
◉ Sheet ○ Slides

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| Subject : | Synthesis of Fatty Acids |
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| Number : | 22 |

# Synthesis of Fatty Acids

It occurs mainly in the Liver and to some extent in the adipose tissue (for storage) and in the lactating mammary glands for the production of milk.

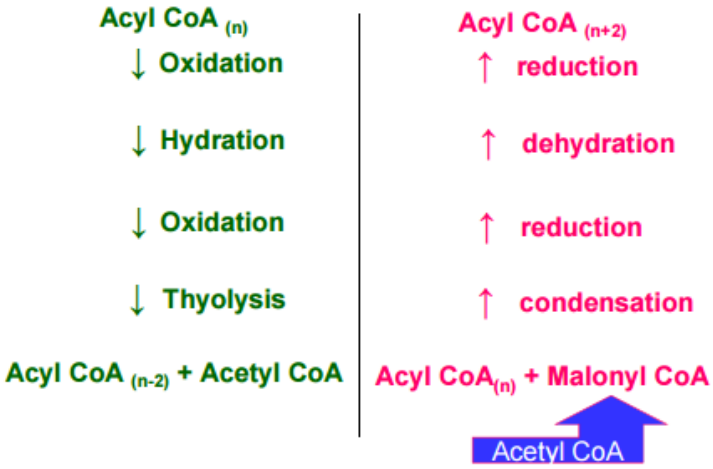
It requires: -

- Carbon Source: Acetyl CoA.
- Reducing Power: NADPH (because it is a reductive biosynthesis process and the end product is more reduced/has less oxygen than the initial).
- Energy Input: ATP. (Making a larger, higher energy compound)

To go from fatty acid to acetyl CoA you liberate energy → $\Delta G^{o}$: -ve; thus, if we go back to fatty acid from acetyl CoA → $\Delta G^{o}$: +ve (with the same value); so we need to couple the reaction with hydrolysis of ATP to make $\Delta G^{o}$ negative.

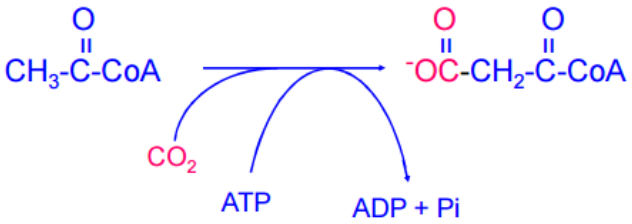
## Comparison between FA degradation and synthesis

In chemical point of view, synthesis is just the reverse of degradation: Condensation, reduction and dehydration are the opposite of thyolysis, oxidation and hydration, respectively.
Malonyl CoA comes from acetyl CoA




*Note: They use different enzymes and occur at different places in the cell; Oxidation occurs in the Mitochondria whereas Synthesis occurs in the cytoplasm

First of all, we produce malonyl CoA by carboxylation of Acetyl CoA

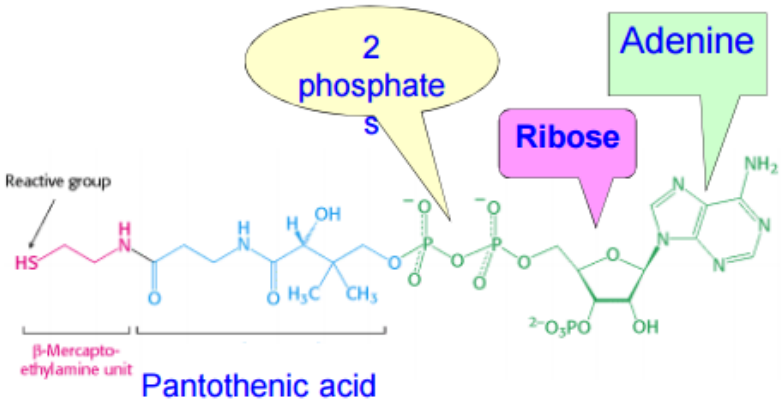



- Malonyl CoA is a dicarboxylic Acid (Having two carboxylic groups) with three carbon atoms. It is similar to Succinyl CoA but Succinyl CoA has four carbon atoms.
  *We can consider malonyl CoA as the active form of acetyl CoA.
- Energy is needed (Carboxylation reactions are always endergonic while decarboxylation reactions are always exergonic).
- The enzyme needed is **Acetyl CoA Carboxylase**. (the rate limiting step)
- Acetyl CoA Carboxylase is a **Biotin**-Containing Enzyme (Biotin is the carrier of the active $CO_2$).

◘ All the remaining steps are catalyzed by the same enzyme which is **Fatty Acid Synthase**.

- Multifunctional Enzyme Complex (The same enzyme molecule has several active sites and each site is responsible for part of the reaction)
- Dimer of two Identical Chains (Although the two chains are identical, one is not active alone, but when they dimerize they complete the action of each other).
- Each has Seven Catalytic Activities
- One Active site is a Condensing Enzyme **CE** with –SH group (catalyzing the condensation reaction that will be discussed later in this lecture).
- One Domain carries Intermediates (Acyl, Acetyl and Malonyl Groups) during Catalysis; it is Acyl Carrier protein **ACP** and is linked to Phosphopantetheine with Reactive –SH group.

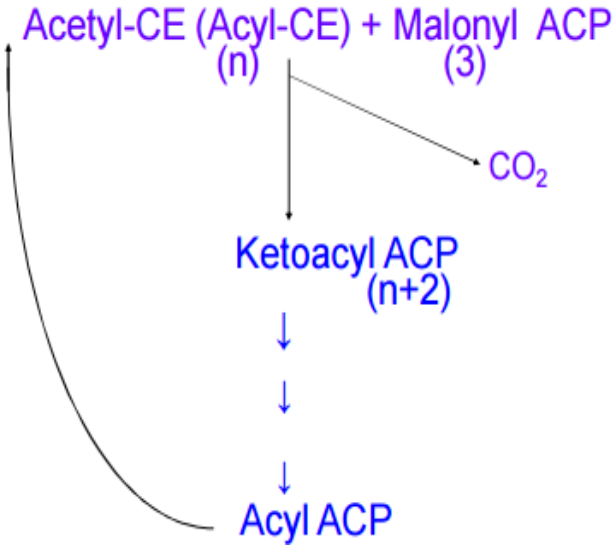
In the figure below is CoA; if you link pantothenic acid to the protein, instead of what it is now, you will have ACP, so ACP is considered a large CoA as both carry acyl groups. But note that CoA carries them during oxidation not synthesis.




SH can form a thioester bond with a carboxyl group; it is a high energy bond.

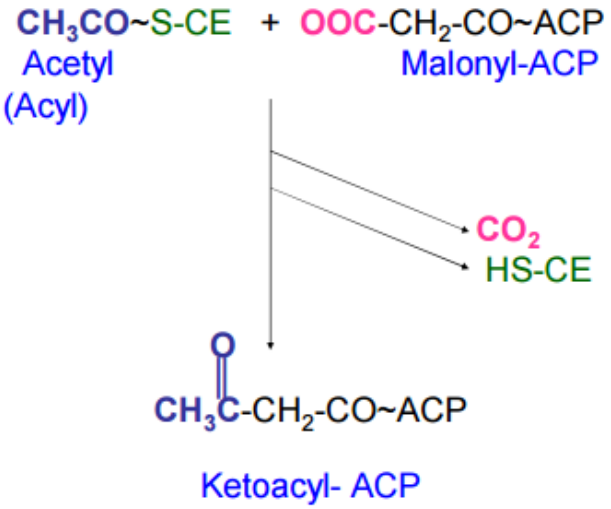
**An overview of FA synthesis**

- ➔ We start with Acyl CoA (or Acetyl CoA initially) and Malonyl CoA.
- ➔ They are joined together by the condensing enzyme and $CO_2$ is released forming Ketoacyl CoA which has 2 more carbon atoms than the Acyl CoA.
- ➔ Ketoacyl is reduced, dehydrated and then reduced forming Acyl CoA.
- ➔ Acyl CoA will repeat the cycle.



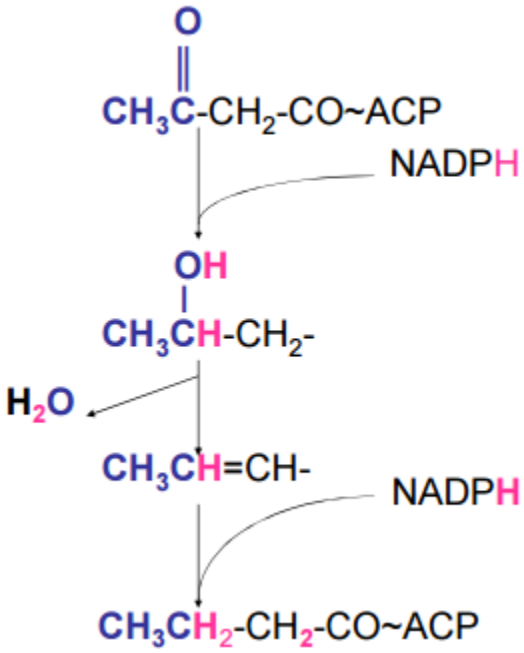

It is the reverse of Oxidation.

**Condensation**




- Acetyl (Connected to CE) and malonyl (connected to ACP) condense together and $CO_2$ and CE are released forming Ketoacyl-ACP.
- It is the reverses of cleavage.
- Decarboxylation and the Cleavage of the thioester bond between Acetyl and CE drive the forward reaction and make it exergonic.
- $CO_2$ that is added to Acetyl CoA is now removed, which means we added it just to raise the energy level. (it's like what we did to Pyruvate when we transformed it into Oxaloacetate then to Phosphoeneol Pyruvate)

**Reduction → Dehydration → Reduction**

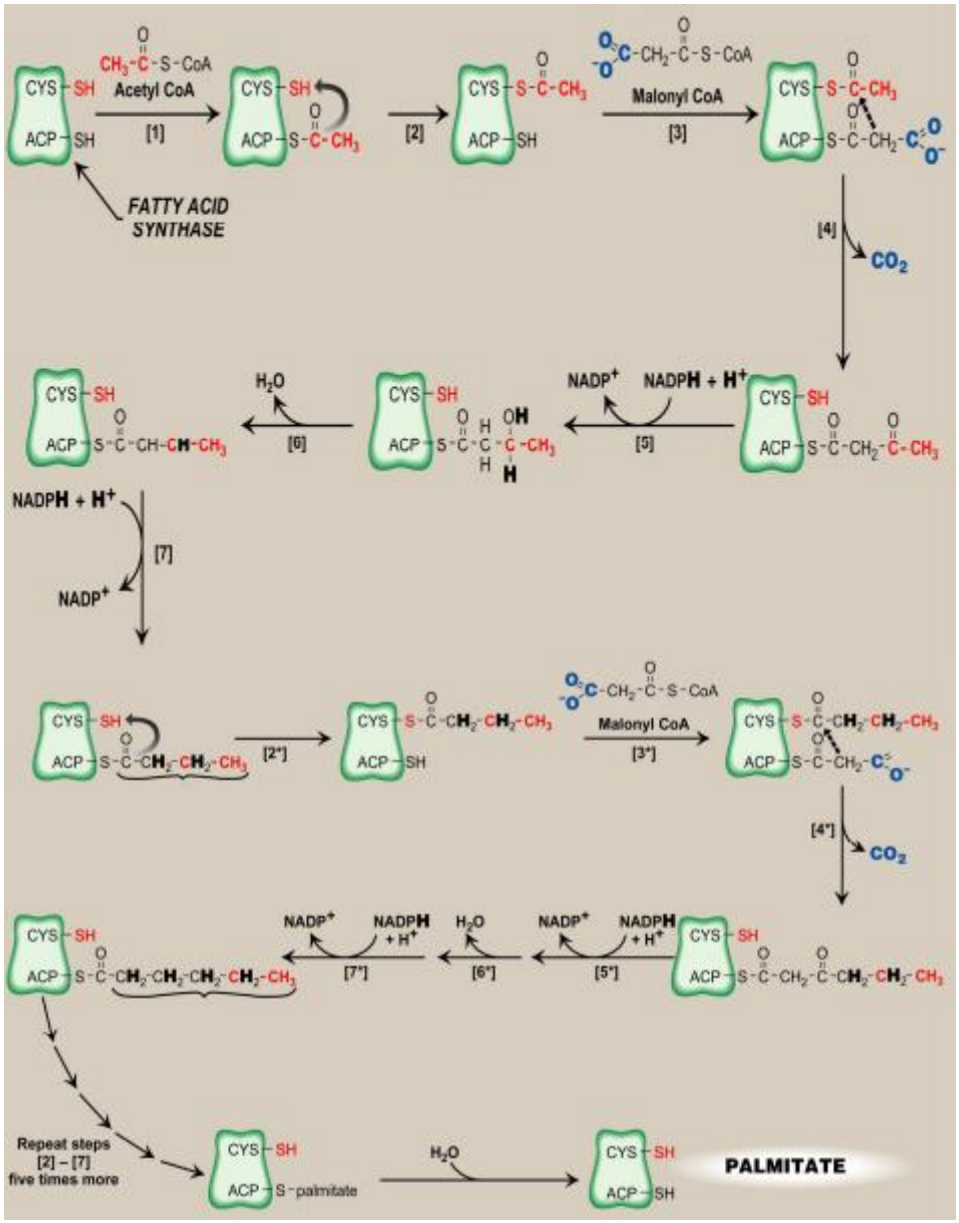



1. Reduction of Ketone group forming a hydroxyl group using NADPH.
2. Dehydration to form a double bond.
3. Then another reduction forming Acyl-Acp. (adding hydrogen atoms to make a single bond)
4. Then Acyl CoA goes through condensation and the whole cycle again.

## Synthesis of Palmitate by Fatty Acid Synthase

The figure below illustrates the steps of FA synthesis (specifically Palmitate).

-Note before you go through the figure: the upper part of FA synthases is the condensing enzyme domain and the lower is ACP.




(1) Acetyl CoA links to ACP

(2) Acetyl CoA enters the CE domain

(3) Malonyl CoA links ACP

(4) Condensation reaction occurs between the Malonyl on the ACP and Acetyl on the CE forming Ketoacyl-ACP and releasing $CO_2$
(5) Reduction of the ketone group into a hydroxyl group
(6) Dehydration reaction occur forming a double bond
(7) Reduction of the double bond into a single bond forming Acyl-ACP with four carbons
*If it was in the mammary gland we stop here ,but in the liver we continue and repeat the cycle again and again until the end product is palmitate (16 carbon atoms)

➔ The last step is hydrolysis of Palmatyl-ACP to release Palmitate and the enzyme is now free.

IMPORTANT NOTES: -

- For each cycle we use 2 NADPH molecules and 1 Malonyl CoA to be added to the Acyl CoA
- We are adding carbon atoms two by two, and that's why Fatty Acids usually have an even number of carbons.

Q) In synthesis of Palmitate: -

1. How many cycles of reaction are needed?

→ 7

2. How many Malonyl CoA (remember that is produced form Acetyl CoA)?

→ 7

3. How many Acetyl CoA (as such -not as Malonyl)?

→1 (In the first condensation reaction we added Malonyl CoA to Acetyl CoA then Malonyl CoA is added to Acyl CoA)

4. How many NADPH?

→ 14 (2 for each cycle)

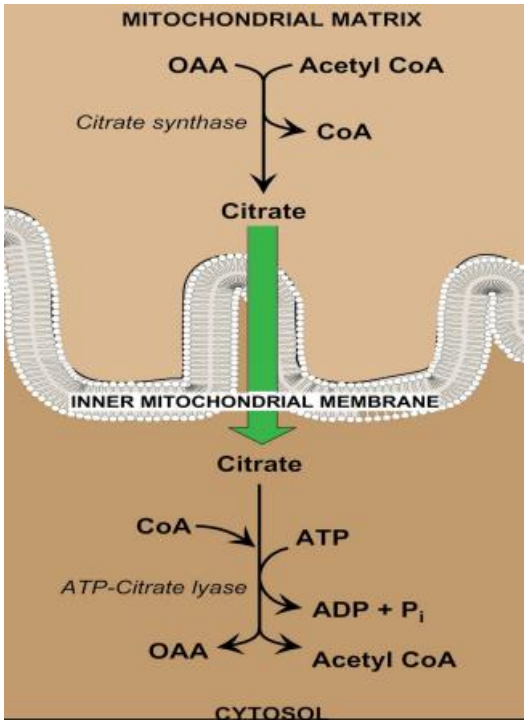
Now what is the source of the Acetyl CoA used in the synthesis?

From the excess carbohydrates mainly (Glucose) and from protein and to very less extent from previous degradation of Fatty acids (but it is not logical to degrade fatty acids to build fatty acids).

Pyruvate Dehydrogenase is the main producer of Acetyl CoA and it is present in the Mitochondria; Acetyl CoA needs to go to the cytosol to be used in synthesis, but the inner mitochondrial membrane is impermeable to Acetyl CoA. So the Acetyl CoA reacts with oxaloacetate producing citrate (The first reaction in TCA cycle), and the next reaction in TCA

cycle is transforming it into Isocitrate; now if energy is available Isocitrate dehydrogenase (which transforms Isocitrate into α-ketoglutarate) will be inhibited, causing the increase of the level of Isocitrate and thus the level of Citrate.

The citrate now passes to the cytosol and is cleaved again to oxaloacetate and Acetyl CoA.




1- OOA + Acetyl CoA → Citrate
   Enzyme : ***Citrate synthase***
   No ATP used
2- Citrate → OOA + Acetyl CoA
   Enzyme: ***Citrate Lyase***
   ATP is required because one of the products has a high energy bond (with CoA).

Similar reactions but not identical (one is not simply the reverse of the other), and thus they are catalyzed by different enzymes.

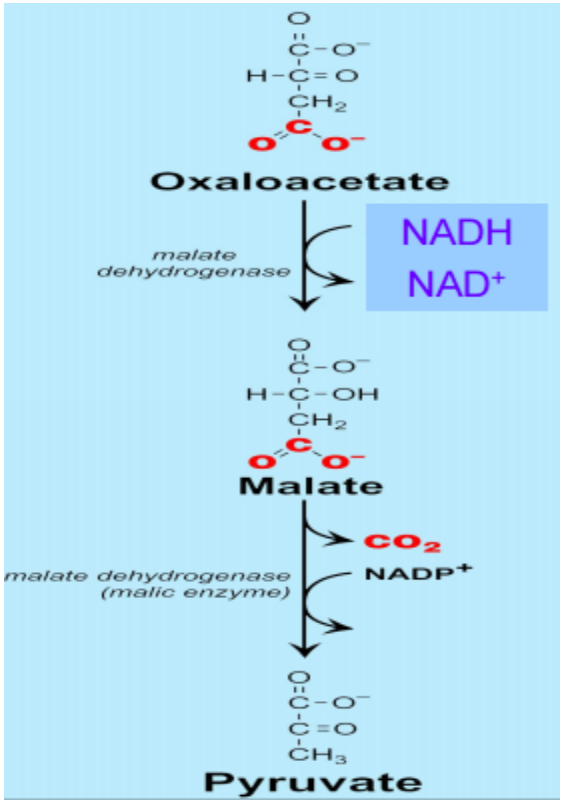
Oxaloacetate cannot pass the inner membrane to go back to the matrix.

So now **Oxaloacetate** is reduced producing **Malate** using NADH molecule and producing $NAD^+$. The enzyme use is Malate dehydrogenase.

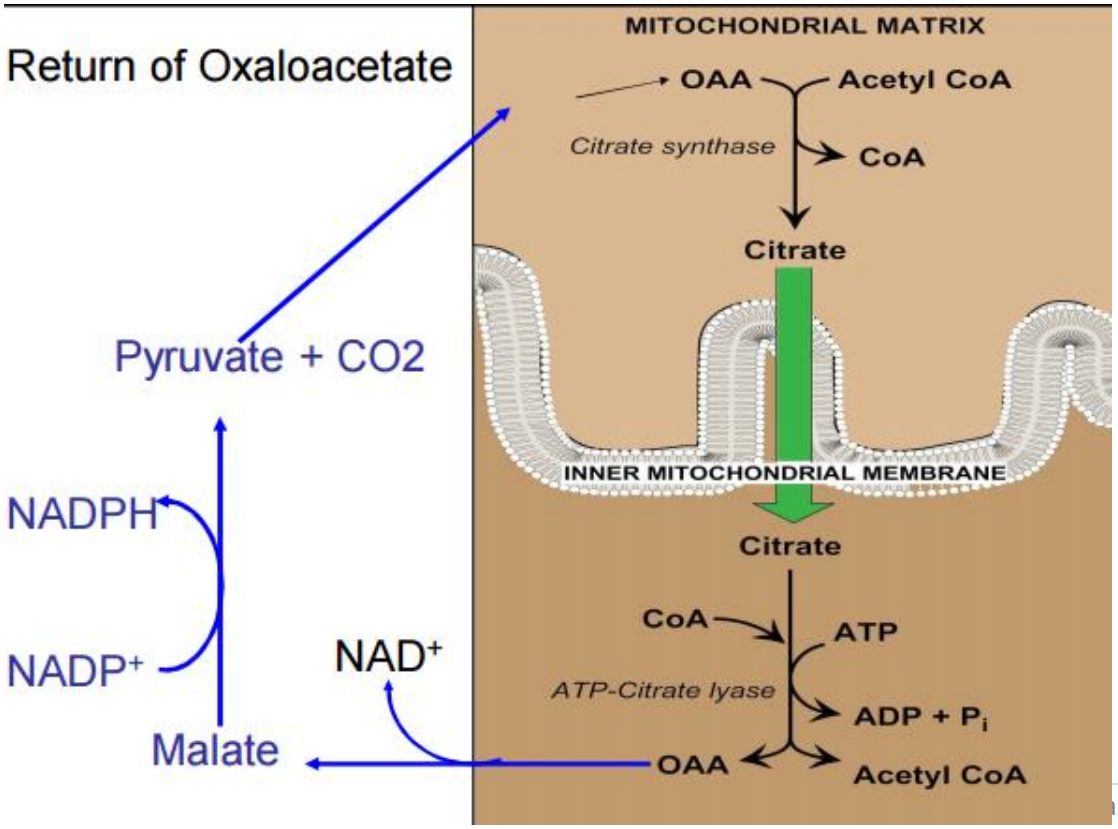
**Malate** undergoes oxidative decarboxylation (Loss of $CO_2$ and oxidation of a hydroxyl group to a ketone group) producing **Pyruvate**. The enzyme used is $NADP^+$ dependent dehydrogenase (producing NADPH from $NADP^+$).

<u>NADPH produced is used for the synthesis of FA**.**</u>

How many NADPH is produced in the synthesis of Palmitate? → ##




Then **Pyruvate** enters the matrix again to be converted to **Oxaloacetate**



## Regulation of Fatty Acids Synthesis and Degradation

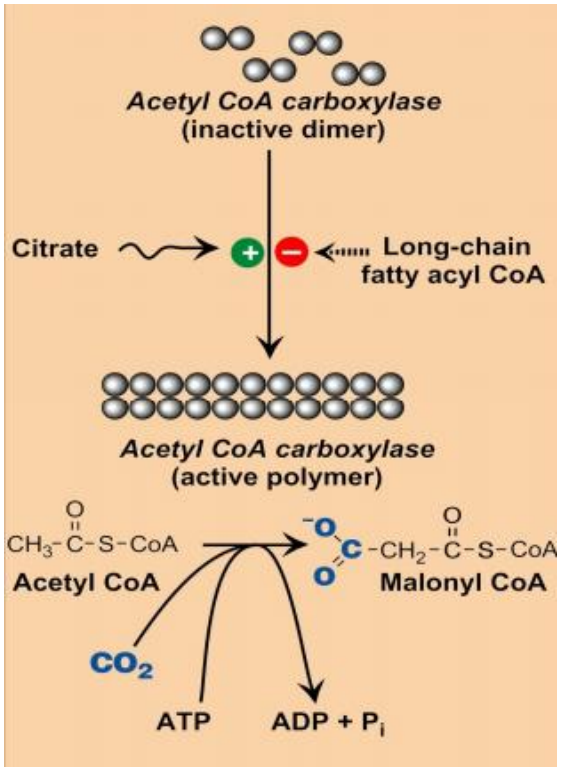
Degradation of Fatty Acids by itself is not going to produce ATP directly; but synthesis consumes ATP, that's why they shouldn't run at the same time because we are just wasting ATP.

Oxidation is regulated by: -Supply of FA's –Entry of FA's into the mitochondria –Hormonal regulation –Availability of $NAD^+$.

Synthesis is regulated by: - Regulation of Acetyl CoA carboxylase (by allosteric mechanism which is rapid or by Phosphorylation which requires several seconds or minutes) –Amount of Enzymes (Requires several hours or days).

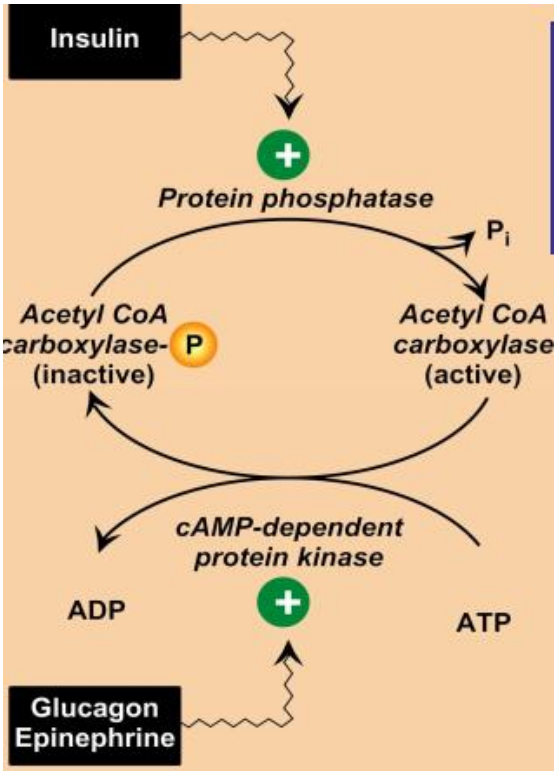
Acetyl CoA Carboxylase is suitable for regulation because it catalyzes an early step and it requires energy

- **Allosteric Regulation of Acetyl CoA carboxylase**




- Citrate stimulates the conversion of the inactive (dimer) form into the active (polymer) form.
  "Citrate means that energy level is high".
- Long fatty acyl CoA which is the end product acts as an inhibitor.

- **Regulation by phosphorylation**




- When Glucagon or Epinephrine level is high is stimulates cAMP dependent kinase which adds a phosphate group to Acetyl CoA Carboxylase transforming it to the in active form. (Because blood Glucose is low).
- When insulin level is high Protein phosphatase removes the phosphate transforming it to the active form. (Blood Glucose is high).

** Phosphorylation ALWAYS leads to sparing Glucose (making it more available).

- **Amount of enzymes** also play a role in regulation; if someone is not eating enough carbohydrates the level of enzymes involved in synthesis will decrease.

- ↑acetyl CoA >> exits the mitochondria as citrate >> synthesis of malonyl CoA>>it inhibits fatty acid carnitine (inhibiting the movement of fatty acids into the matrix), because we are synthesizing fatty acids and we don't want them to go back to the matrix (where oxidation occurs).

# The End