Fatty acid oxidation and disorders

Methods by which fatty acids are oxidized in the body are as follows:

A. **β-oxidation**: Principal method of oxidation of FA.
B. α-oxidation,
C. ω-oxidation, and
D. Peroxisomal FA oxidation.

A. β-OXIDATION

Principal method by which FA is oxidised is called β-oxidation.

1- The circulating FA are taken up by various tissues and oxidized.
2- Tissues like liver, heart, kidney, muscle, brain, lungs, testes and adipose tissue have the ability to oxidise long chain FA.
3- In cardiac muscle, fatty acids are an important fuel of respiration (80% of energy derived from FA oxidation).

Enzymes Involved in β-Oxidation

1- β-oxidation takes place in **mitochondrion**.
2- Several enzymes known collectively as FA-oxidase system are found in the mitochondrial matrix
3- These enzymes catalyse the oxidation of FA to acetylCoA.

Steps of FA oxidation

- First step must be

Activation of FA: Fatty acids are in cytosol of the cell (extramitochondrial).

- The activation requires energy which is provided by ATP.
- In presence of ATP, and coenzyme A, the enzyme acyl-CoA synthetase (previously called as thiokinases) catalyses the conversion of a free fatty acid to an 'active' FA (acyl-CoA). This step needs 2 ATP after enter and in mitochondria the B-oxidation began. (Figure 1)

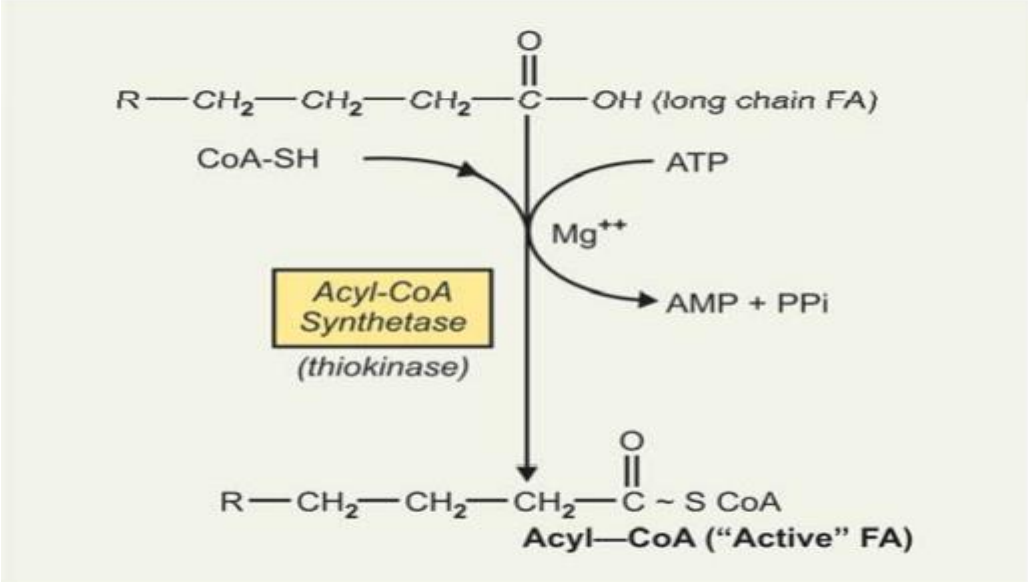


Figure 1: Activation of FA

❖ Carnitine and Its Role In Fa Metabolism

"Active" FA (acyl-CoA) are formed in cytosol, whereas β-oxidation of FA occurs in mitochondrial matrix. AcylCoA are impermeable to mitochondrial membrane. Long chain activated FA penetrate the inner mitochondrial membrane **only** in combination with carnitine.

Second step

- An enzyme carnitine-palmitoyl transferase I, present on the inner side of the outer mitochondrial membrane, converts long-chain acyl-CoA to acyl-carnitines; which is able to penetrate mitochondria and gain access to the β-oxidation systems of the enzymes (figure 2).

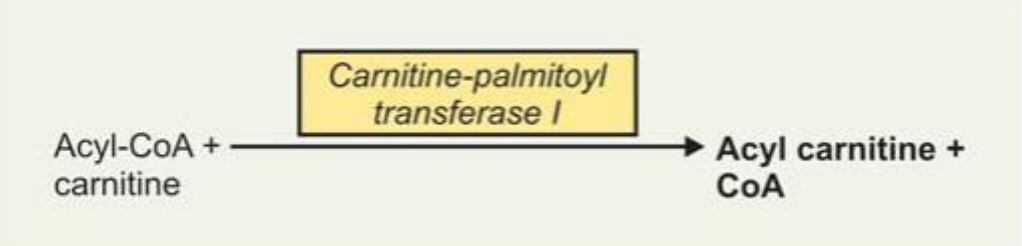


Figure 2: penetrate mitochondria

Step 3

- carnitine-acyl-carnitine translocase acts as a membrane-carnitine exchange transporter.

Step 4

The acyl-carnitine then reacts with CoA-SH, catalysed by *carnitine-palmitoyl transferase II*, attached to the inside of the inner membrane. Acyl-CoA is reformed in the mitochondrial matrix and carnitine is liberated (figure 4).

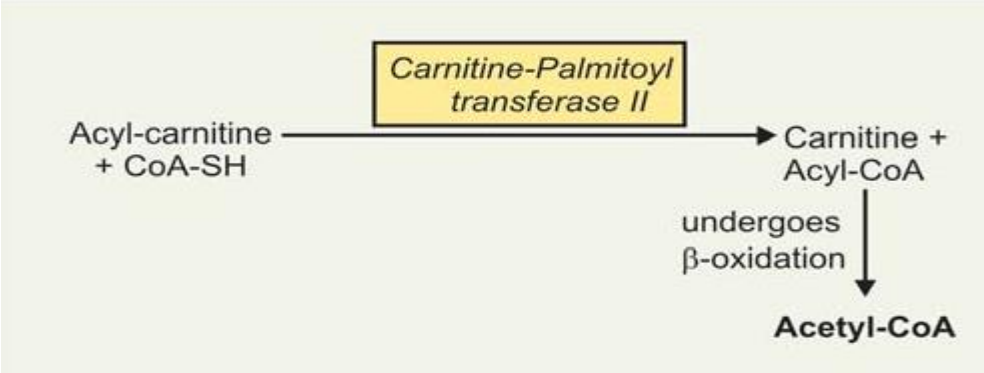
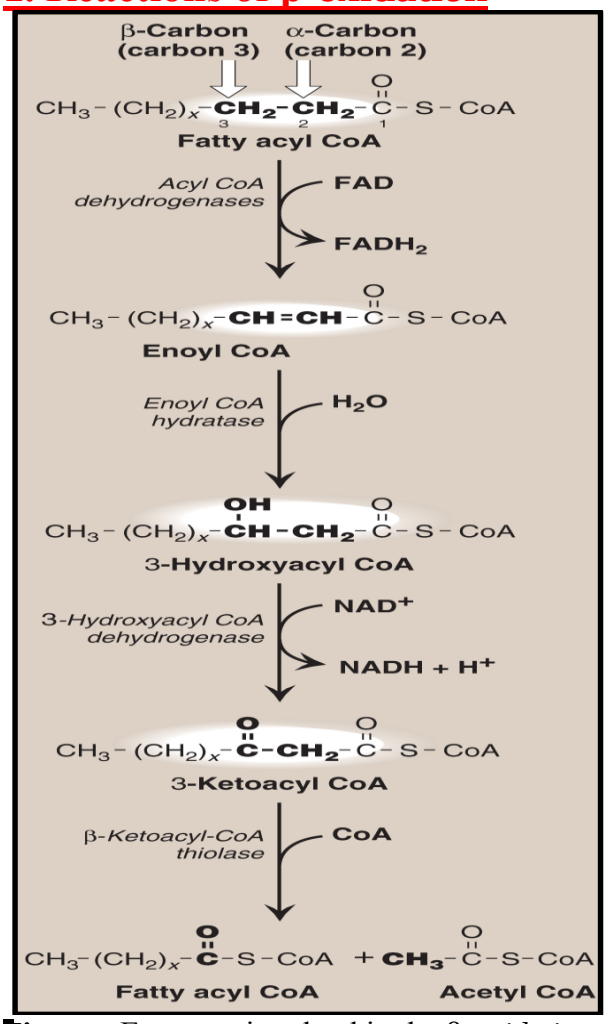


Figure 4: shows the mechanism of action of carnitine.

1. Reactions of β-oxidation



The first cycle of β-oxidation is shown in figure below. It consists of a sequence of four reactions involving the β-carbon (carbon 3) that result in shortening the fatty acid chain by two carbons. The steps include an oxidation that produces FADH2, a hydration step, a second oxidation that produces NADH, and a thiolytic cleavage that releases a molecule of acetyl CoA. These four steps are repeated for saturated fatty acids of even-numbered carbon chains (n/2) – 1 times (where n is the number of carbons), each cycle producing an acetyl group plus one NADH and one FADH2. The final thiolytic cleavage produces two acetyl groups.

Figure: Enzymes involved in the β-oxidation of fatty acyl CoA

Energy yield from fatty acid oxidation

The energy yield from the β-oxidation pathway is high. For example, the oxidation of a molecule of palmitoyl CoA to CO_2 and H_2O produces (8) acetyl CoA, 7 NADH, and 7 $FADH_2$, from which 131 ATP can be generated; however, activation of the fatty acid requires 2 ATP. Thus, the net yield from palmitate is 129 ATP:

Fatty acyl CoA + [(No.C/2)-1] **FAD** + [(No.C/2)-1] **CoA** + [(No.C/2)-1] **NAD^+** + [(No.C/2)-1] **H_2O**

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(No.C/2)**Acetyl CoA** + [(No.C/2)-1] **$FADH_2$** + [(No.C/2)-1] **NADH** + [(No.C/2)-1] **H^+**

N = number of carbon atoms of a fatty acid, so for palmitic acid:

[(16/2 – 1) X 5 ATP] + [16/2 X 12 ATP] – 2 ATP [7 x 5] + [96] – 2

35 +96-2 131 – 2

= 129 ATP

Importance or the functions of β – oxidation:

1- Production of energy: Oxidation of F.As is a major source of energy particularly during starvation.

2- Production of acetyl CoA which is converted into several compounds

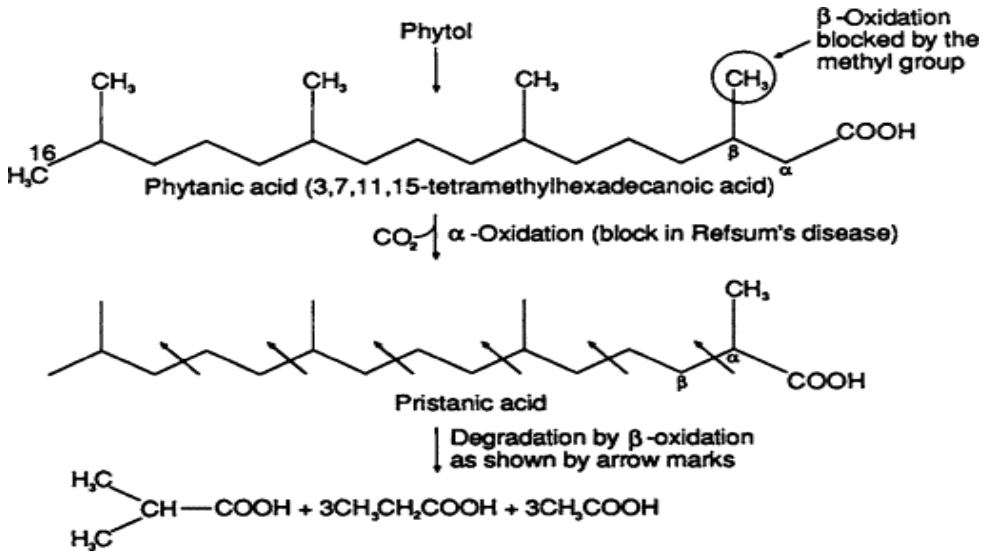
Fate of Acetyl CoA:

1. Oxidation through TCA.
2. Lipogenesis: F.As synthesis.
3. Ketogenesis: Ketone body formation.
4. Steroid formation: Cholesterol and its derivatives.
5. Formation of acetylcholine.

B. α-OXIDATION

- α-oxidation is another alternative pathway for oxidation of FA which involves decarboxylation of the COOH group after hydroxylation and the formation of a FA containing an "odd" number of carbon atoms, which subsequently undergoes repeated β-oxidation.

No initial activation of FA is necessary in this process.



C. ω-OXIDATION

1- The omega carbon (the terminal methyl group) of a F.A is oxidized into –CH2 OH and subsequently into –COOH, thus forming a dicarboxylic acid. It is brought about by hydroxylases enzymes such as cytochrome P-450 of the endoplasmic reticulum.

2- β – oxidation can then occur in mitochonria at both ends of the dicarboxylic acid, usually to reach to adipic acid (C6), which is excreted in the urine .

ω -oxidation represents a minor pathway of overall fatty acid oxidation. However, in certain pathophysiological states, such as diabetes, chronic alcohol consumption, and starvation, the ω-oxidation pathway may provide an effective means for the elimination of toxic levels of free fatty acids.

D. Peroxisomal pathway:

- Peroxisomes facilitate the oxidation of very long chain fatty acids like C20, C22,.

- The enzymes in peroxisomes do not attack shorter chain fatty acids.

- Carnitine is not required for penetrating peroxisomes.

- A modified form of β-oxidation is found in peroxisomes and leads to the formation of acetylCoA and H2O2.

- H2O2 formed in the process is broken down by the enzyme Catalase.

- The dehydrogenation in peroxisomes is not linked to phosphorylations and thus there is no ATP formation.

- The enzymes of peroxisomes are induced by high fat diets and in some speices by hypolipidaemic drugs like clofibrate.

- Oxidation of unsaturated F.As:

These F.As need isomerization of the cis double bonds into trans and hydrogenation of some double bonds before undergoin β-oxidation.

- Oxidation of fatty acids with an odd number of carbon atoms:

F.As with an odd number of carbon atoms are oxidized by the pathway of β - oxidation producing acetyl CoAs until a 3 – carbon residue (propionyl-CoA) remains.

Propionyl-CoA is converted into succinyl CoA, a constituent of the citric acid cycle.

Notice that the propionyl residue from some F.As is the only part of a F.A that is glucogenic.

Disorders of F.A oxidation:

A. Carnitine deficiency:

This can occur:

- In a newborn, particularly a preterm infant due to inadequate biosynthesis or renal leakage.

- In patients on hemodialysis.

Signs and symptoms:

- Episodic periods of hypoglycemia due to impaired F.A oxidation.

- Low plasma ketone bodies (hypoketonemia) in presence of raised levels of F.F.As.

- Muscular weakness and myoglobinuria

- Lipid accumulation.

B- Inherited CPT-I deficiency, CPT-II deficiency, or MCAD deficiency (medium chain acyl CoA dehydrogenase deficiency) can also cause hypoketotic hypoglycemia.

C- Zellweger's syndrome :

An inherited absence of peroxisomes cause an inability to oxidize long – chain F.As leading to accumulation of C26 – C38 polyenoic acids in brain tissue.

D- Refsume's disease:

It is due to an inherited defect in α –oxidation. Such a defect would prevent oxidation of phytanic acid which contains– CH3 group on the β – carbon that blocks β – oxidation and it needs α –oxidation to overcome such a block.

The accumulated phytanic acid may cause damage to cell membranes and results in peripheral polyneuropathy, retinitis pigmentosa, and ichthyosis (rough, dry and scaly skin and curled hair) as main clinical features of Refsume's disease.

REFRANCES

1. Harper's Biochemistry. Lange, USA.

2. Lippincott Illustrated Reviews: Biochemistry, 7e. Denise R. Ferrier

3. Text book of medical biochemistry. Chtterjea MN. India. Latest edition.