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QUESTION

Describe the three (3) stages of beta oxidation. (Show pathways where necessary)

ANSWER

β-oxidation pathway occurs in mitochondria. It involves following three steps:

A) Activation of fatty acid to acyl-CoA

B)Transfer of acyl CoA into mitochondria by carnitine

transport system

C) Reactions of β-oxidation in mitochondria.

A) Activation of Fatty Acid

Before being catabolised, free fatty acids are converted to an active form called acyl-CoA. It occurs in the cytosol in the presence of ATP, coenzyme-A (CoA-SH) and the enzyme acyl-CoA synthetase also called this kinase. Subsequent steps of β-oxidation occur in the mitochondria of the liver and other tissue cells.

In the cytosol of the cell, long-chain fatty acids are activated by ATP and coenzyme A, and fatty acyl-CoA is formed. Short-chain fatty acids are activated in mitochondria.

The ATP is converted to AMP and pyrophosphate (PPi), which is cleaved by pyrophosphatase to two inorganic phosphates (2 Pi). Because two high-energy phosphate bonds are cleaved, the equivalent of two molecules of ATP is used for fatty acid activation.

B) Transport of Acyl-CoA into Mitochondria by Carnitine Transport System

Activation of fatty acids occur in the cytosol, whereas they are oxidized in the mitochondrial matrix. The mitochondrial inner membrane is impermeable to fatty acids. So a special transport mechanism is needed.

Activated long chain fatty acids are carried across the inner mitochondrial membrane by carnitine, (β-hydroxy γ-trimethyl ammonium butyrate), formed from lysine and methionine in liver and kidney. This occurs in four steps

1. The acyl group of acyl-CoA is transferred to the carnitine to form acyl-carnitine. This reaction is catalyzed by carnitine acyltransferase-I (CAT-I). which is located on the cytosolic face of the inner mitochondrial membrane.

2. Acyl-carnitine is then transported across the inner mitochondrial membrane by an enzyme translocase.

3. The acyl group is transferred back to CoA in the mitochondrial matrix by the enzyme carnitine acyl transferase-ll (CAT-II), located on the inside of the inner mitochondrial membrane.

4. Acyl-CoA is reformed in the mitochondrial matrix with liberation of carnitine which is returned to the cytosolic side by the translocase in exchange for an incoming acyl-carnitine.

C)Reactions of β-oxidation of Fatty Acid

After the penetration of the acyl-CoA into mitochondria, it undergoes β-oxidation.

- **Sequence of Reactions of β-oxidation**

A saturated acyl-CoA is degraded by a repeated sequence of four reactions

1. Oxidation by FAD: The first reaction is the oxidation of acyl-CoA by an acyl-CoA dehydrogenase to give an Δ2-trans enoyl-CoA (a trans double bond between C2 and C3). The coenzyme for the dehydrogenase is FAD which is converted to FADH2.

2. Hydration: The next step is the hydration (addition of water) of the double bond between C2 and C3 by Δ2-enoyl-CoA hydratase to form β-hydroxy acyl-CoA.

3. Oxidation by NAD: The β-hydroxy derivative undergoes second oxidation reaction catalyzed by β- hydroxyacyl-CoA dehydrogenase to form β-ketoacyl- CoA and generates NADH.

4. Cleavage: Finally β-ketoacyl-CoA is split at the β-carbon by thiolase to yield acetyl-CoA and an acyl- CoA which is shorter by two carbon atoms than the original acyl-CoA that underwent oxidation.

The new acyl-CoA, containing two carbons less than the original, re-enters the β-oxidation pathway at reaction catalyzed by acyl-CoA dehydrogenase). The process continues till the fatty acid degraded completely to acetyl-CoA.

Acetyl-CoA can be oxidized to CO2 and H2O via citric acid cycle in mitochondria and thus oxidation of fatty acids is completed.

- FAD accepts hydrogens from a fatty acyl-CoA in the first step. A double bond is produced between the α- and β-carbons, and an enoyl-CoA is formed. The FADH2 that is produced interacts with the electron transport chain, generating ATP.
- Enzyme: **Acyl-CoA dehydrogenase** (Multiple variants of this enzyme)
- H2O adds across **the double bond,** and a **β-hydroxyacyl-CoA** is formed.
- **Enzyme: Enoyl-CoA hydratase**
- β -Hydroxyacyl-CoA is oxidized by NAD+ to a **β-ketoacyl-CoA**. The NADH that is produced interacts with the electron transport chain, generating ATP.
- **Enzyme: L-3-hydroxyacyl-CoA dehydrogenase (which is specific for the L-isomer** of the β-hydroxyacyl-CoA).
- The bond between the alpha and beta carbons of the β-ketoacyl-CoA is cleaved by a thiolase that requires coenzyme A. Acetyl-CoA is produced from the two carbons at

the carboxyl end of the original fatty acyl-CoA, and the remaining carbons form a fatty acyl-CoA that is two carbons shorter than the original.

- **Enzyme: β -ketothiolase**
- The shortened fatty acyl-CoA repeats these four steps. Repetitions continue until all the carbons of the original fatty acyl-CoA are converted to acetyl-CoA.

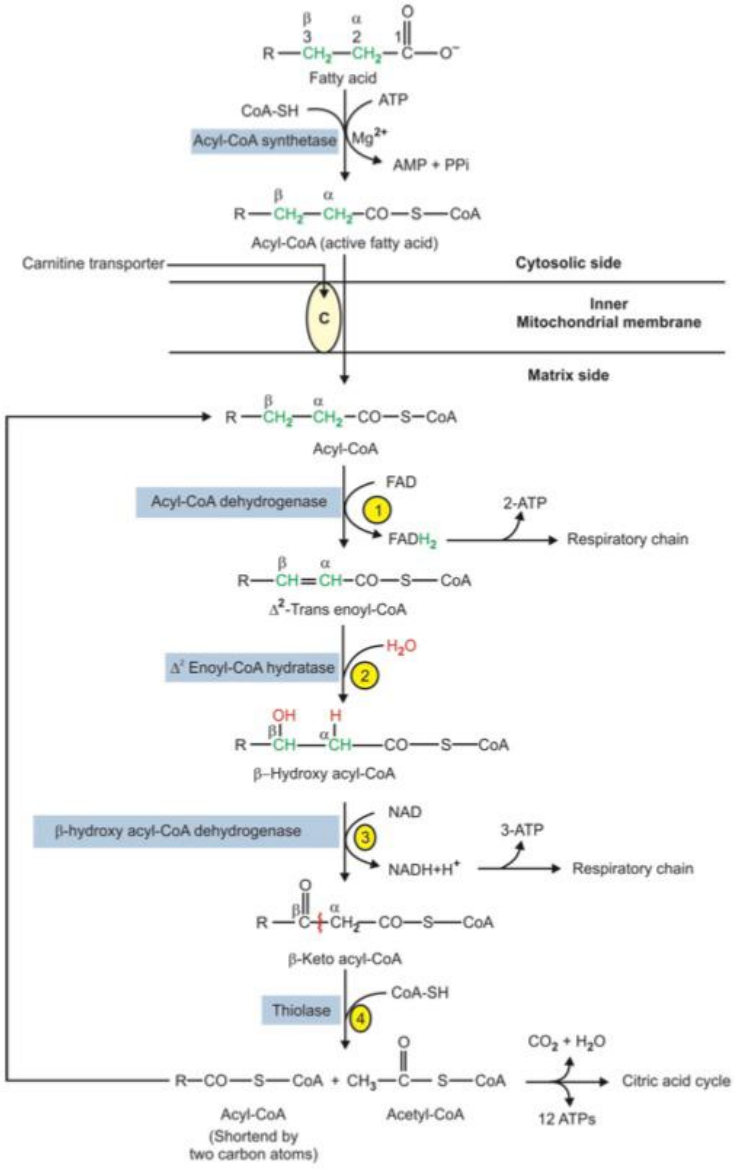

Figure 13.5: β-oxidation of fatty acids