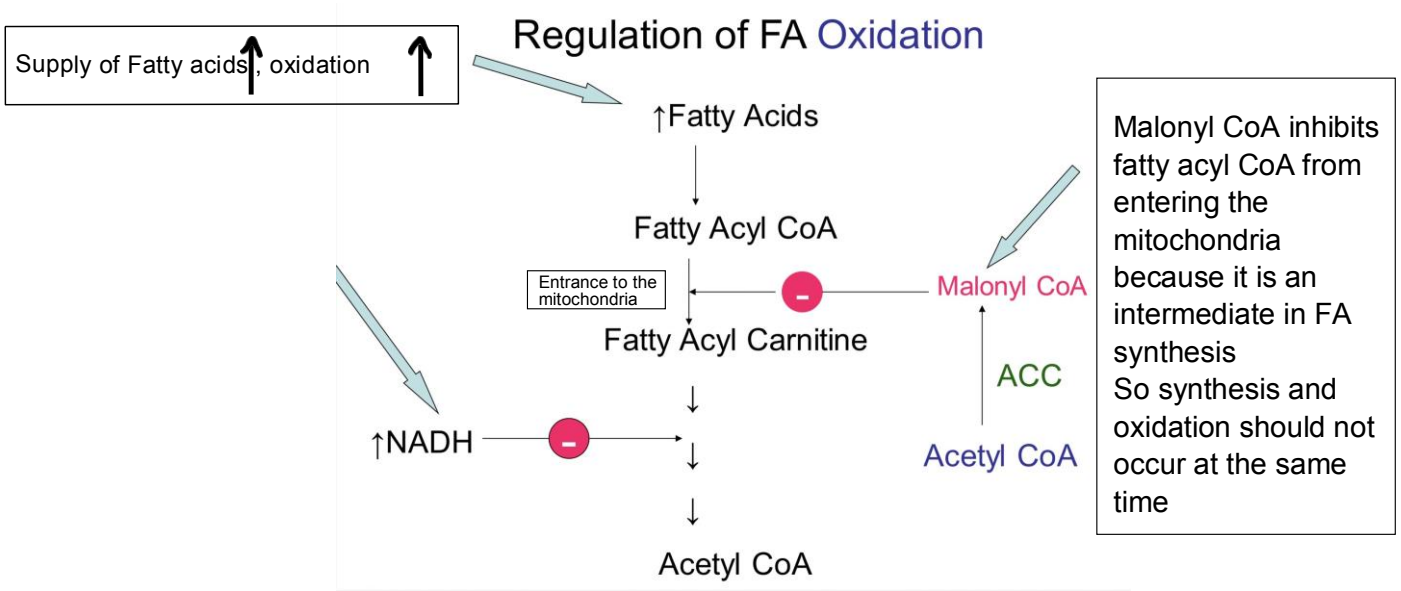
• Covalent Regulation of Acetyl CoA Carboxylase (Phosphorylation)

- glucagon and epinephrine act by stimulating protein kinase .
- protein kinase phosphorylates acetyl CoA carboxylase making it inactive.
- high glucagon means low blood glucose level, so the body doesn't synthesize fatty acids .
- insulin stimulates protein phosphatase that removes the phosphate group from acetyl CoA carboxylase converting it to the active form



• Regulation of FA Oxidation

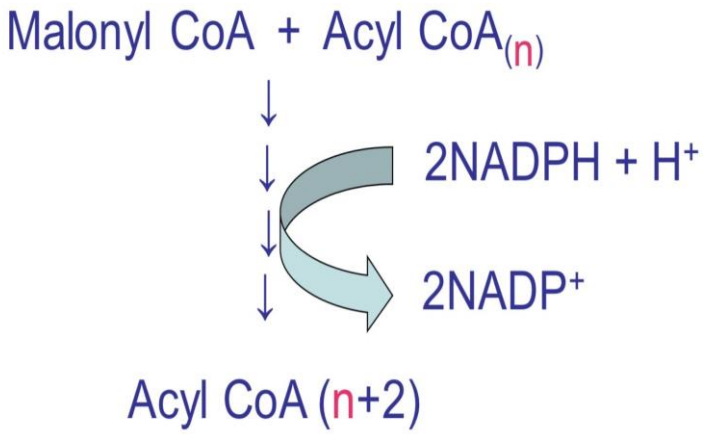
- Supply of Fatty Acids
- when there is abundant amount of fatty acids the oxidation pathway is activated.
- Hormonal Control : because the mobilisation of fatty acids from the adipose tissue is under the hormonal control.
- Entry into Miochondria.
- Availability of NAD+.



Malonyl CoA inhibits fatty acyl CoA from entering the mitochondria because it is an intermediate in FA synthesis
So synthesis and oxidation should not occur at the same time

Elongation of Fatty Acids

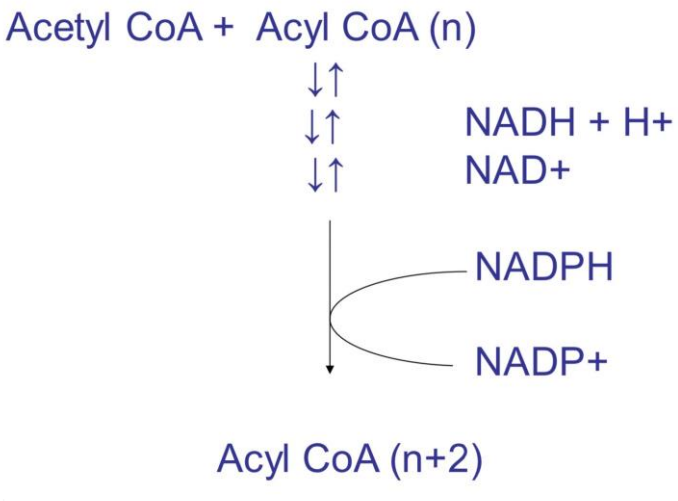
- fatty acids can be synthesized in the cytoplasm up to 16 carbons , but what about 18 or more carbon fatty acids ?
- they are elongated in the endoplasmic reticulum by similar sequence of reactions but by different enzymes .
- fatty acid synthase is specific for producing fatty acid with 16 carbons , after that the fatty acid is released.
- if the cell requires 18 carbons fatty acids (or more) , it takes this fatty acid into the endoplasmic reticulum and makes it longer and longer.



n = 16 or more carbons

• Elongation of Fatty Acids in Mitochondria

- If you take food that contains short and medium chain fatty acids, these are not stored in the body as such, rather, they are elongated in the mitochondria .



n = less than16 carbons

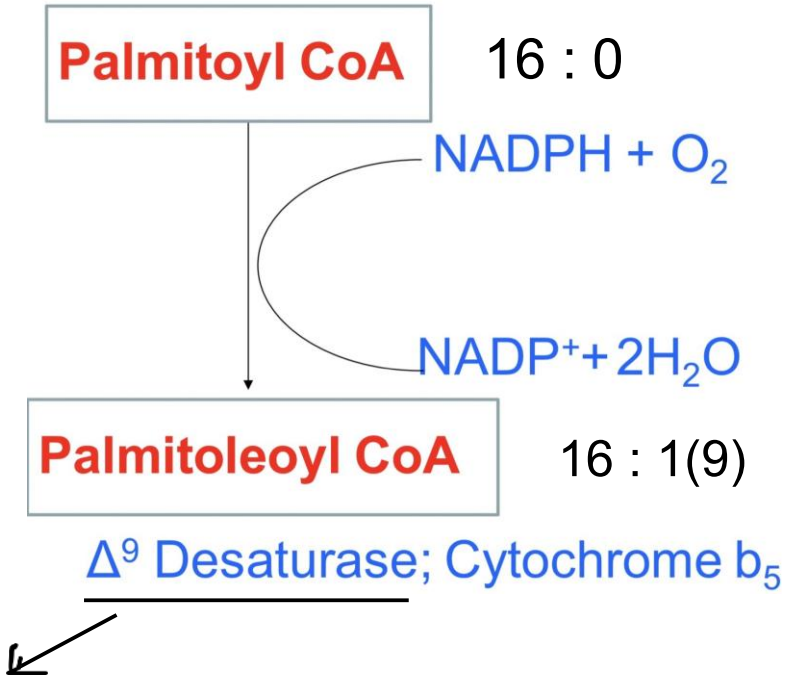
Introduction of Double Bonds

1- Synthesis of Monounsaturated FA .

- Oleic Acid 18:Δ9
- Palmitoleic 16:Δ9

One double bond between C9 and C10

- occurs in the endoplasmic reticulum .
- No double bond can be introduced beyond carbon 9 in human .
- in human cells double bonds can be introduced only before C9 .



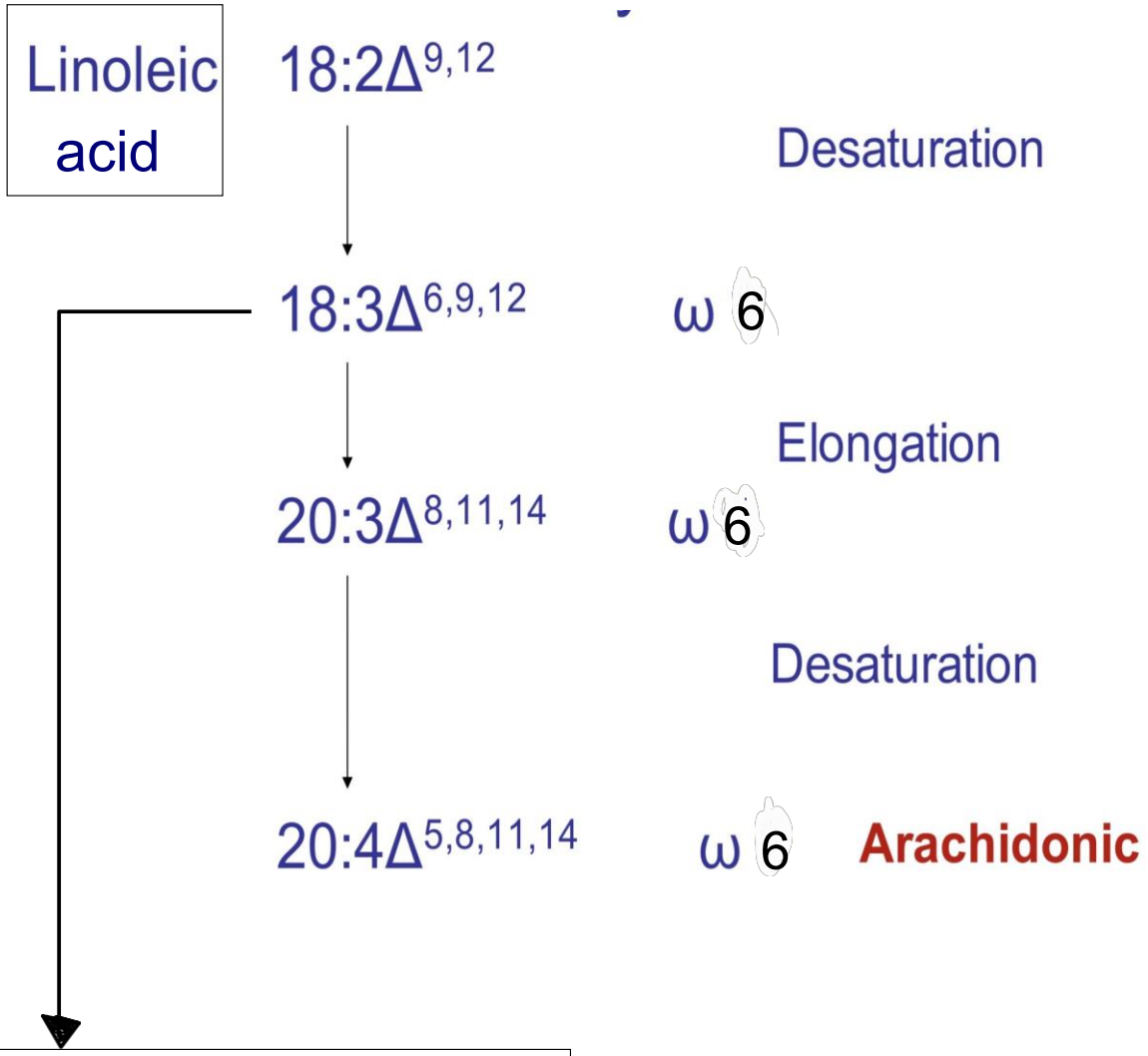
The enzyme that catalyze the process

2- Formation and Modification of Polyunsaturated FA

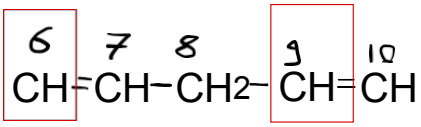
- introduction of double bonds can be used to modify fatty acids (adding additional bonds)
- the additional bond can be introduced between the carboxyl group and the first double bond but not after C9 .
- Modification of Polyunsaturated FA can occur by Elongation or Desaturation.
- Additional double bonds can be introduced by:

Δ4 Desaturase Δ5 Desaturase Δ6 Desaturase

Modification of Polyunsaturated FA



The double bond is introduced between carbon 6 and 7 , because the double bonds should be separated by CH_2



- note: elongation and desaturation don't change the omega classification because all modifications occur from the carboxyl end .

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