Biochemistry
2nd stage

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Objectives:

The students are learned to understand the OXIDATION OF THE FATTY ACIDS including the following points:

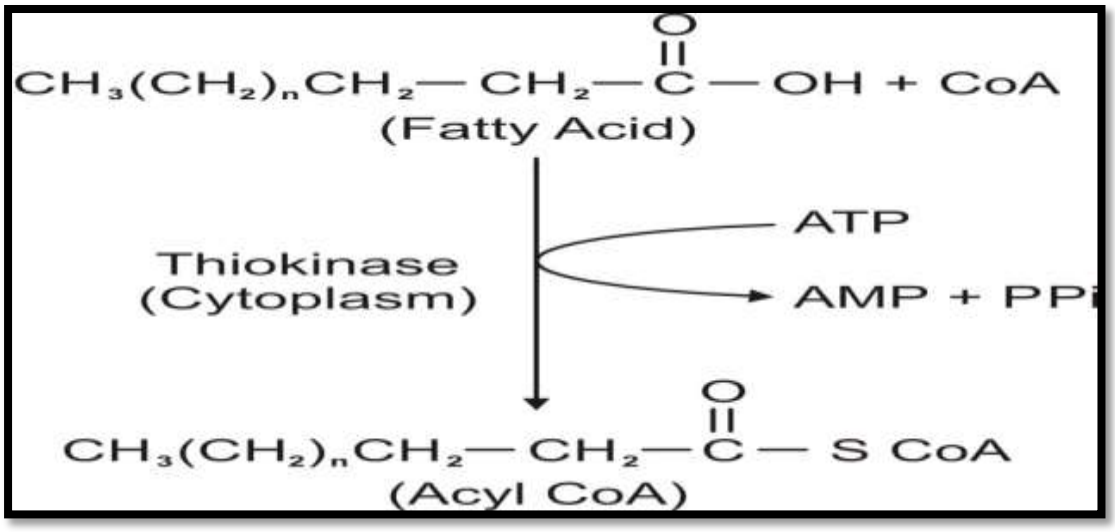
- **Beta oxidation pathway**
- **Carnitine shuttle**
- **Oxidation of the Fatty Acids with Odd Number of C atoms**
- **Oxidation of the unsaturated Fatty Acids**
- **Regulation of oxidation**

OXIDATION OF THE FATTY ACIDS

Fatty acids, mobilized from adipose tissues (lipolysis) by glucagon-mediated activation of enzyme hormone sensitive lipase. Activated lipase converts the triacylglycerol into free fatty acids and glycerol. Glycerol enters into gluconeogenesis.

Preparative Step 1: Activation of Fatty Acids

Fatty acids are activated to their co-enzyme A (CoA) derivative. This activation is taking place in **cytoplasm**.

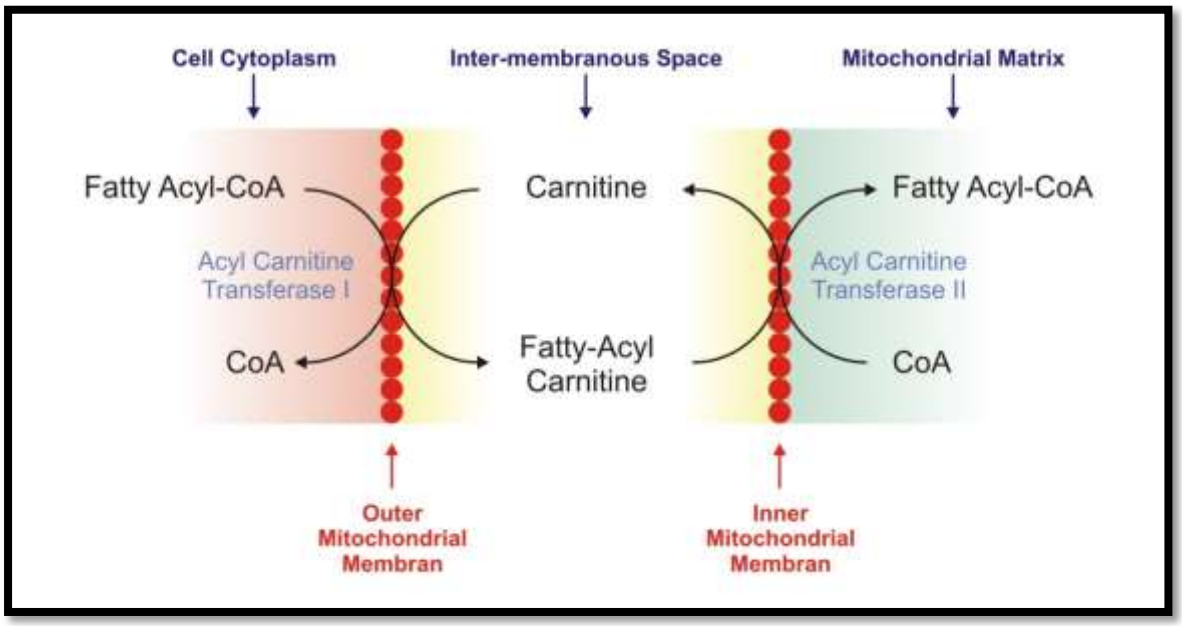


This is the only step in the fatty acid oxidation that requires ATP and it is irreversible step.

Carnitine Shuttle:

Fatty acids are activated in the cytoplasm; but the **beta oxidation is in mitochondria.** So transport of fatty acids through the mitochondrial membrane is essential. The long chain fatty acyl CoA cannot pass through the inner mitochondrial membrane. Therefore a transporter, carnitine is involved in transfer of fatty acids.

Carnitine could be obtained either from the diet (meat and meat products) or by being synthesized inside the body (from amino acids lysine and methionine) through an enzymatic system found in the liver and the kidneys.



Medium chain fatty acids (shorter than 12 carbon atoms) can cross the mitochondrial membrane without the aid of carnitine, and even its entry to the cell does not require fatty acid binding proteins .

The deficiency of carnitine occurs due to many reasons :

-Could be congenital

-Could occur in newborn babies (especially pre-mature) and this is due to immaturity of the enzymatic system which will lead to inadequate synthesis of carnitine.

-Malnutrition and those on strictly vegetarian diet

-Liver disease (because it is a main site for the synthesis).

-Increased requirement to carnitine

*Pregnancy.

*Severe Infection.
*Severe Burns.
*Trauma.
*Hemodialysis.

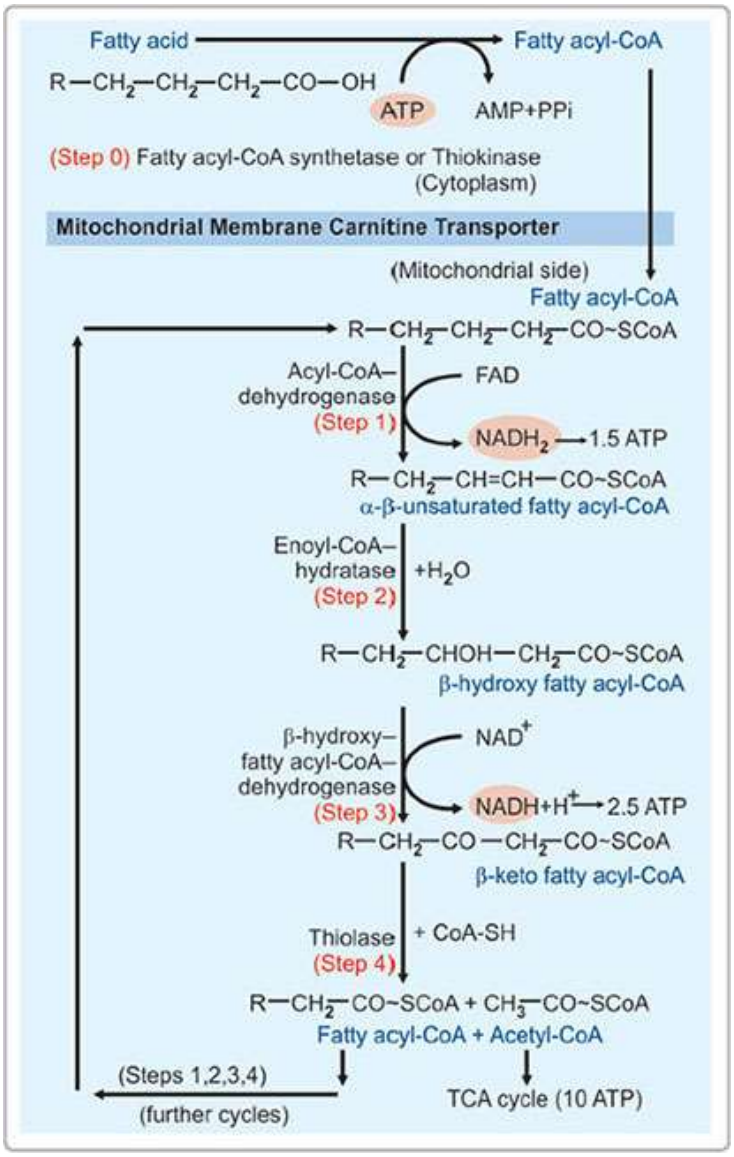
The effect of carnitine deficiency is decrease in the ability of oxidizing long chain fatty acids and this may lead to weight loss, fatty liver, and hypoglycemia.

Beta oxidation pathway

β -oxidation is defined as oxidation of fatty acids in which two carbon fragments are successively removed at ' β ' position from the carboxyl end , so in each oxidation for (n carbon atoms) fatty acyl CoA the product is acetyl CoA (two carbon atoms) and (n-2) fatty acyl CoA, and it will also produce one FADH2 and one NADH.

β -oxidation involves four steps:

- Oxidation
- Hydration
- Oxidation
- Cleavage.



Energetics in β-oxidation

Palmitic acid (16C) undergoes seven cycles of b-oxidation to produce:

8 acetyl-CoA → TCA cycle → 10 ATP × 8 = +80 ATP

7 FADH2 → ETC → 1.5 ATP × 7 = +10.5 ATP

7 NADH → ETC → 2.5 ATP × 7 = +17.5 ATP.

Total = 108 ATPs.

Activation of fatty acid = -2 ATP.

Net ATP yield = 108 - 2 = 106.

Important Note: *previously calculations were made assuming that NADH produces 3 ATPs and FADH generates 2 ATPs. This will amount to a net generation of 129 ATP per palmitate molecule. Recent*

experiments show that these old values are overestimates, and net generation is only 106 ATPs.

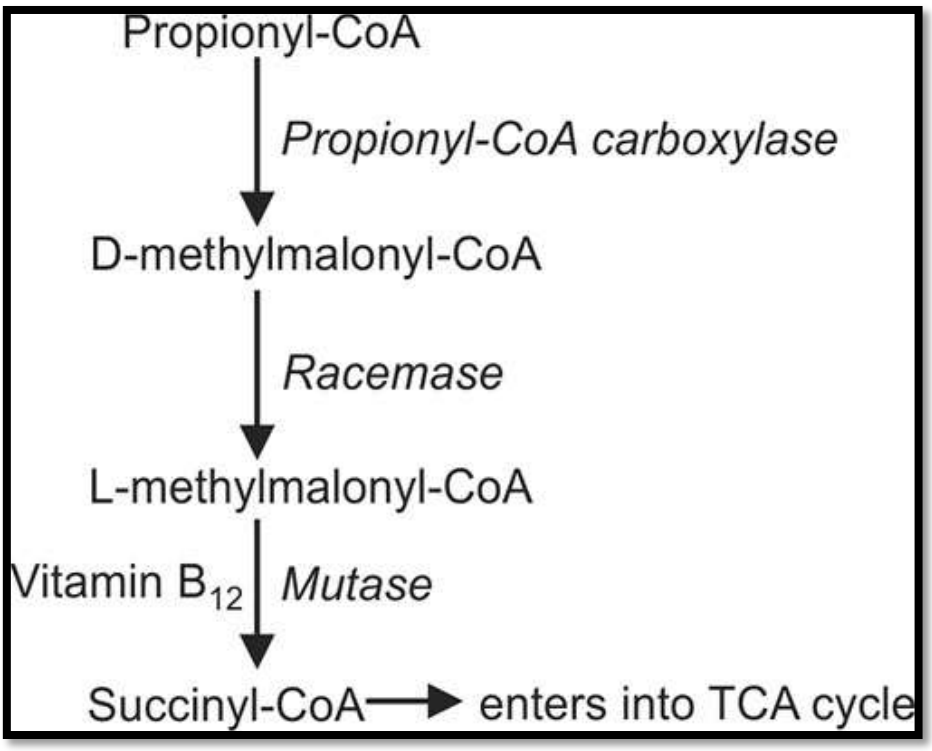
Regulation of β-oxidation

1. **Energy status:** In well-fed state, β-oxidation is blocked and fatty acid synthesis is active. During starvation, β-oxidation is active and fatty acid synthesis is blocked.
2. **Hormones:** Insulin stimulates lipogenesis and blocks lipolysis, whereas glucagon stimulates lipolysis and blocks lipogenesis.
3. **Malonyl-CoA (precursor for fatty acid synthesis):** It blocks the entry of fatty acids from cytosol to mitochondria by inhibiting carnitine palmitoyltransferase I.

Oxidation of the Fatty Acids with Odd Number of C atoms:

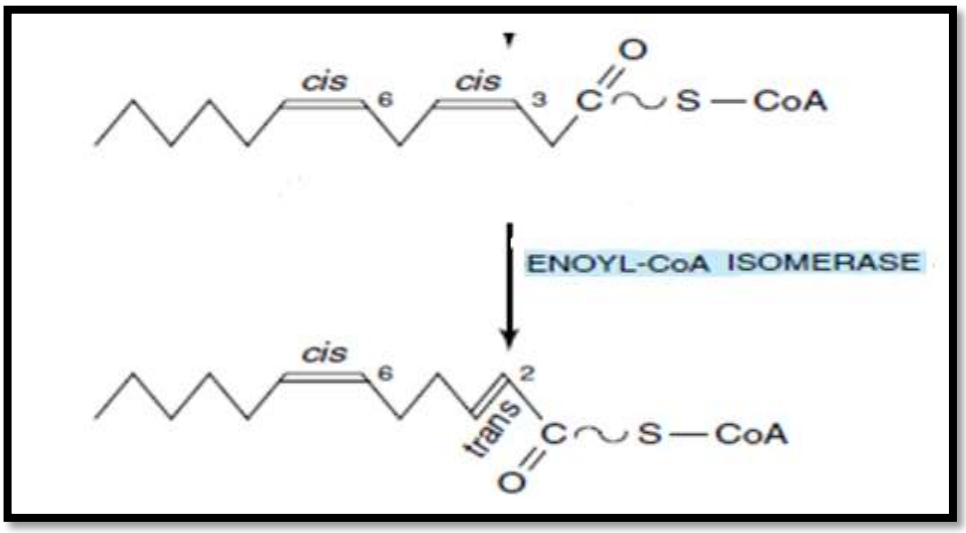
It gives acetyl-CoA (depending on number of carbons in the fatty acid), one propionyl-CoA, NADH and FADH2 as end products. Propionyl-CoA enters into tricarboxylic acid (TCA) cycle after being converted into succinyl-CoA.

Fate of propionyl-CoA: Enters into TCA cycle as a precursor for gluconeogenesis after getting converted into succinyl-CoA.



OXIDATION OF UNSATURATED FATTY ACIDS:

Undergo the same sequence of reaction as saturated fatty acid until we reach to the double bond between carbon 3 & 4.Usually the configuration around the double bond is cis. In the saturated fatty acid we make a double bond between C2 & C3 but in the unsaturated fatty acid the last double bond is found between C3 & C4 so we will transfer the double bond to put it between the C2 & C3 by the enzyme **Enoyl CoA isomerase**. This enzyme transfer the double bond and change the configuration from cis to trans.



After the transforming of the double bond to C2-C3 position now the fatty acid will undergo the same reaction of β oxidation but it will not pass in the first step that yield the FADH2.{so the oxidation of unsaturated fatty acid with 16 carbon atom will give only 6 FADH2 and not 7 FADH2). So removal of acetyl CoA in this step will produce only 3ATP not 5ATP.

PROBLEMS

Q.1. saturated fatty acid contain 16 carbon atom {palmatic acid} how many the ATP produced after the oxidation of it ?

Answer: by β oxidation pathway it will give:

7 FADH2 and each FADH2 will give 2 ATP (so 7×1.5 =10.5 ATP).

7 NADH2 and each NADH2 will give 3ATP (so 7×2.5= 17.5 ATP).

8 acetyl CoA and each one will enter the citric acid cycle and give 10 ATP (so 8×10=80 ATP).

10.5+17.5+80= 108 ATP.

But we need 2ATP IN THIOKINASE REACTION thus the no. Of ATP 108-2= 106 ATP produced from palmatic acid

Q.2. unsaturated fatty acid contain 16 carbon atom how many the ATP produced after the oxidation of it?
Answer: by β oxidation
6 FADH2 (so 6×1.5= 9 ATP).
7 NADH2 (so 7×2.5=17.5 ATP).
8 Acetyl CoA (so 8×10=80 ATP).
9+17.5+80 = 106.5 ATP.
106.5-2= 104.5 ATP.

Q.3. saturated fatty acid contain 17 carbon atom how many the ATP produced after the oxidation of it?
7 FADH2 (7×1.5=10.5 ATP).
7 NADH2 (7×2.5= 17.5 ATP).
7 Acetyl CoA (7×10= 70 ATP).
10.5+17.5+70= 98 ATP.
98-2 = 96 ATP.
5 ATP from succinyl-CoA
96+ 5= 101 ATP

Q.4. unsaturated fatty acid contain 17 carbon atom how many ATP produced after its oxidation ?

6 FADH2 (6×1.5=9 ATP).
7 NADH2 (7×2.5 =17.5 ATP).
7 Acetyl CoA (7×10=70 ATP).
9+17.5+70= 96.5 ATP.
96.5-2= 94.5 ATP.
5 ATP from succinyl-CoA
115+ 5= 99.5 ATP