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 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.

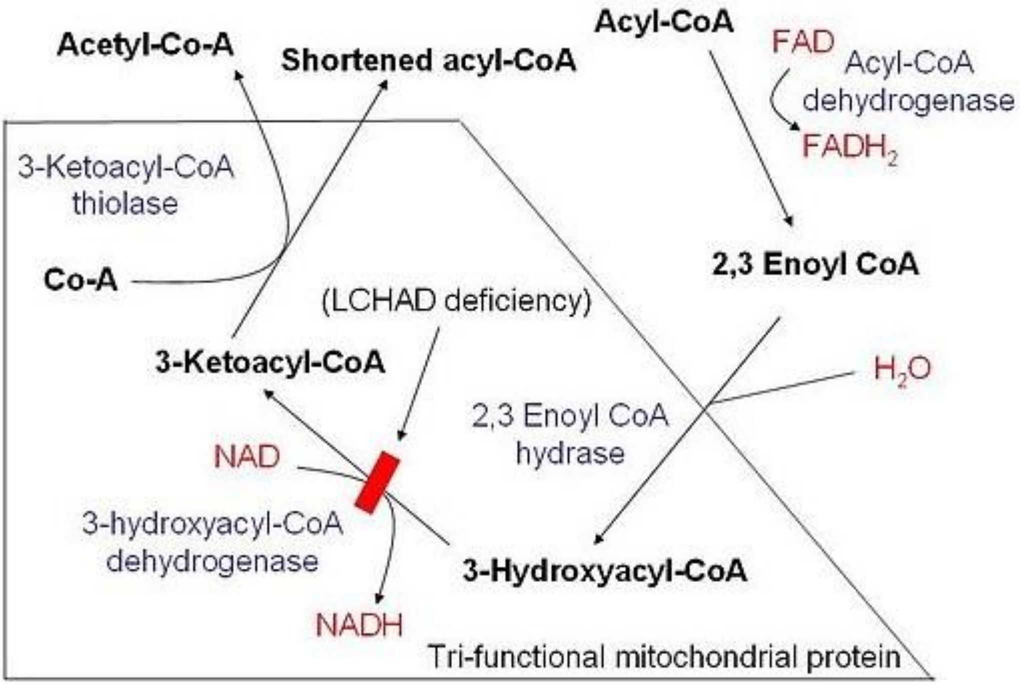


Figure: Schematic demonstrating mitochondrial fatty acid beta-oxidation

Site:

Beta-Oxidation takes place in the mitochondria of eukaryotes while in the cytosol in the prokaryotes.

- **Substrates:** Free fatty acids; H_2O.
- **Products:** One acetyl CoA, one NADH, and one $FADH_2$ for every removal of a two-carbon group from the fatty acid chain.
- In the mitochondria, the fatty acid undergoes a series of oxidation and hydration reactions, which results in the removal of a two-carbon group (in the form of acetyl CoA) from the fatty acid chain as well as the formation of one NADH and one $FADH_2$, which enter the electron transport chain to form five ATP.
- The acetyl CoA formed will enter the citric acid cycle and then the electron transport chain, leading to the formation of another 12 ATP. The cycle continues, with each turn of the cycle removing another two-carbon group, until the formerly long-chain fatty acid has been reduced to acetyl CoA or propionyl CoA.

- Propionyl CoA can be converted to succinyl CoA through three enzymatic events, which require biotin and vitamin B12 as cofactors, and then succinyl CoA can enter the citric acid cycle.

A. Activation of Fatty acids:

1. 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.
2. 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 Fatty Acyl CoA from cytosol into mitochondria:

1. Fatty acyl-CoA from the cytosol reacts with carnitine in the outer mitochondrial membrane, forming fatty acylcarnitine. The enzyme is carnitine acyltransferase I (CAT I), which is also called carnitine palmitoyltransferase I (CPT I). Fatty acylcarnitine passes to the inner membrane, where it re-forms to fatty acyl-CoA, which enters the matrix. The second enzyme is carnitine acyltransferase II (CAT II).
2. Carnitine acyltransferase I, which catalyzes the transfer of acyl groups from coenzyme A to carnitine, is inhibited by malonyl-CoA, an intermediate in fatty acid synthesis. Therefore, when fatty acids are being synthesized in the cytosol, malonyl-CoA inhibits their transport into mitochondria and, thus, prevents a futile cycle (synthesis followed by immediate degradation).
3. Inside the mitochondrion, the fatty acyl-CoA undergoes beta-oxidation.

C. Beta oxidation of even chain fatty acids:

β-Oxidation (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.

- 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.

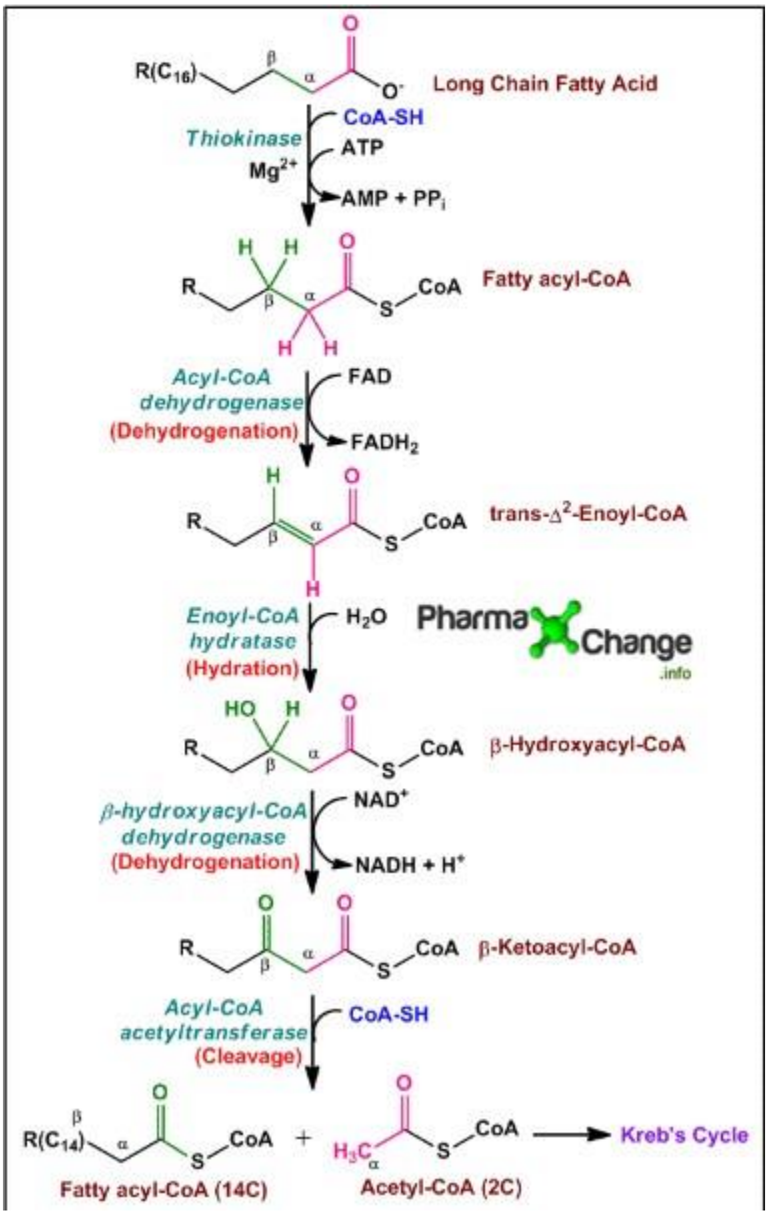


Figure: Beta oxidation of Saturated Fatty Acids with Even Carbon Chain Length.

Energy Yield for Even-chain Fatty Acids

- Energy is generated from the products of β-oxidation.
- The 16-carbon palmitoyl-CoA undergoes seven repetitions.
- In the last repetition, a 4-carbon fatty acyl-CoA (butyryl-CoA) is cleaved to two acetyl-CoAs.

1. When one palmitoyl-CoA is oxidized, seven $FADH_2$, seven NADH, and eight acetyl-CoA are formed.

- The seven $FADH_2$ each generate approximately 1.5 ATP, for a total of about 10.5 ATP.
- The seven NADH each generate about 2.5 ATP, for a total of about 17.5 ATP.

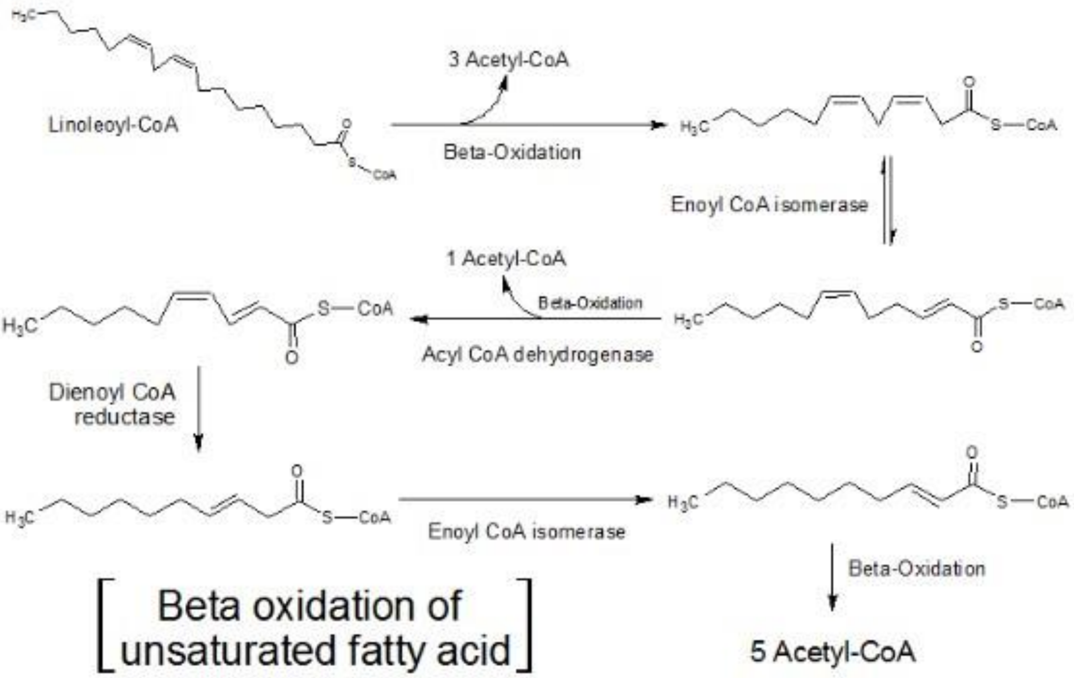
- The eight acetyl-CoA can enter the TCA cycle, each producing about 10 ATP, for a total of about 80 ATP.
- From the oxidation of palmitoyl-CoA to CO_2 and H_2O, a total of about 108 ATP are produced.

2. The net ATP produced from palmitate that enters the cell from the blood is about 106 because palmitate must undergo activation (a process that requires the equivalent of 2 ATP) before it can be oxidized (108 ATP − 2 ATP = 106 ATP).
3. The oxidation of other fatty acids will yield different amounts of ATP.

D. Oxidation of odd chain and unsaturated fatty acids:

- **Odd-chain fatty acids** produce acetyl-CoA and propionyl-CoA.
  - These fatty acids repeat the four steps of the β-oxidation spiral, producing acetyl-CoA until the last cleavage when the three remaining carbons are released as propionyl-CoA.
  - Propionyl-CoA, but not acetyl-CoA, can be converted to glucose.
- **Unsaturated fatty acids**, which comprise about half the fatty acid residues in human lipids, require enzymes in addition to the four that catalyze the repetitive steps of the β-oxidation spiral.
- The reaction pathway differs depending on whether the double bond is at an even- or odd-numbered carbon position.
  - β -Oxidation occurs until a double bond of the unsaturated fatty acid is near the carboxyl end of the fatty acyl chain.

(1) If the double bond originated at an odd carbon number (such as 3, 5, 7, etc.), an isomerase will convert the eventual cis-Δ 3 to a trans-Δ 2 fatty acid.
(2) If the double bond originated at an even carbon number (such as 4, 6, 8, etc.), the eventual trans-Δ 2, cis-Δ 4 fatty acid will be reduced by a 2,4-dienoyl-CoA reductase, which requires NADPH and generates a trans-Δ 3-acyl-CoA and NADP1. The isomerase will convert the trans-Δ 3 fatty acyl-CoA to a trans-Δ 2 fatty acyl-CoA to allow β-oxidation to continue.



ATP yield of unsaturated Fatty acids:

(1) If the double bond originated at an odd carbon position, then compared to a fully saturated fatty acid of the same carbon length, there will be 1.5 ATP less for each unsaturation at the odd carbon position, due to one less FADH2 being produced for each unsaturation.
(2) If the double bond originated at an even-numbered carbon position, then compared to an equivalent length fully saturated fatty acid, there is one less NADH equivalent (or 2.5 ATP) produced, due to the use of NADPH in the step catalyzed by the 2,4-dienoyl-CoA reductase.
Overall reaction of Overall reaction of beta-beta-beta-oxidation:
The overall reaction for one cycle of beta oxidation is:
C_n-acyl CoA + FAD + NAD^+ + H_2O + CoA → C_{n-2}-acyl CoA + $FADH_2$ + NADH + H^+ + acetyl CoA

Important Enzymes
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- **Acyl CoA dehydrogenase:** Forms a double bond between the α and β carbon atoms in the fatty acid chain. Produces one $FADH_2$.
- **Enoyl CoA hydratase:** Incorporates a water molecule into the fatty acid chain, thereby breaking the double bond between the α and β carbon atoms.
- **3-Hydroxy-acyl CoA dehydrogenase:** Dehydrogenates the fatty acid chain again, thereby forming a double bond between the β carbon and the oxygen molecule. Produces one NADPH.
- **Acyl CoA acyltransferase:** Cleaves acetyl CoA off the end of the fatty acid chain with the addition of CoA to the β carbon.

Regulation:

β-Oxidation is regulated by the mechanisms that control oxidative phosphorylation (i.e., by the demand for ATP).

- **Activators:** Epinephrine stimulates β-oxidation by activating a cAMP–dependent protein kinase, which leads to the phosphorylation and thus activation of HSL. When activated, HSL releases fatty acids and glycerol from adipose tissue for β-oxidation.
- **Inhibitors:** Insulin inhibits β-oxidation by dephosphorylating HSL and thus inhibiting the release of fatty acids from adipose tissue.