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Department: pharmacology

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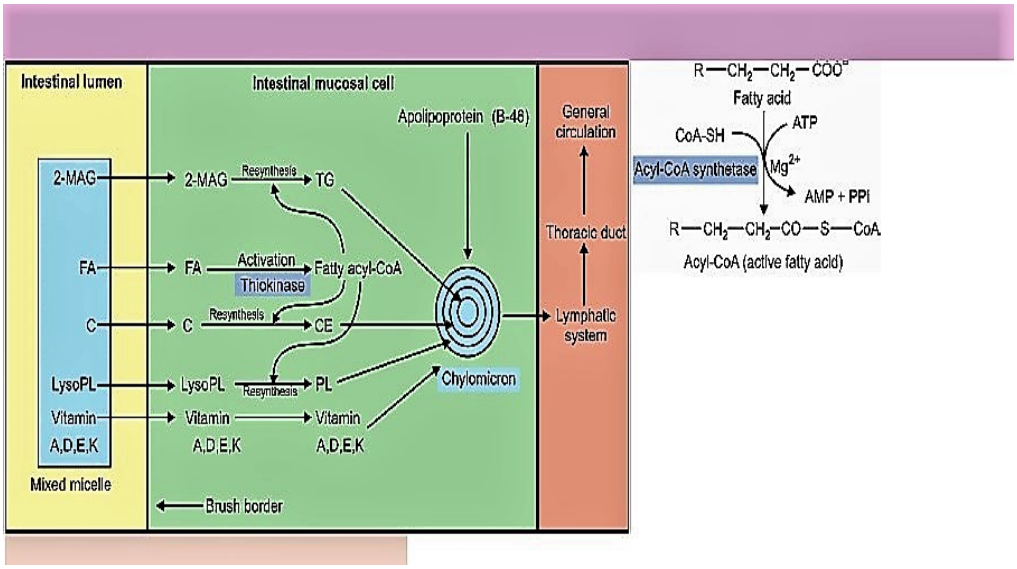
Question:

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

1. Activation of Fatty Acid

• Before being catabolized, 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 thiokinase Subsequent steps of β-oxidation occur in the mitochondria of the liver and other tissue cells. The ATP is converted to AMP and pyrophosphate (PPI). Which is cleaved by pyrophosphatase to two inorganic phosphate. Because two high energy phosphate bonds are cleaved, the equivalent of two molecules of ATP is used for fatty acid activation.



2. 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-hydroxyl γ- trim ethyl

ammonium butyrate), formed from lysine and methionine in liver and kidney. This occurs in four steps.

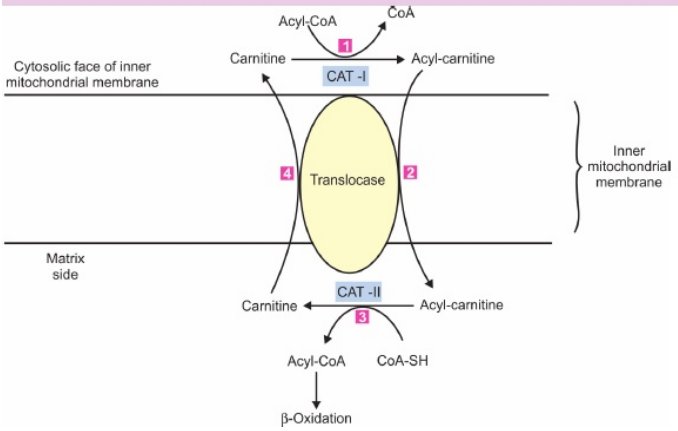
- The acyl group of acyl-CoA is transferred to the carnitine to form acyl-carnitine. This reaction is catalyzed by carnitine acyltransferase-I (CAT-I). Which is located on the cytosolic face of the inner mitochondrial membrane.
- Acyl-carnitine is then transported across the inner mitochondrial membrane by an enzyme

Translocase

- The acyl group is transferred back to CoA in the mitochondrial matrix by the enzyme

Carnitine acyltransferase-II (CAT-II), located on the inside of the inner mitochondrial membrane.

- 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.



3. 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

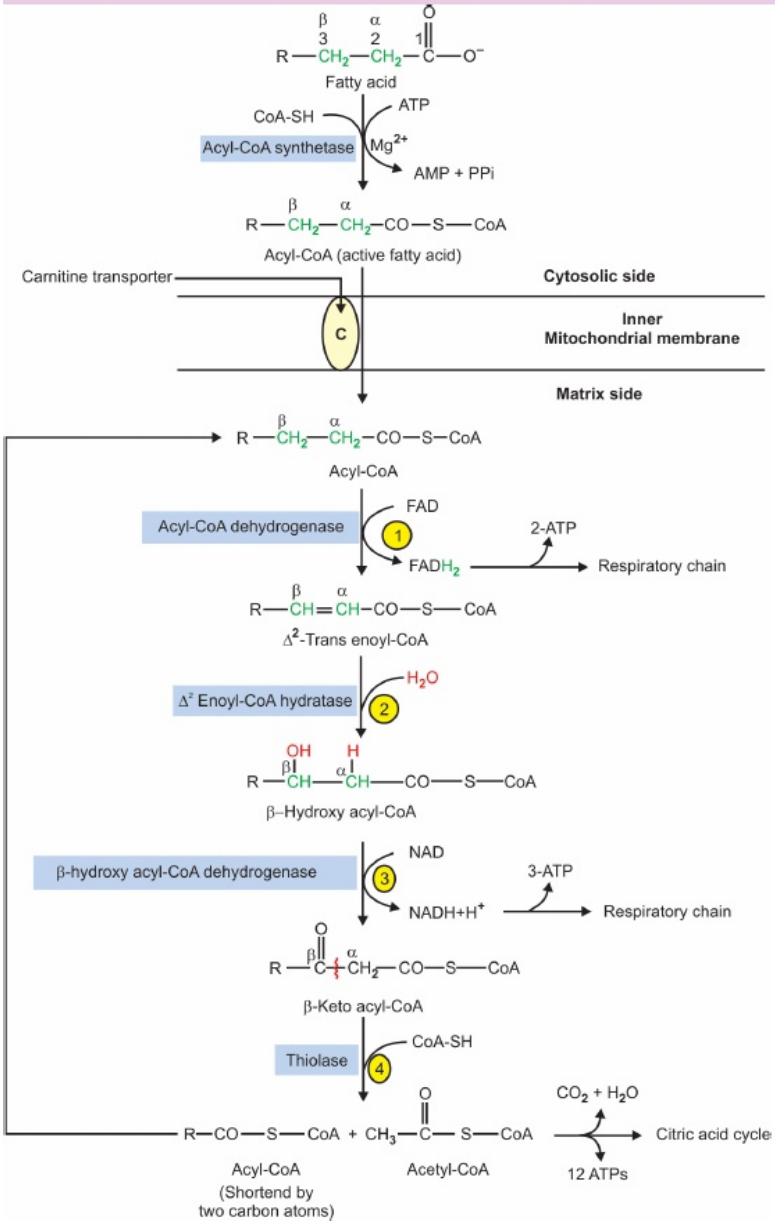
1. Oxidation by FAD

2. Hydration

3. Oxidation by NAD

4. Cleavage

- Oxidation by FAD: The first reaction is the oxidation of acyl-CoA by an acyl-CoA dehydrogenase to give a Δ^2-trans enoyl-CoA (a Tran's double bond between C_2 and C_3). The coenzyme for the dehydrogenase is FAD which is converted to $FADH_2$.
- Hydration: The next step is the hydration (addition of water) of the double bond between $C_2$and C_3 By Δ^2-enoyl-CoA hydratase to form β-hydroxyl acyl-CoA
- Oxidation by NAD: The β-hydroxyl derivative undergoes second oxidation reaction catalyzed by β-hydroxyacyl-CoA dehydrogenase to form β-ketoacyl-CoA and generates NADH.
- Cleavage: 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 CO_2 and H2O via citric acid cycle in mitochondria and thus oxidation of fatty acids is completed.


Fatty acid
CoA-SH
ATP
Acyl-CoA synthetase
Mg2+
AMP + PPi
Acyl-CoA (active fatty acid)
Carnitine transporter
Cytosolic side
Inner
Mitochondrial membrane
Matrix side
Acyl-CoA
Acyl-CoA dehydrogenase
FAD
2-ATP
FADH2
Respiratory chain
Δ2-Trans enoyl-CoA
Δ2 Enoyl-CoA hydratase
H2O
β–Hydroxy acyl-CoA
β-hydroxy acyl-CoA dehydrogenase
NAD
3-ATP
NADH+H+
Respiratory chain
β-Keto acyl-CoA
Thiolase
CoA-SH
CO2 + H2O
Citric acid cycle
12 ATPs
Acyl-CoA
(Shortend by
two carbon atoms)
Acetyl-CoA