

# Highlights - Fatty Acid Oxidation

1. Fats are broken down to fatty acids and glycerol by enzymes known as lipases. One of these, hormone sensitive triacylglycerol lipase, is the only regulated enzyme of fat or fatty acid breakdown. It is located in fat-storing cells called adipocytes.
2. Triacylglycerol lipase action cleaves the first fatty acid off of a fat and this step is necessary before the other lipase can act to remove the other fatty acids from a fat.
3. Glycerol, is the only part of a fat that can be made into glucose (via gluconeogenesis). Fatty acids travel in the bloodstream carried by serum albumin.
4. Fatty acid oxidation occurs in the matrix of the mitochondrion. In the cell, fatty acids are attached to CoA and then at the mitochondrion, the CoA is replaced by carnitine. Inside the mitochondrial matrix, the carnitine is replaced by CoA again.
5. Steps in fatty acid oxidation include dehydrogenation, hydration, oxidation, and thiolytic cleavage. The dehydrogenation and oxidation reactions yield reduced electron carriers (FADH<sub>2</sub> and NADH). The double bond formed in the first dehydrogenation reaction is in the *trans* form. The hydration yields a hydroxyl group on the third carbon from CoA end in the "L" configuration. Thiolytic cleavage is catalyzed by the enzyme called thiolase. Two enzymes you should know include acyl-CoA dehydrogenase, which come in three forms (specialized for long, medium, and short chain fatty acyl-CoAs) and thiolase, which catalyzes the thiolytic cleavage to release acetyl-CoA.
6. The first reaction of fatty acid oxidation involves a set of enzymes known as acyl dehydrogenases. These are specific for fatty acids with long, medium, or short chains. The medium chain acyl dehydrogenase has been implicated in some instances of sudden infant death syndrome.
7. The long chain acyl dehydrogenases are found in peroxisomes and this is where oxidation of long chain fatty acids (longer than 16 carbons) begins (not in the mitochondrial matrix). Oxidation here involves transfer of electrons to oxygen to make hydrogen peroxide, instead of FADH<sub>2</sub>. Peroxisomal fatty acid oxidation is therefore LESS efficient than mitochondrial beta oxidation.
8. The first step of oxidation generates a *trans*-intermediate plus FADH<sub>2</sub>. The second step involves addition of water across the *trans* double bond to create an intermediate in with an OH on carbon 3 in the L configuration. The third step involves oxidation of the hydroxyl intermediate to a ketone on carbon 3. The last step involves cleaving off of an acetyl-CoA and production of a fatty acyl-CoA with two fewer carbons. The last step is catalyzed by the enzyme thiolase.
9. The reactions of beta oxidation up to the thiolase reaction chemically mirror the reactions of the oxidation of succinate up to oxaloacetate.

10. Seven cycles of beta oxidation of palmitoyl-CoA in the matrix yield 8 acetyl-CoAs.
11. Oxidation of biologically occurring fatty acids with *cis* double bonds requires two additional enzymes compared to oxidation of saturated fatty acids. These enzymes are enoyl-CoA-isomerase and 2,4-dienoyl-CoA-reductase.
12. Enoyl-CoA-isomerase converts *cis* or *trans* bonds between carbons 3 and 4 to *trans* bonds between carbons 2 and 3. Since beta oxidation normally has *trans* bonded intermediates between carbons 2 and 3, this enzyme is sufficient for conversion of many naturally occurring fatty acids to be oxidized.
13. 2,4-dienoyl-CoA reductase acts on intermediates that have double bonds between carbons 2-3 and 4-5. It uses NADPH to reduce the two double bonds to one double bond and the resulting double bond is placed in a *cis* configuration between carbons 3-4. Enoyl-CoA-isomerase then can convert this intermediate to one with a *trans* double bond between carbons 2-3, thus allowing beta oxidation to continue.
14. Oxidation of fatty acids with odd numbers of carbons yields a final product of propionyl-CoA, not acetyl-CoA. Conversion of propionyl-CoA to succinyl-CoA requires an enzyme that uses a coenzyme B<sub>12</sub> group. This coenzyme contains a cobalt atom that provide a means of generating the radical necessary for the reaction.
15. Conversion of propionyl-CoA to succinyl-CoA requires three steps. The first is addition of a carboxyl-group to the middle carbon in the molecule. The overall process involves two unusual isomerizations and movement of a methyl group that utilizes the cobalt atom of vitamin B<sub>12</sub>.
16. Ketone bodies are produced by the body when glucose precursors are not available to make glucose. Examples of ketone bodies include acetoacetate and hydroxybutyrate. Diabetics have problems with glucose metabolism and may produce ketone bodies to provide energy to keep the brain alive. One can detect this by the smell of acetone on their breath. The thiolase reaction in ketone body formation is the reversal of the same reaction that occurs in fatty acid beta oxidation.

## Fatty Acid Biosynthesis

1. The process occurs similarly to beta-oxidation, though in reverse. Important distinctions are noted below in a-f.
  - a. Fatty acid synthesis up to palmitate occurs in the cytoplasm, but beta oxidation occurs in mitochondrial matrix.
  - b. Fatty acids are built using an acyl carrier protein (ACP), but beta oxidation uses CoA.
  - c. NADPH is used to donate electrons in synthesis, but NAD<sup>+</sup> or FAD are used to accept electrons in oxidation in the mitochondrion.
  - d. A three carbon molecule, malonyl-ACP donates two carbons to the growing fatty acid chain - a carbon dioxide is lost in the process. Beta oxidations yield two carbon acetyl-CoA units.

- e. Synthesis of fatty acids longer than 16 carbons occurs in endoplasmic reticulum or mitochondrion. Oxidation of fatty acids longer than 16 carbons begins in peroxisomes.
  - f. In fatty acid biosynthesis, a D-hydroxyl intermediate is formed at carbon #3. In fatty acid oxidation, an L-hydroxyl intermediate is formed at carbon #3.
2. Acetyl-CoA carboxylase catalyzes the addition of a carboxyl group to acetyl-CoA to form malonyl-CoA. I will discuss its regulation in the next period.
  3. The enzymes of fatty acid synthesis apart from acetyl-CoA carboxylase are contained in a complex known as fatty acid synthase. We will refer to that complex as the name of all of the enzyme for the reactions after acetyl-CoA carboxylase.
  4. Fatty acid synthase produces the saturated 16 carbon fatty acid known as palmitate.