Beta oxidation

In biochemistry and metabolism, **beta-oxidation** is the catabolic process by which fatty acid molecules are broken down[1] in the cytosol in prokaryotes and in the mitochondria in eukaryotes to generate acetyl-CoA, which enters the citric acid cycle, and NADH and $FADH_2$, which are co-enzymes used in the electron transport chain. It is named as such because the beta carbon of the fatty acid undergoes oxidation to a carbonyl group. Beta-oxidation is primarily facilitated by the mitochondrial trifunctional protein, an enzyme complex associated with the inner mitochondrial membrane, although very long chain fatty acids are oxidized in peroxisomes.

The overall reaction for one cycle of beta oxidation is:

$$C_n\text{-acyl-CoA} + FAD + NAD^+ + H_2O + CoA \rightarrow C_{n-2}\text{-acyl-CoA} + FADH_2 + NADH + H^+ + \text{acetyl-CoA}$$

Activation and membrane transport: Free fatty acids cannot penetrate any biological membrane due to their negative charge. Free fatty acids must cross the cell membrane through specific transport proteins, such as the SLC27 family fatty acid transport protein.–Once in the cytosol, the following processes bring fatty acids into the mitochondrial matrix so that beta-oxidation can take place.

1. Long-chain-fatty-acid—CoA ligase catalyzes the reaction between a fatty acid with ATP to give a fatty acyl adenylate, plus inorganic pyrophosphate, which then reacts with free coenzyme A to give a fatty acyl-CoA ester and AMP.
2. If the fatty acyl-CoA has a long chain, then the carnitine shuttle must be utilized:
    1. Acyl-CoA is transferred to the hydroxyl group of carnitine by carnitine palmitoyltransferase I, located on the cytosolic faces of the outer and inner mitochondrial membranes.
    2. Acyl-carnitine is shuttled inside by a carnitine-acylcarnitine translocase, as a carnitine is shuttled outside.
    3. Acyl-carnitine is converted back to acyl-CoA by carnitine palmitoyltransferase II, located on the interior face of the inner mitochondrial membrane. The liberated carnitine is shuttled back to the cytosol, as an acyl-carnitine is shuttled into the matrix.
3. If the fatty acyl-CoA contains a short chain, these short-chain fatty acids can simply diffuse through the inner mitochondrial membrane.
4.

General mechanism

Once the fatty acid is inside the mitochondrial matrix, beta-oxidation occurs by cleaving two carbons every cycle to form acetyl-CoA. The process consists of 4 steps.

1. A long-chain fatty acid is dehydrogenated to create a trans double bond between C2 and C3. This is catalyzed by acyl CoA dehydrogenase to produce trans-delta 2-enoyl CoA. It uses FAD as an electron acceptor and it is reduced to $FADH_2$.
2. Trans-delta2-enoyl CoA is hydrated at the double bond to produce L-3-hydroxyacyl CoA by enoyl-CoA hydratase.
3. L-3-hydroxyacyl CoA is dehydrogenated again to create 3-ketoacyl CoA by 3-hydroxyacyl CoA dehydrogenase. This enzyme uses NAD as an electron acceptor.
4. Thiolysis occurs between C2 and C3 (alpha and beta carbons) of 3-ketoacyl CoA. Thiolase enzyme catalyzes the reaction when a new molecule of coenzyme A breaks the bond by nucleophilic attack on C3. This releases the first two carbon units, as acetyl CoA, and a fatty acyl CoA minus two carbons. The process continues until all of the carbons in the fatty acid are turned into acetyl CoA.

Fatty acids are oxidized by most of the tissues in the body. However, some tissues such as the red blood cells of mammals (which do not contain mitochondria),[5] and cells of the central nervous system do not use fatty acids for their energy requirements,[6] but instead use carbohydrates (red blood cells and neurons) or ketone bodies (neurons only).[7][6]

Because many fatty acids are not fully saturated or do not have an even number of carbons, several different mechanisms have evolved, described below.

Even-numbered saturated fatty acids[edit]

Once inside the mitochondria, each cycle of β-oxidation, liberating a two carbon unit (acetyl-CoA), occurs in a sequence of four reactions:

Description	Diagram	Enzyme	End product
Dehydrogenation by FAD: The first step is the oxidation of the fatty acid by Acyl-CoA-Dehydrogenase. The enzyme catalyzes the formation of a double bond between the C-2 and C-3.		acyl CoA dehydrogenase	trans-Δ^2-enoyl-CoA
Hydration: The next step is the hydration of the bond between C-2 and C-3. The reaction is stereospecific, forming only the L isomer.		enoyl CoA hydratase	L-β-hydroxyacyl CoA
Oxidation by NAD^+: The third step is the oxidation of L-β-hydroxyacyl CoA by NAD^+. This converts the hydroxyl group into a keto group.		3-hydroxyacyl-CoA dehydrogenase	β-ketoacyl CoA
Thiolysis: The final step is the cleavage of β-ketoacyl CoA by the thiol group of another molecule of Coenzyme A. The thiol is inserted between C-2 and C-3.		β-ketothiolase	An acetyl-CoA molecule, and an acyl-CoA molecule that is two carbons shorter

This process continues until the entire chain is cleaved into acetyl CoA units. The final cycle produces two separate acetyl CoAs, instead of one acyl CoA and one acetyl CoA. For every cycle, the Acyl CoA unit is shortened by two carbon atoms. Concomitantly, one molecule of $FADH_2$, NADH and acetyl CoA are formed.

Energy yield[edit]

The ATP yield for every oxidation cycle is theoretically a maximum yield of 17, as NADH produces 3 ATP, $FADH_2$ produces 2 ATP and a full rotation of the citric acid cycle produces 12 ATP.[citation needed] In practice it is closer to 14 ATP for a full oxidation cycle as the theoretical yield is not attained - it is generally closer to 2.5 ATP per NADH molecule produced, 1.5 ATP for each $FADH_2$ molecule produced and this equates to 10 ATP per cycle of the TCA[citation needed](according to the P/O ratio), broken down as follows:

Source	ATP	Total
1 $FADH_2$	x 2 ATP	= 2 ATP
1 NADH	x 3 ATP	= 3 ATP
1 acetyl CoA	x 12 ATP	= 12 ATP
TOTAL		= 17 ATP

For an even-numbered saturated fat (C_{2n}), n - 1 oxidations are necessary, and the final process yields an additional acetyl CoA. In addition, two equivalents of ATP are lost during the activation of the fatty acid. Therefore, the total ATP yield can be stated as:

(n - 1) * 17 + 12 - 2 = total ATP

For instance, the ATP yield of palmitate (C_{16}, $n = 8$) is:

(8 - 1) * 17 + 12 - 2 = 129 ATP

Represented in table form:

Source	ATP	Total
7 $FADH_2$	x 2 ATP	= 14 ATP
7 NADH	x 3 ATP	= 21 ATP
8 acetyl CoA	x 12 ATP	= 96 ATP
Activation		= -2 ATP
NET		= 129 ATP

For sources that use the larger ATP production numbers described above, the total would be 129 ATP ={(8-1)*17+12-2} equivalents per palmitate.

Beta-oxidation of unsaturated fatty acids changes the ATP yield due to the requirement of two possible additional enzymes.

Similarities between beta-oxidation and citric acid cycle[edit]

The reactions of beta oxidation and part of citric acid cycle present structural similarities in three of four reactions of the beta oxidation: the oxidation by FAD, the hydration, and the oxidation by NAD^+. Each enzyme of these metabolic pathways presents structural similarity.[

Clinical significance[edit]

There are at least 25 enzymes and specific transport proteins in the β-oxidation pathway Of these, 18 have been associated with human disease as inborn errors of metabolism.

Fatty acid oxidation

See how fatty acids are broken down and used to generate ATP.

Fatty acids provide highly efficient energy storage, delivering more energy per gram than carbohydrates like glucose. In tissues with high energy requirement, such as heart, up to 50–70% of energy, in the form of ATP production, comes from fatty acid (FA) beta-oxidation.
During fatty acid β-oxidation long chain acyl-CoA molecules – the main components of FAs – are broken to acetyl-CoA molecules.

Pathway overview

Fatty acid transport into mitochondria

Fatty acids are activated for degradation by conjugation with coenzyme A (CoA) in the cytosol. The long-chain fatty-acyl-CoA is then modified by carnitine palmitoyltransferase 1 (CPT1) to acylcarnitine and transported across the inner mitochondrial membrane by carnitine translocase (CAT). CPT2 then coverts the long chain acylcarnitine back to long-chain acyl-CoA before beta-oxidation.

Beta-oxidation

Beta-oxidation consists of four steps:

1) Dehydrogenation catalyzed by acyl-CoA dehydrogenase, which removes two hydrogens between carbons 2 and 3.

2) Hydration catalyzed by enoyl-CoA hydratase, which adds water across the double bond.

3) Dehydrogenation catalyzed by 3-hydroxyacyl-CoA dehydrogenase, which generates NADH.

4) Thiolytic cleavage catalyzed beta-ketothiolase, which cleaves the terminal acetyl-CoA group and forms a new acyl-CoA which is two carbons shorter than the previous one.

The shortened acyl-CoA then reenters the beta-oxidation pathway.

Acetyl-CoA generated by the beta-oxidation pathway enters the mitochondrial TCA cycle, where is further oxidized to generate NADH and $FADH_2$. The NADH and $FADH_2$ produced by both beta oxidation and the TCA cycle are used by the mitochondrial electron transport chain to produce ATP. Complete oxidation of one palmitate molecule (fatty acid containing 16 carbons) generates 129 ATP molecules.

Schematic diagram of fatty acid transport and beta-oxidation in the mitochondria. **ATP synthesis** of the fatty acid beta-oxidation pathway