**Chapter 17** **Fatty Acid Catabolism**

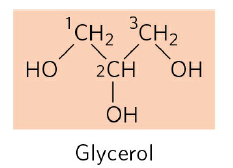
* The oxidation of long-chain fatty acids to acetyl-CoA is a central energy-yielding pathway in many organisms and tissues.
* In mammalian heart and liver, it provides as much as 80% of the energetic needs under all physiological circumstances.
* The electrons removed from fatty acids during oxidation pass through the respiratory chain, driving ATP synthesis.
* The acetyl-CoA produced from the fatty acids may be completely oxidized to CO2 in the citric acid cycle, resulting in further energy conservation.
* Triacylglycerols (also called triglycerides or neutral fats) are suitable as storage fuels.
* The long alkyl chains of fatty acids are essentially hydrocarbons and have an energy more than twice that for the same weight of carbohydrate or protein.

**17.1 Digestion, Mobilization and Transport of Fats**

* Cells can obtain fatty acid fuels from three sources:
* fats consumed in the diet,
* fats stored in cells as lipid droplets,
* fats synthesized in one organ for export to another.

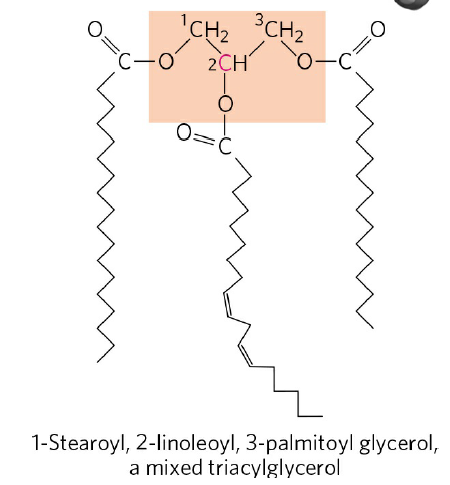
**Dietary Fats Are Absorbed in the Small Intestine**

* Triacylgycerols (**Fig. 10-2)** are degraded to fatty acids and glycerols by intestinal lipases.



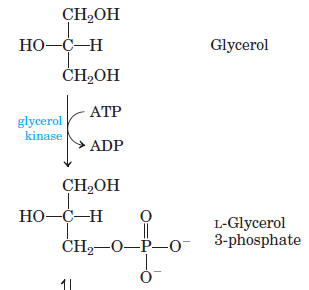
R-COOH

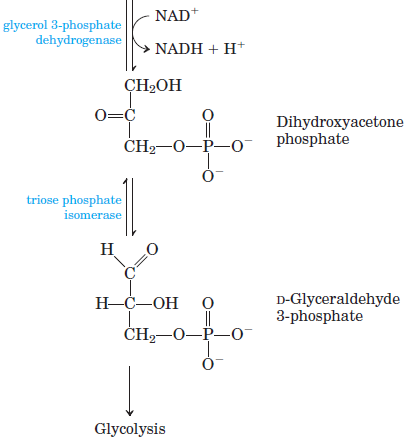
Fatty acid



**FIGURE 10-2** The mixed triacylglycerol shown here has three different fatty acids attached to the glycerol backbone.

* The fatty acids are packaged and delivered to muscle and adipose tissues by blood.
* In muscle, the fatty acids are oxidized for energy.
* In adipose tissue, they are reesterified for storage as triacylglycerols.
* The glycerols enter into the glycolytic pathway (**Fig. 17-4)**.

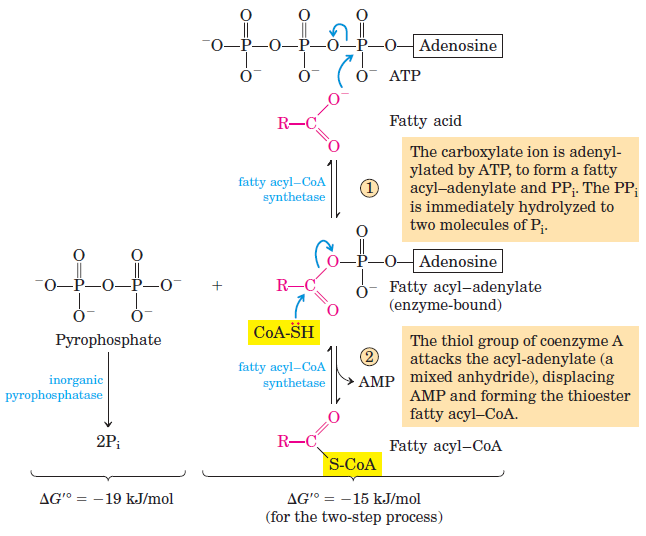






**Fatty Acids Are Activated and Transported into Mitochondria**

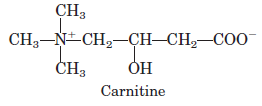
* The enzymes of fatty acid oxidation in animal cells are located in the mitochondrial matrix.
* The fatty acids with chain lengths of 12 or fewer carbons enter mitochondria without the help of membrane transporters.
* Those with 14 or more carbons cannot pass directly through the mitochondrial membranes and three enzymatic reactions are required to transport into mitochondria.
* The first reaction is catalyzed by **fatty acyl-CoA synthetase** present in the outer mitochondrial membrane. Fatty acyl–CoA esters are formed at the cytosolic side of the outer mitochondrial membrane **(Fig. 17-5)**.

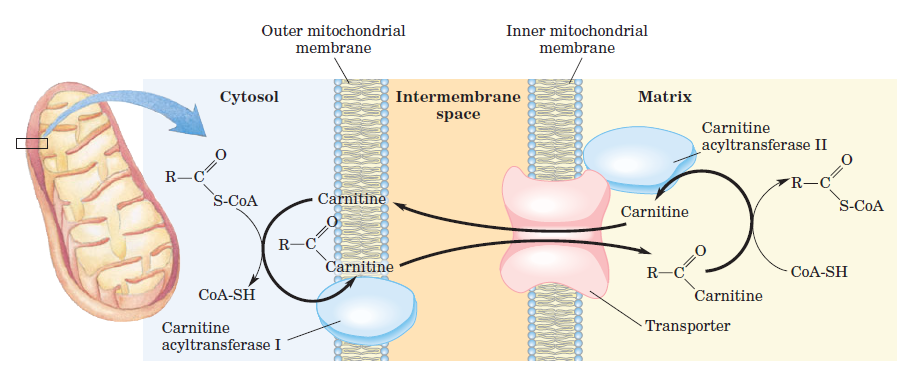




Fatty acid + CoA + ATP fatty acyl-CoA + AMP + 2 Pi

* The second reaction is catalyzed by **carnitine acyltransferase I.** Fatty acyl–carnitine is formed at the outer membrane or in the intermembrane space (**Fig. 17-6).**





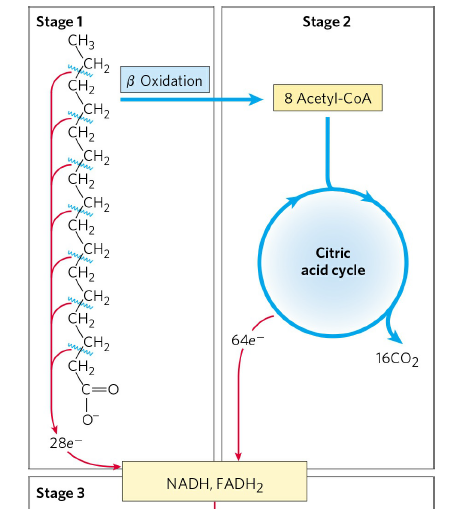
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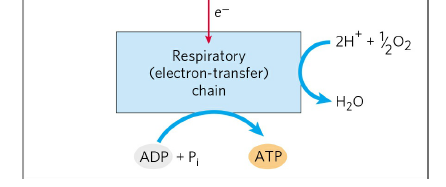
* The fatty acyl-carnitine enters the matrix by **acyl-carnitine/carnitine transporter** of the inner mitochondrial membrane (**Fig. 17-6)**.
* The third reaction is regeneration of fatty acyl-CoA by **carnitine acyltransferase II** on the inner face of the inner mitochondrial membrane (**Fig. 17-6)**.
* Carnitine reenters the intermembrane space via the acyl-carnitine/carnitine transporter (**Fig. 17-6)**.

**17.2 Oxidation of Fatty Acids**

* Mitochondrial oxidation of fatty acids takes place in three stages (**Fig. 17-7)**.

Stage 1: A long-chain fatty acid is oxidized to yield acetyl residues in the form of acetyl-CoA, starting from the carboxyl end. This process is called ** oxidation**. For example, the 16-carbon palmitic acid undergoes seven passes, in each pass losing two carbons as acetyl-CoA. At the end of seven cycles, the last four carbons of palmitate give two acetyl-CoA. The overall result is the conversion of the 16-carbon chain of palmitate to 8 acetyl-CoA and production of 7 FADH2 and 7 NADH.





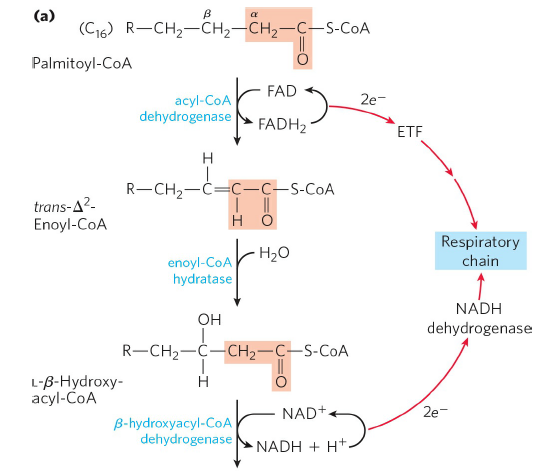
Stage 2: The acetyl groups are oxidized to CO2 via the citric acid cycle.

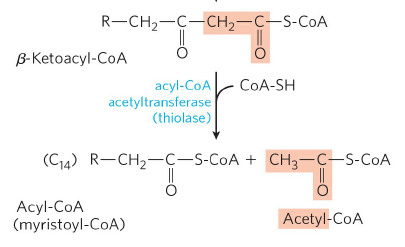
Stage 3: Electrons derived from the oxidations of stage 1 and 2 pass to O2 via the mitochondrial respiration chain, providing the energy for ATP synthesis by oxidative phosphorylation.

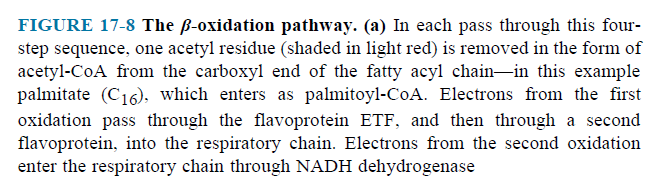
* The energy released by fatty acid oxidation is thus conserved as ATP.

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

1. Dehydration of fatty acyl-CoA by **acyl-CoA dehydrogenase (Fig. 17-8a)**
2. Water is added to the double bond by **enoyl-CoA hydratase (Fig. 17-8a)**
3. Dehydration of -hydroxyacyl-CoA by ****-hydroxyacyl-CoA dehydrogenase (Fig. 17-8a)**
4. Production of acetyl-CoA by **acyl-CoA acetyltransferase (thiolase) (Fig. 17-8a)**

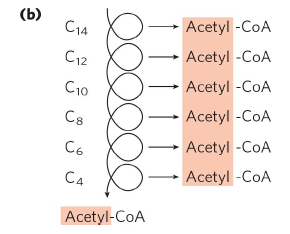






**The Four -Oxidation Steps Are Repeated to Yield Acetyl-CoA and ATP**

* Seven passes through the -oxidation sequence are required to oxidize one molecule of palmitoyl-CoA to eight molecules of acetyl-CoA **(Fig. 17-8b)**.

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**FIGURE 17-8 (b)** Six more passes through the *β*-oxidation pathway yield seven more moleculesof acetyl-CoA, the seventh arising from the last two carbon atoms of the 16- carbon chain. Eight molecules of acetyl-CoA are formed in all. The acetyl-CoA may be oxidized in the citric acid cycle, donating more electrons to the respiratory chain.

* The overall equation is

Palmitoyl-CoA + 7 FAD + 7 NAD+ + 7 H2O + 7 CoA

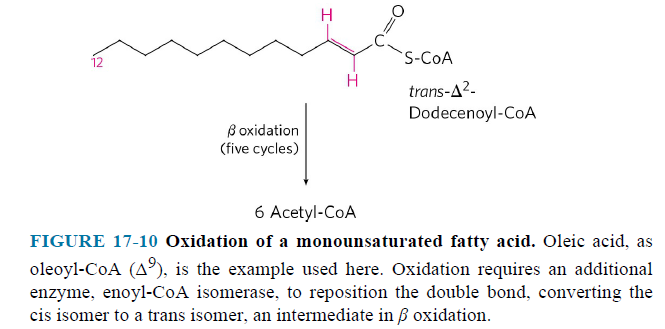
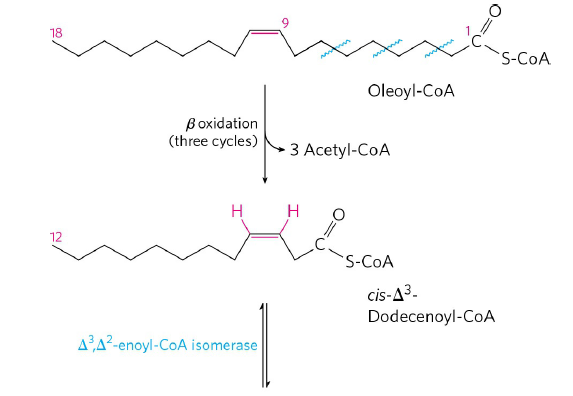
8 Acetyl-CoA + 7 FADH2 + 7 NADH + 7 H+

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

* 1 Acetyl-CoA produces 3 NADH, 1 FADH2 and 1 GTP (or ATP).
* 8 Acetyl-CoA produce 24 NADH, 8 FADH2 and 8 GTP (or ATP).
* 1 Palmitoyl-CoA produces 31 NADH, 15 FADH2 and 8 GTP (or ATP).
* 31 NADH produce 77.5 ATP and 15 FADH2 produce 22.5 ATP. Total ATP is 108.
* Remember, 1 ATP was used at activation of fatty acid.
* Because the activation of palmitate to palmitoyl- CoA breaks both phosphoanhydride bonds in ATP, the energetic cost of activating a fatty acid is equivalent to two ATP, and the net gain per molecule of palmitate is 106 ATP.

**Oxidation of Monounsaturated Fatty Acids Requires One Additional Reaction**

* Oleate is an 18-carbon monounsaturated fatty acid with a cis double bond between C-9 and C-10.
* Oleoyl-CoA undergoes three passes through the fatty acid oxidation cycle to yield three molecules of acetyl-CoA **(Fig. 17- 10)**.

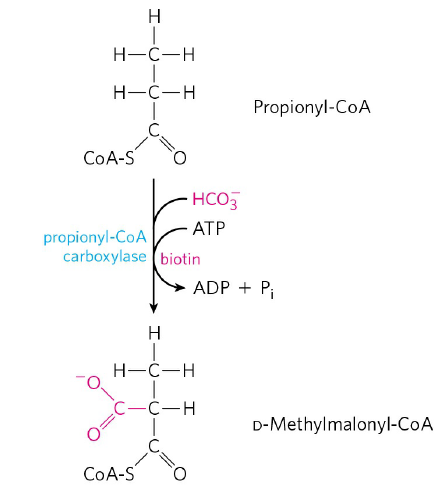


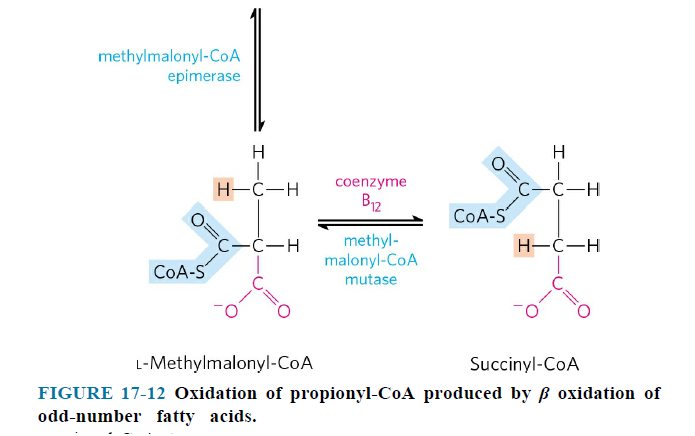
* 12-carbon unsaturated fatty acid cannot serve as a substrate for enoyl-CoA hydratase, which acts only on trans double bonds.
* Enoyl-CoA isomerase isomerizes the cis-enoyl-CoA to the trans-enoyl-CoA.
* This intermediate is now acted upon by the remaining enzymes of  oxidation to yield acetyl-CoA.
* Altogether, nine acetyl-CoAs are produced from one molecule of the 18-carbon oleate.

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

* Long-chain odd-number fatty acids are oxidized in the same pathways as the even-number fatty acids. For example, 17-carbon
* at the last pass, fatty acyl-CoA has five carbon atoms.
* the products are acetyl-CoA and propionyl-CoA.
* the acetyl-CoA can be oxidized in the citric acid cycle, but propionyl-CoA enters a different pathway having three enzymes (**Fig. 17-12)**.

1. Carboxylation of propionyl-CoA





1. Epimerization of D-Methylmalonyl-CoA
2. Production of succinyl-CoA which can enter the citric acid cycle

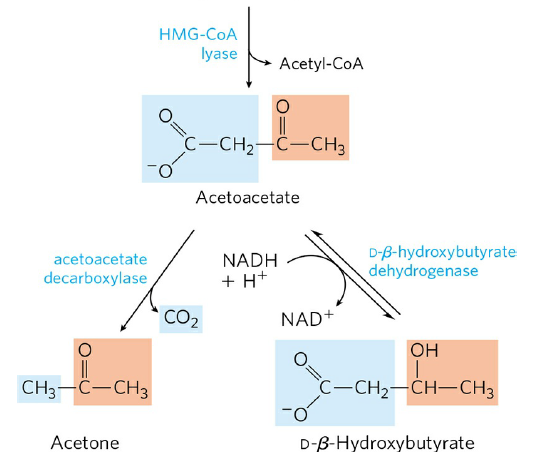
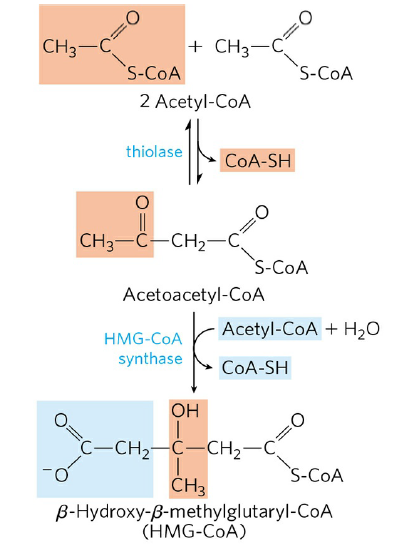
* 17-carbon fatty acid gives 2 NADH less than 16-carbon fatty acid.

**Fatty Acid Oxidation is Regulated**

* Carnitine acyltransferase 1 is inhibited by malonyl-CoA.
* -hydroxyacyl-CoA dehydrogenase is inhibited by [NADH/NAD+] ratio.
* Thiolase is inhibited by high concentrations of acetyl-CoA.

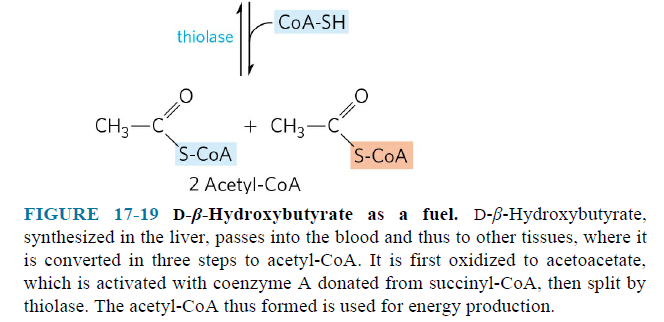
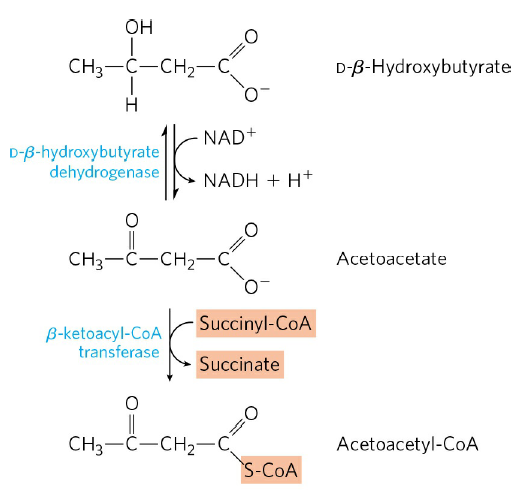
**17.3 Ketone Bodies**

* In humans and most other mammals, acetyl-CoA formed in the liver during oxidation of fatty acids
* can enter the citric acid cycle or
* can be converted the ketone bodies (**acetoacetate, acetone** and **-hydroxybutyrate**) **(Fig. 17-18)**.



**FIGURE 17-18 Formation of ketone bodies from acetyl-CoA.**

* Acetoacetate and -hydroxybutyrate are transported by the blood to tissues as fuels.
* They are converted to acetyl-CoA **(Fig. 17-20)**.



* Liver does not have -ketoacyl-CoA transferase.
* Acetyl-CoAs are oxidized in the citric acid cycle to provide much of the energy required by tissues such as skeletal and heart muscle, kidney and brain.