**FATTY ACID SYNTHESIS**

A large proportion of the fatty acids used by the body is supplied by the diet. Occurs mainly in liver adipocytes, in mammary glands during lactation Occurs in cytoplasm .When glucose is plentiful, large amounts of acetyl CoA are produced by glycolysis and can be used for fatty acid synthesis .

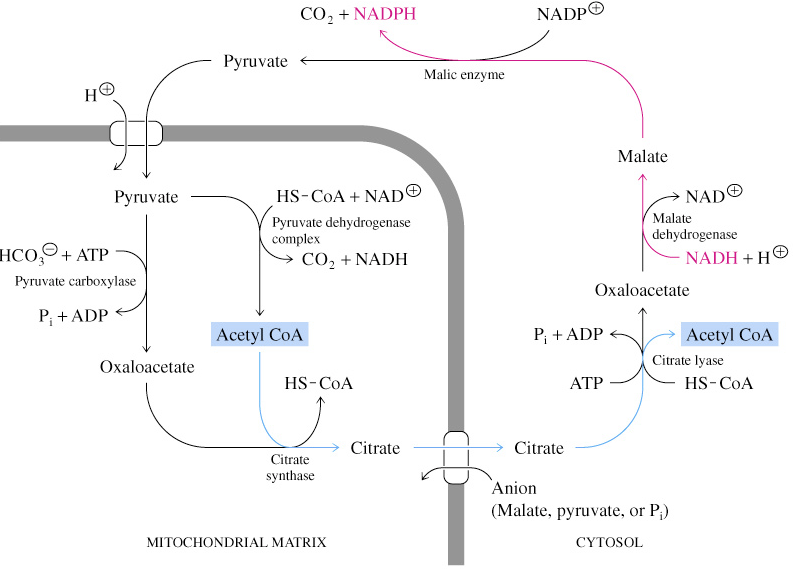
In fatty acid synthesis occurs primarily in the liver and adipose tissue, the process incorporates carbons from ***acetyl CoA*** into the growing fatty acid chain, using ATP and reduced ***nicotinamide adenine dinucleotide phosphate (NADPH).***

**Three stages of fatty acid synthesis:**

**A. Production of cytosolic acetyl CoA and NADPH**

The first step in fatty acid synthesis is the transfer of acetate units from mitochondrial acetyl CoA to the cytosol. Mitochondrial acetyl CoA is produced by the oxidation of pyruvate. The coenzyme A portion of acetyl CoA, however, cannot cross the mitochondrial membrane; only the acetyl portion is transported to the cytosol. It does so in the form of citrate produced by the condensation of oxaloacetate (OAA) and acetyl CoA

1. This process of **translocation** of citrate from the mitochondrion to the cytosol, where it is cleaved by *ATP-citrate lyase* to produce cytosolic acetyl CoA and OAA, occurs when the mitochondrial citrate concentration is high. Therefore, cytosolic citrate may be viewed as a high-energy signal. Because a large amount of ATP is needed for fatty acid synthesis, the increase in both ATP and citrate enhances this pathway.



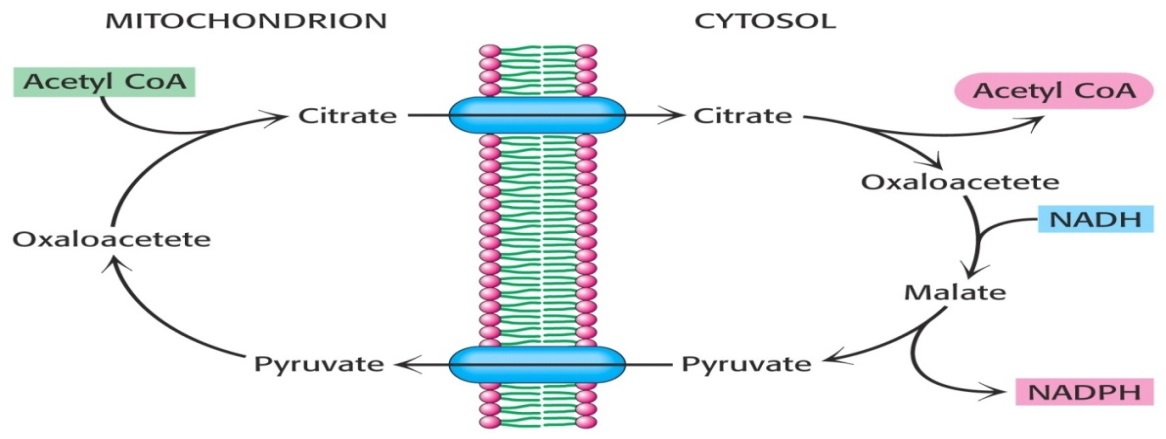
**Citrate + HSCoA + ATP**  **ADP + Pi + oxaloacetate + acetyl-CoA**

Oxaloacetate is reduced to malate by cytoplasmic NADH

* **Acetyl CoA from catabolism of carbohydrates and amino acids is exported from mitochondria via the citrate transport system**
* **Cytosolic NADH also converted to NADPH**
* **Two molecules of ATP are expended for each round of this cyclic pathway**

**Sources of NADPH for Fatty Acid Synthesis**

**1.** One molecule of NADPH is generated for each molecule of acetyl CoA that is transferred from mitochondria to the cytosol by (malic enzyme).



**2.** NADPH molecules come from the pentose phosphate pathway.

**B. Acetyl CoA Carboxylase makes the malonyl CoA for fatty acid synthesis**

***Acetyl CoA carboxylase*** (ACC) is organized in three components, which like pyruvate carboxylase, includes a central biotin carrier protein (BCP) which has a biotin molecule covalently bonded to a lysine side chain. On one side is the ATP driven biotin carboxylase, which generates the active carboxylate donor carboxybiotin from bicarbonate ion at the cost of ATP hydrolysis:

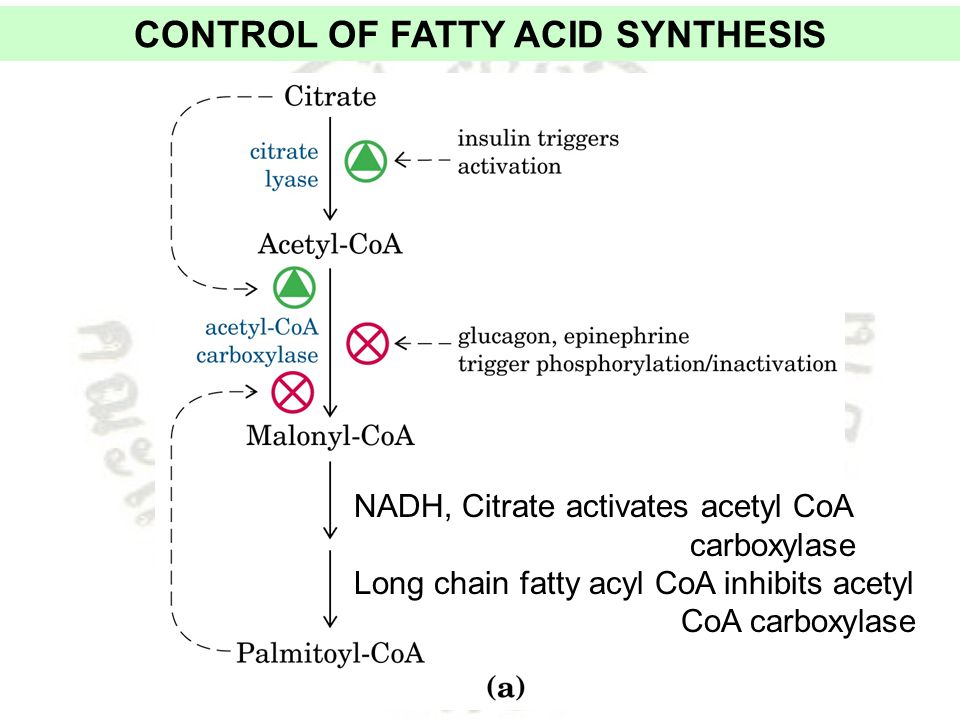
**ATP + biotin + HCO3–ADP + Pi + biotin-CO2 –**

On the other side is the substrate specific transcarboxylase (or carboxyltransferase), which uses acetyl CoA as the carboxylate acceptor .

**biotin-CO2 – + acetyl-CoA biotin + malonyl-CoA.**

Reaction catalyzed by Acetyl CoA Carboxylase ACC 

\*These enzymes adapt to the body’s physiologic needs by increasing in total amount in the fed state and by decreasing in starvation, feeding of fat, and in diabetes. Insulin (secreted when blood glucose levels are high) stimulates citrate lyase. Glucagon (secreted when blood glucose levels are low) and epinephrine (secreted when demand for ATP is anticipated) induce cyclic AMP, which stimulates protein kinase A to phosphorylate and inactivate acetyl CoA carboxylase. Feeding fats containing polyunsaturated fatty acids coordinately regulates the inhibition of expression of key enzymes of glycolysis and lipogenesis.



* **The Control OF Fatty Acid Metabolism**

The *Acetyl CoA carboxylase* plays an essential role in regulating fatty acid synthesis and degradation*.*

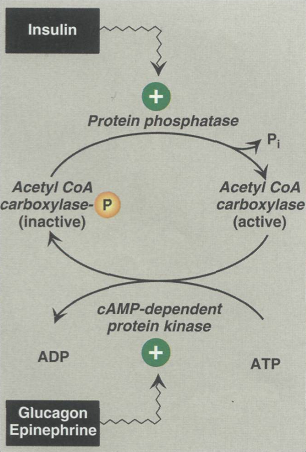
* **The *carboxylase* is controlled by hormones:**

**glucagon, epinephrine, and insulin.**

**Another regulatory factors:**

**citrate, palmitoyl CoA, and AMP**

Global Regulation is carried out by means of reversible phosphorylation .Acetyl CoA carboxylase is switched off by phosphorylation and activated by dephosphorylation Insulin stimulates fatty acid synthesis causing dephosphorylation of carboxylase. Glucagon and epinephrine have the reverse effect (keep the carboxylase in the inactive phosphorylated state). Protein kinase is activated by AMP and inhibited by ATP.

***Response to Diet******Fed state:***

**Insulin** level is increased

* Inhibits hydrolysis of stored TGs
* Stimulates formation of malonyl CoA, which inhibits *carnitine acyltransferase I*
* **FA remain in cytosol** (FA oxidation enzymes are in the mitochondria)

**Starvation: Epinephrine** and **glucagon** are produced and stimulate adipose cell *lipase* and the level of free fatty acids rises

* Inactivate ***carboxylase,*** so decrease formation of malonyl CoA (lead to increased transport of FA into mitochondria and activate the B-oxidation pathway)

**C. Fatty acid synthase: a multifunctional enzyme**

The remaining series of reactions of fatty acid synthesis is catalyzed by the multifunctional, dimeric enzyme, fatty acid *synthase*. Each fatty acid synthase monomer is a multicatalytic polypeptide with seven different enzymic activities.