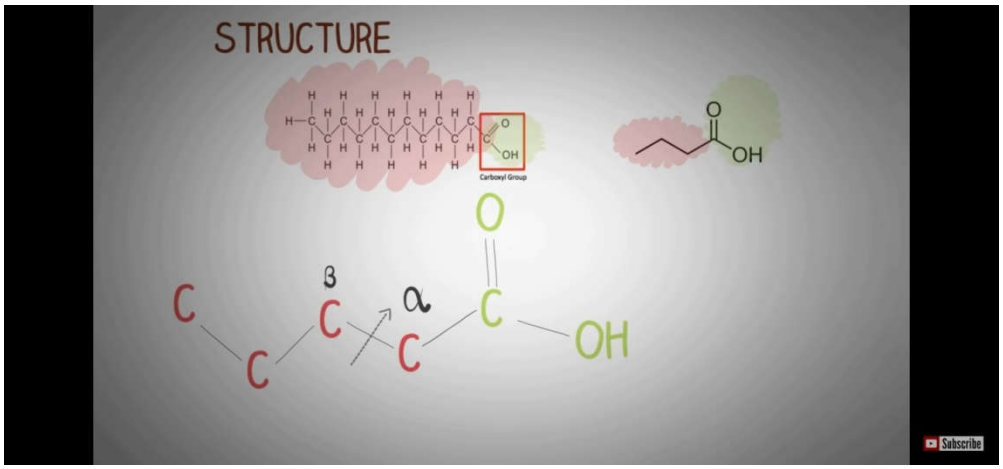
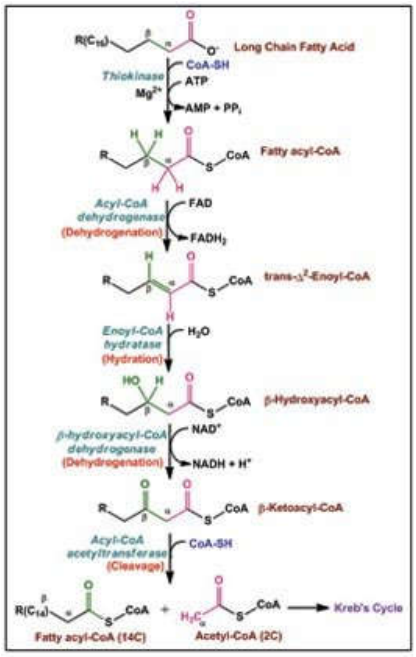
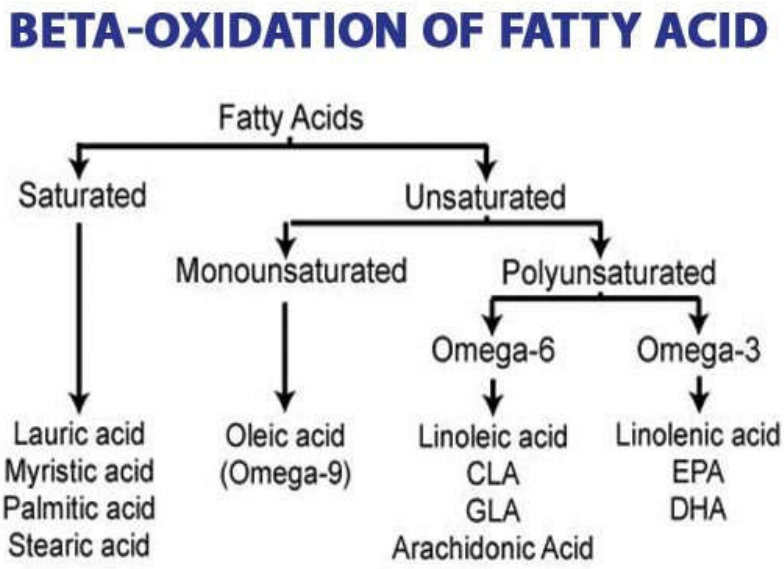
UNIT-3- BETA OXIDATION OF FATTY ACIDS.



- **Beta-oxidation** is the catabolic process by which **fatty acid** molecules are broken down in the cytosol in prokaryotes and in the mitochondria in eukaryotes cell lacking mitochondria (e.g. RBC) to generate acetyl-CoA.
- Acetyl-CoA enters the **citric acid cycle** while NADH and $FADH_2$, which are co-enzymes, are used in the electron transport chain. It is referred as "beta oxidation" because the beta carbon of the fatty acid undergoes oxidation to a carbonyl group.





Steps in beta-oxidation of fatty acids:

1. Activation of Fatty acid
2. Transport of fatty acyl coA into mitochondria
3. Beta- oxidation

Step I: Activation of fatty acid

1. Fatty acid is converted to fatty acyl CoA by thiokinase or fattyacyl CoA synthetase. This reaction occurs in cytoplasm and 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.

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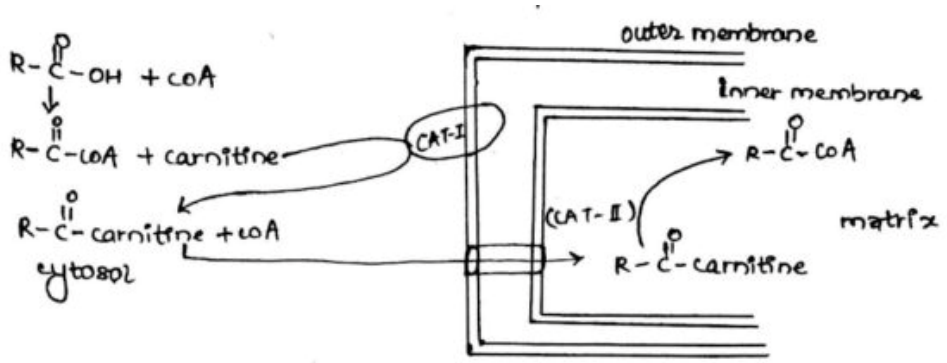
Step II: Transport of acetyl coA into mitochondria

- The inner mitochondrial membrane doesn't permit fatty acids to pass through it. The activated FA enter mitochondria through carnitine shutter.
- This occurs in 4 steps:
- Fatty acyl coA is transferred to carnitine to form fatty acyl carnitine. This is catalyzed by enzyme **carnitine acyl transferase I (CAT-I)** present on outer surface of mitochondria. Then acyl carnitine enters into matrix through carnitine shutter. Fatty acyl carnitine is converted into fatty acyl CoA by an enzyme **carnitine acyl transferase** II (CAT-II) formed in inner mitochondrial membrane. The carnitine is released and return to cytosol for re-use.
- Step III: **Beta-oxidation**
- For **example; Beta-oxidation of saturated FA (palmitic acid):**
- Beta-oxidation occurs in cycle (in which all reactions involve the β-carbon of a fatty acyl-CoA) is a spiral consisting of four sequential steps, the first three of which are similar to those in the TCA cycle between succinate and oxaloacetate. These steps are repeated until all the carbons of an even-chain fatty acyl-CoA are converted to acetyl-CoA.
  - An oxidation step that produce $FADH_2$
  - A hydration step
  - A second oxidation step that produce NADH+ H^+
- A thiolytic cleavage that release a molecule of acetyl coA.
- 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 $FADH_2$ that is produced interacts with the electron transport chain, generating ATP.
- Enzyme: **Acyl-CoA dehydrogenase** (Multiple variants of this enzyme).H_2O 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.

The fourth step of beta-oxidation repeated for (n/2-1) times where n=no. of carbon atoms.

- For e.g. Palmitic acid consists of (16/2-1) = 7 beta-oxidation cycle.
- Each beta-oxidation cycle produces 1 $FADH_2$, 1 NADHA + H^+ and 1 acetyl CoA.
- Total (for palmitoyl CoA):
  - $FADH_2$ -7
  - $NADH_2$ – 7
  - Acetyl CoA – 8
- Total of 7 $FADH_2$, 7NADH+ H^+ and 8 acetyl CoA are generated from production of palmitic acid.
- Acetyl CoA enter into TCA and each acetyl CoA release 12 ATP.
- Similarly, $FADH_2$ and NADH+H^+ enter ETS cycle to generate 2ATP and 3ATP respectively.
- Therefore,
  - 8 acetyl CoA = 8X12=96
  - 7 $FADH_2$= 7X2= 14
  - 7 $NADH_2$ + H^+ = 7X3 = 21
  - Total——————131 ATP
- Net ATP gain is 129 (131-2).
- This is because 2ATP are utilized during conversion of fatty acid (palmitic acid) into fatty acyl CoA (palmitoyl CoA).



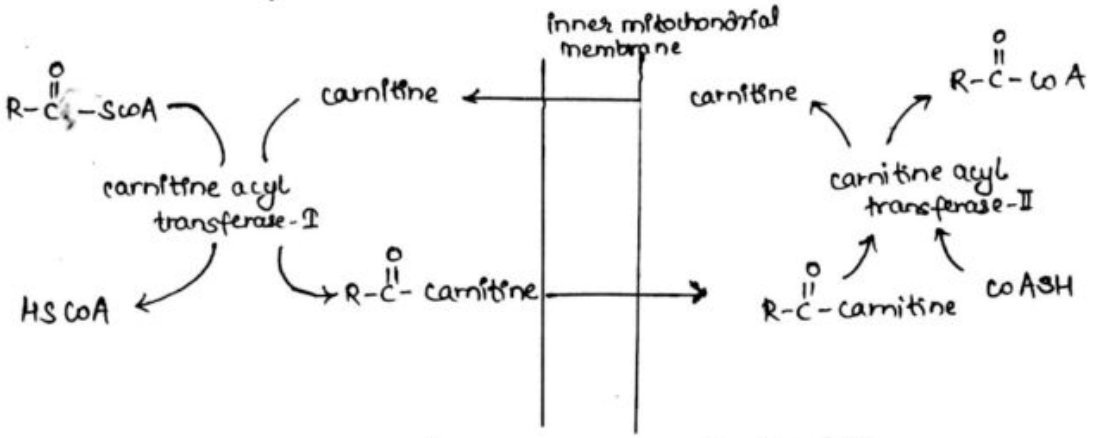


Fig: Transport of fatty acyl coA into mitochondria

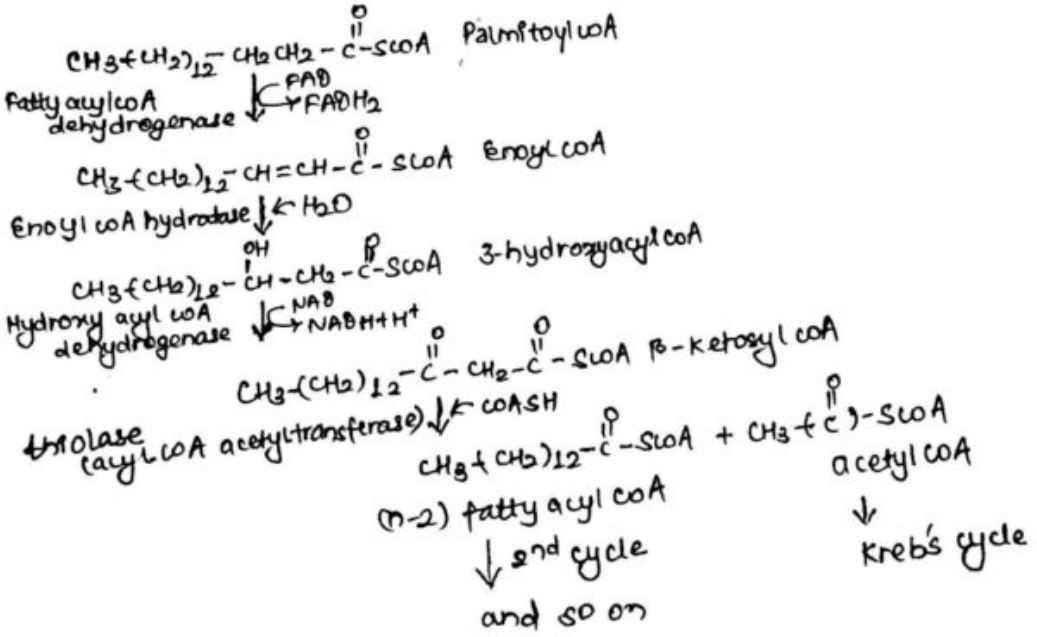


Fig: β-oxidation of saturated FA