Chapter 8 FATTY ACID CATABOLISM

Digestion, Mobilization, and Transport of Fats

On average, 40% or more of the daily energy requirement of humans in highly industrialized countries is supplied by dietary triacylglycerols. The oxidation of long-chain fatty acids to acetyl-CoA is a central energy-yielding pathway in many organisms and tissues.

Cells can obtain fatty acid fuels from three sources: fats consumed in the diet, fats stored in cells as lipid droplets, and fats synthesized in one organ for export to another. Some species use all three sources under various circumstances, others use one or two. Vertebrates, for example, obtain fats in the diet, mobilize fats stored in specialized tissue (adipose tissue, consisting of cells called adipocytes), and, in the liver, convert excess dietary carbohydrates to fats for export to other tissues.

Dietary Fats Are Absorbed in the Small Intestine

In vertebrates, before ingested triacylglycerols can be absorbed through the intestinal wall they must be converted from insoluble macroscopic fat particles to finely dispersed microscopic micelles. This solubilization is carried out by bile salts. Micelle formation enormously increases the fraction of lipid molecules accessible to the action of water-soluble lipases in the intestine, and lipase action converts triacylglycerols to monoacylglycerols (monoglycerides) and diacylglycerols (diglycerides), free fatty acids, and glycerol. These products of lipase action diffuse into the epithelial cells lining the intestinal surface (the intestinal mucosa) where they are reconverted to triacylglycerols and packaged with dietary cholesterol and specific proteins into lipoprotein aggregates called **chylomicrons**.

Hormones Trigger Mobilization of Stored Triacylglycerols

Fatty Acids Are Activated and Transported into Mitochondria

Once inside cells, fatty acids are activated at the outer mitochondrial membrane by conversion to fatty acyl–CoA thioesters. Fatty acyl–CoA to be oxidized enters mitochondria in three steps, via the carnitine shuttle.

Oxidation of Fatty Acids (β- oxidation)

The complete oxidation of fatty acids to CO2 and H2O takes place in three stages: the oxidation of long-chain fatty acids to two-carbon fragments, in the form of acetyl-CoA the oxidation of acetyl-CoA to CO2 in the citric acid cycle. The first two stages of fatty acid oxidation produce the reduced electron carriers NADH and FADH2, which in the third stage donate electrons to the mitochondrial respiratory chain, through which the electrons pass to oxygen with the concomitant phosphorylation of ADP to ATP.The energy released by fatty acid oxidation is thus conserved as ATP.

The chemical steps of fatty acid oxidation (β- oxidation); in mitochondria.

The *β* Oxidation of Saturated Fatty Acids Has Four Basic Steps

In the first stage of β oxidation, four reactions remove each acetyl-CoA unit from the carboxyl end of a saturated fatty acyl–CoA.

The Four Beta-Oxidation Steps Are Repeated to Yield Acetyl-CoA and ATP

Acetyl-CoA Can Be Further Oxidized in the Citric Acid Cycle

The acetyl-CoA produced from the oxidation of fatty acids can be oxidized to CO2 and H2O by the citric acid cycle.

Oxidation of Unsaturated Fatty Acids Requires Two Additional Reactions

Most of the fatty acids in the triacylglycerols and phospholipids of animals and plants are unsaturated, having one or more double bonds. These bonds are in the cis configuration and cannot be acted upon by enoyl-CoA hydratase, the enzyme catalyzing the addition of H2O to the trans double bond of the Δ2-enoyl-CoA generated during β oxidation. Two auxiliary enzymes are needed for β oxidation of the common unsaturated fatty acids: an isomerase and a reductase.

Complete Oxidation of Odd-Number Fatty Acids Requires Three Extra Reactions

Long-chain odd-number fatty acids are oxidized in the same pathway as the even-number acids, beginning at the carboxyl end of the chain. However, the substrate for the last pass through the β oxidation sequence is a fatty acyl–CoA with a five-carbon fatty acid. When this is oxidized and cleaved, the products are acetyl-CoA and propionyl-CoA. Propionyl-CoA is first carboxylated to form the D stereoisomer of **methylmalonyl-CoA** (Fig. 17–11) by **propionyl-CoA carboxylase,** which contains the cofactor biotin.

Ketone Bodies

In humans and most other mammals, acetyl-CoA formed in the liver during oxidation of fatty acids can either enter the citric acid cycle or undergo conversion to the “ketone bodies,” acetone, acetoacetate, and D- β -hydroxybutyrate, for export to other tissues.

Ketone Bodies, Formed in the Liver, Are Exported to Other Organs as Fuel

Ketone Bodies Are Overproduced in Diabetes and during Starvation

Starvation and untreated diabetes mellitus lead to overproduction of ketone bodies, with several associated medical problems.