Oxidation of Long Chain Fatty Acids

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Oxidation of long chain fatty acids is the primary source of energy supply in man and animals. Hibernating animals utilise fat stores to maintain body heat, water and energy during prolonged periods of sleep. In an average 70kg man, glycogen stores are able to sustain energy levels for approximately 12 hours. In contrast, lipid energy reserves can provide energy for up to 12 weeks.

Fatty acids must be activated in the cytoplasm before being oxidized in the mitochondria. Activation is catalyzed by fatty acyl-CoA ligase (also called acyl-CoA synthetase or thiokinase). The net result of this activation process is the consumption of 2 molar equivalents of ATP.

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\text{Fatty acid} + \text{ATP} + \text{CoA} \rightarrow \text{Acyl-CoA} + \text{PPi} + \text{AMP}
\]

Oxidation of fatty acids occurs in the mitochondria. The transport of fatty acyl-CoA into the mitochondria is accomplished via an acyl-carnitine intermediate, which itself is generated by the action of carnitine acyltransferase I, an enzyme that resides in the outer mitochondrial membrane. The acyl-carnitine molecule then is transported into the mitochondria where carnitine acyltransferase II catalyzes the regeneration of the fatty acyl-CoA molecule. Once inside the mitochondrion the fatty-CoA is a substrate for the b-oxidation machinery.

The process of fatty acid oxidation is termed b-oxidation since it occurs through the sequential removal of 2-carbon units by oxidation at the b-carbon position of the fatty acyl-CoA molecule. Each round of b-oxidation produces one mole of NADH, one mole of FADH2 and one mole of acetyl-CoA. The acetyl-CoA--- the end product of each round of b-oxidation--- then enters the TCA cycle, where it is further oxidized to CO2 with the concomitant generation of three moles of NADH, one mole of FADH2 and one mole of ATP. The NADH and FADH2 generated during the fatty acid and acetyl-CoA oxidation in the TCA cycle then can enter the respiratory pathway for the production of ATP.

The oxidation of fatty acids yields significantly more energy per carbon atom than does the oxidation of carbohydrates. The net result of the
oxidation of one mole of oleic acid (an 18-carbon fatty acid) will be 146 moles of ATP (2 mole equivalents are used during the activation of the fatty acid), as compared with 114 moles from an equivalent number of glucose carbon atoms.

Overview of routes into the TCA cycle

Overview of β oxidation.

Absorption of Lipids

Dietary lipids are emulsified in the small intestine by bile salts. These emulsified fats are then degraded by pancreatic lipase to their constituent fatty acids before absorption by the mucosal cells lining the small intestine. Following this the triacylglycerols are re-constituted and complexed to ApoC carrier proteins to form chylomicrons. Triacylglycerols synthesized by the liver are packaged as very low density lipoproteins (VLDL) and released into the blood directly. Lipoprotein lipase catalyzes the breakdown of both chylomicrons and
Overview of lipid absorption and transport.

Energy production pathways in hepatocytes
Ketogenesis

During high rates of fatty acid oxidation, primarily in the liver, large amounts of acetyl-CoA are generated. These exceed the capacity of the TCA cycle, and one result is the synthesis of ketone bodies, or ketogenesis. The ketone bodies are acetoacetate, b-hydroxybutyrate, and acetone. The formation of acetoacetyl-CoA occurs by condensation of two moles of acetyl-CoA through a reversal of the thiolase catalyzed reaction of fat oxidation. Acetoacetyl-CoA and an additional acetyl-CoA are converted to b-hydroxy-b-methylglutaryl-CoA (HMG-CoA) by HMG-CoA synthase, an enzyme found in large amounts only in the liver. Some of the HMG-CoA leaves the mitochondria, where it is converted to mevalonate (the precursor for cholesterol synthesis) by HMG-CoA reductase. HMG-CoA in the mitochondria is converted to acetoacetate by the action of HMG-CoA lyase. Acetoacetate can undergo spontaneous decarboxylation to acetone, or be enzymatically converted to b-hydroxybutyrate through the action of b-hydroxybutyrate dehydrogenase. When the level of glycogen in the liver is high the production of b-hydroxybutyrate increases.

When carbohydrate utilization is low or deficient, the level of oxaloacetate will also be low, resulting in a reduced flux through the TCA cycle. This in turn leads to increased release of ketone bodies from the liver for use as fuel by other tissues. In early stages of starvation, when VLDLs to free fatty acids for β oxidation.

the last remnants of fat are oxidized, heart and skeletal muscle will consume primarily ketone bodies to preserve glucose for use by the brain. Acetoacetate and b-hydroxybutyrate, in particular, also serve as major substrates for the biosynthesis of neonatal cerebral lipids. Ketone bodies are utilized by extrahepatic tissues through the conversion of b-hydroxybutyrate to acetoacetate and of acetoacetate to acetoacetyl-CoA. The first step involves the reversal of the b-hydroxybutyrate dehydrogenase reaction, and the second involves the action (shown below) of acetoacetate:succinyl-CoA transferase, also called ketoacyl-CoA-transferase.

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\text{Acetoacetate + Succinyl-CoA} \rightleftharpoons \text{Acetoacetyl-CoA + succinate}
\]

The latter enzyme is present in all tissues except the liver. Importantly, its absence allows the liver to produce ketone bodies but not to utilize them. This ensures that extrahepatic tissues have access to ketone bodies as a fuel source during prolonged starvation.

Regulation of Ketogenesis

The fate of the products of fatty acid metabolism is determined by an individual’s physiological status. Ketogenesis takes place primarily in the liver and may by affected by several factors:

1. Control in the release of free fatty acids from adipose tissue directly affects the level of ketogenesis in the liver. This is, of course, substrate-level regulation.

2. Once fats enter the liver, they have two distinct fates. They may be activated to acyl-CoAs and
oxidized, or esterified to glycerol in the production of triacylglycerols. If the liver has sufficient supplies of glycerol-3-phosphate, most of the fats will be turned to the production of triacylglycerols.

* 3. The generation of acetyl-CoA by oxidation of fats can be completely oxidized in the TCA cycle. Therefore, if the demand for ATP is high the fate of acetyl-CoA is likely to be further oxidation to CO2. * 4. The level of fat oxidation is regulated hormonally through phosphorylation of ACC, which may activate it (in response to glucagon) or inhibit it (in the case of insulin).

Clinical significance of Ketogenesis

The production of ketone bodies occurs at a relatively low rate during normal feeding and under conditions of normal physiological status. Normal physiological responses to carbohydrate shortages cause the liver to increase the production of ketone bodies from the acetyl-CoA generated from fatty acid oxidation. This allows the heart and skeletal muscles primarily to use ketone bodies for energy, thereby preserving the limited glucose for use by the brain.

The most significant disruption in the level of ketosis, leading to profound clinical manifestations, occurs in untreated insulin-dependent diabetes mellitus. This physiological state, diabetic ketoacidosis, results from a reduced supply of glucose (due to a significant decline in circulating insulin) and a concomitant increase in fatty acid oxidation (due to a concomitant increase in circulating glucagon). The increased production of acetyl-CoA leads to ketone body production that exceeds the ability of peripheral tissues to oxidize them. Ketone bodies are relatively strong acids (pKa around 3.5), and their increase lowers the pH of the blood. This acidification of the blood is dangerous chiefly because it impairs the ability of haemoglobin to bind oxygen.