

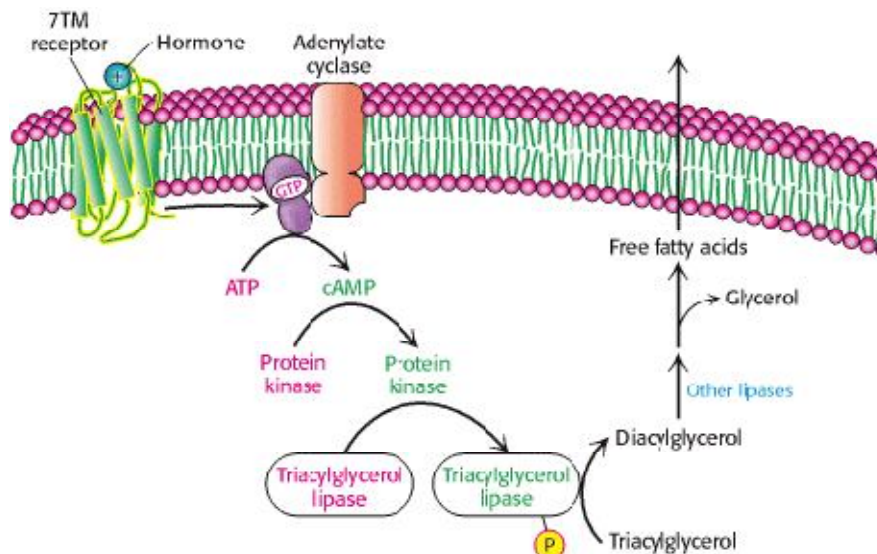
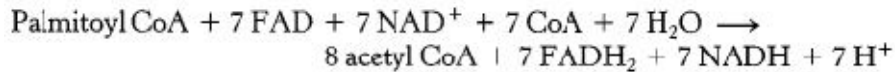
The Complete Oxidation of Palmitate Yields 106 Molecules of ATP

We can now calculate the energy yield derived from the oxidation of a fatty acid. In each reaction cycle, an acyl CoA is

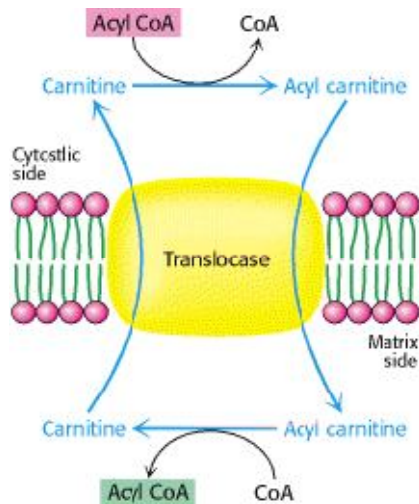
shortened by two carbon atoms, and one molecule each of FADH₂, NADH, and acetyl CoA is formed.

The degradation of palmitoyl CoA (C₁₆-acyl CoA) requires seven reaction cycles. In the seventh cycle, the C₄-ketoacyl

CoA is thiolized to two molecules of acetyl CoA. Hence, the stoichiometry of oxidation of palmitoyl CoA is

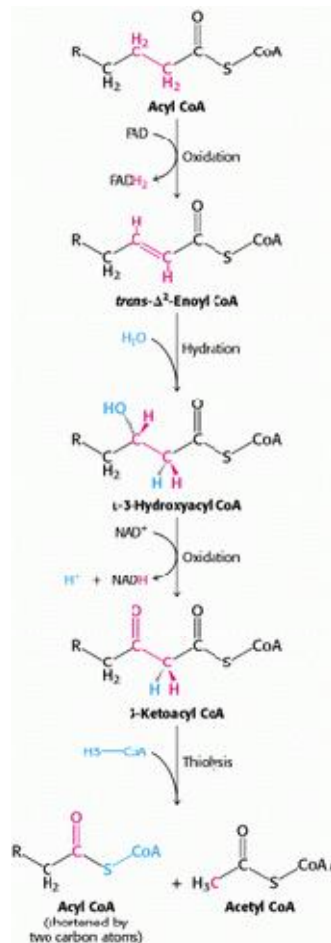


Mobilization of Triacylglycerols. Triacylglycerols in adipose tissue are converted into free fatty acids and glycerol for release into the bloodstream in response to hormonal signals. A hormone-sensitive lipase initiates the process.



Acyl Carnitine Translocase. The entry of acyl carnitine into the mitochondrial matrix is mediated by a translocase. Carnitine returns to the cytosolic side of the inner mitochondrial membrane in exchange for acyl carnitine.

The figure below shows the Reaction Sequence for the Degradation of Fatty Acids. Fatty acids are degraded by the repetition of a four-reaction sequence consisting of oxidation, hydration, oxidation, and thiolysis.



Principal reactions in fatty acid oxidation

Step	Reaction	Enzyme
1	Fatty acid + CoA + ATP \leftrightarrow acyl CoA + AMP + PPi	Acyl CoA synthetase
2	Carnitine + acyl CoA \leftrightarrow acyl carnitine + CoA	Carnitine acyltransferase
3	Acyl CoA + E-FAD \leftrightarrow <i>trans</i> - Δ^2 -enoyl CoA + EFADH ₂	Acyl CoA dehydrogenases
4	<i>trans</i> - Δ^2 -Enoyl CoA + H ₂ O \leftrightarrow 3-hydroxyacyl CoA	Enoyl CoA hydratase
5	3-Hydroxyacyl CoA + NAD ⁺ \leftrightarrow 3-ketoacyl CoA + NADH + H ⁺	3-Hydroxyacyl CoA dehydrogenase
6	3-ketoacyl CoA + CoA \leftrightarrow acetyl CoA + acyl CoA (shortened by C2)	β -Ketothiolase (also called thiolase)

Certain Fatty Acids Require Additional Steps for Degradation

The β -oxidation pathway accomplishes the complete degradation of saturated fatty acids having an even number of carbon atoms. Most fatty acids have such structures because of their mode of synthesis (Section 22.4.3). However, not all fatty acids are so simple. The oxidation of fatty acids containing double bonds requires additional steps. Likewise, fatty acids containing an odd number of carbon atoms yield a propionyl CoA at the final thiolysis step that must be converted into an easily usable form by additional enzyme reactions.

22.3.1. An Isomerase and a Reductase Are Required for the Oxidation of Unsaturated

Fatty Acids

The oxidation of unsaturated fatty acids presents some difficulties, yet many such fatty acids are available in the diet.

Most of the reactions are the same as those for saturated fatty acids. In fact, only two additional enzymes an isomerase

and a reductase are needed to degrade a wide range of unsaturated fatty acids.

Consider the oxidation of palmitoleate. This C₁₆ unsaturated fatty acid, which has one double bond between C-9 and C-

10, is activated and transported across the inner mitochondrial membrane in the same way as saturated fatty acids.

Palmitoleoyl CoA then undergoes three cycles of degradation, which are carried out by the same enzymes as in the

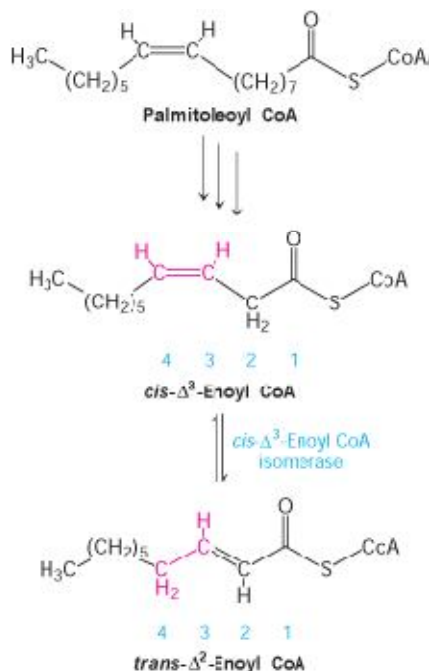
oxidation of saturated fatty acids. However, the *cis*-Δ³-enoyl CoA formed in the third round is not a substrate for acyl

CoA dehydrogenase. The presence of a double bond between C-3 and C-4 prevents the formation of another double bond

between C-2 and C-3. This impasse is resolved by a new reaction that shifts the position and configuration of the *cis*-Δ³

double bond. An isomerase converts this double bond into a *trans*-Δ² double bond. The subsequent reactions are those

of the saturated fatty acid oxidation pathway, in which the *trans*-Δ²-enoyl CoA is a regular substrate.



Another problem arises with the oxidation of polyunsaturated fatty acids. Consider linoleate, a C₁₈ polyunsaturated fatty acid with *cis*-Δ⁹ and *cis*-Δ¹² double bonds (Figure 22.10). The *cis*-Δ³ double bond formed after three rounds of β

oxidation is converted into a *trans*-Δ² double bond by the aforementioned isomerase. The acyl CoA produced by another

round of β oxidation contains a *cis*-Δ⁴ double bond. Dehydrogenation of this species by acyl CoA dehydrogenase yields

a 2,4-dienoyl intermediate, which is not a substrate for the next enzyme in the β-oxidation pathway. This impasse is

circumvented by *2,4-dienoyl CoA reductase*, an enzyme that uses NADPH to reduce the 2,4-dienoyl intermediate to

trans- Δ^3 -enoyl CoA. *cis*- Δ^3 -Enoyl CoA isomerase then converts *trans*- Δ^3 -enoyl CoA into the *trans*- Δ^2 form, a

customary intermediate in the β -oxidation pathway. These catalytic strategies are elegant and economical. Only two

extra enzymes are needed for the oxidation of *any* polyunsaturated fatty acid. *Odd-numbered double bonds are handled*

by the isomerase, and even-numbered ones by the reductase and the isomerase.

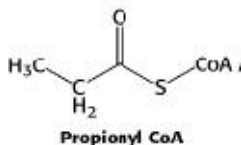
Odd-Chain Fatty Acids Yield Propionyl Coenzyme A in the Final Thiolysis Step

Fatty acids having an odd number of carbon atoms are minor species. They are oxidized in the same way as fatty acids

having an even number, except that propionyl CoA and acetyl CoA, rather than two molecules of acetyl CoA, are

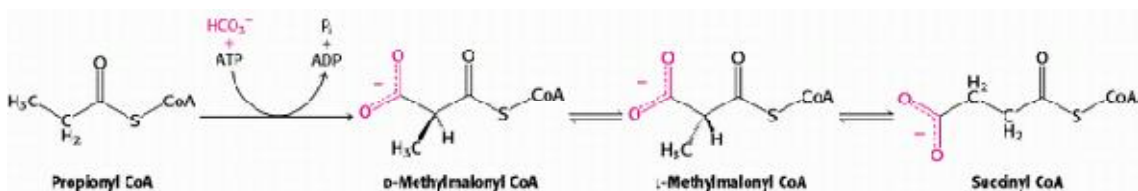
produced in the final round of degradation. The activated three-carbon unit in propionyl CoA enters the citric acid cycle

after it has been converted into succinyl CoA.



Propionyl CoA Is Converted into Succinyl CoA in a Reaction That Requires Vitamin B12

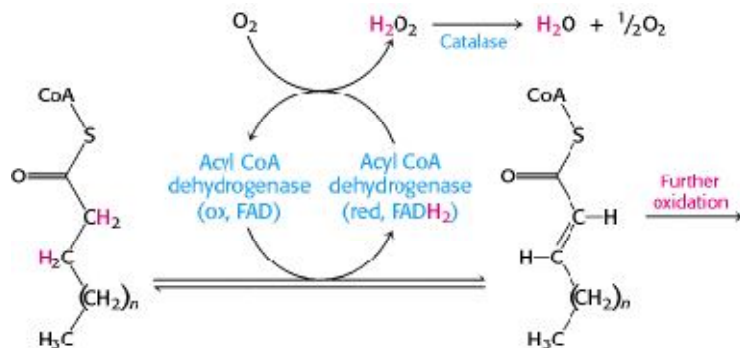
The pathway from propionyl CoA to succinyl CoA is especially interesting because it entails a rearrangement that requires *vitamin B12* (also known as *cobalamin*). Propionyl CoA is carboxylated at the expense of the hydrolysis of an ATP to yield the *d* isomer of methylmalonyl CoA (Figure 22.11). This carboxylation reaction is catalyzed by *propionyl CoA carboxylase*, a biotin enzyme that is homologous to and has a catalytic mechanism like that of pyruvate carboxylase. The *d* isomer of methylmalonyl CoA is racemized to the *l* isomer, the substrate for a mutase that converts it into *succinyl CoA* by an *intramolecular rearrangement*. The -CO-S-CoA group migrates from C-2 to C-3 in exchange for a hydrogen atom. This very unusual isomerization is catalyzed by *methylmalonyl CoA mutase*, which contains a derivative of vitamin B12, cobalamin, as its coenzyme.



Conversion of Propionyl CoA Into Succinyl CoA. Propionyl CoA, generated from fatty acids with an odd number of carbons as well as some amino acids, is converted into the citric acid cycle intermediate succinyl CoA.

Fatty Acids Are Also Oxidized in Peroxisomes

Although most fatty acid oxidation takes place in mitochondria, some oxidation takes place in cellular organelles called *peroxisomes* (Figure 22.17). These organelles are characterized by high concentrations of the enzyme catalase, which catalyzes the dismutation of hydrogen peroxide into water and molecular oxygen (Section 18.3.6). Fatty acid oxidation in these organelles, which halts at octanoyl CoA, may serve to shorten long chains to make them better substrates of β oxidation in mitochondria. Peroxisomal oxidation differs from β oxidation in the initial dehydrogenation reaction (Figure 22.18). In peroxisomes, a flavoprotein dehydrogenase transfers electrons to O_2 to yield H_2O_2 instead of capturing the high-energy electrons as $FADH_2$, as occurs in mitochondrial β oxidation. Catalase is needed to convert the hydrogen peroxide produced in the initial reaction into water and oxygen. Subsequent steps are identical with their mitochondrial counterparts, although they are carried out by different isoforms of the enzymes. Zellweger syndrome, which results from the absence of functional peroxisomes, is characterized by liver, kidney, and muscle abnormalities and usually results in death by age six. The syndrome is caused by a defect in the import of enzymes into the peroxisomes. Here we see a pathological condition resulting from an inappropriate cellular distribution of enzymes.



Initiation of Peroxisomal Fatty Acid Degradation. The first dehydrogenation in the degradation of fatty acids in peroxisomes requires a flavoprotein dehydrogenase that transfers electrons to O_2 to yield H_2O_2 .

Ketone Bodies Are Formed from Acetyl Coenzyme A When Fat Breakdown Predominates

The acetyl CoA formed in fatty acid oxidation enters the citric acid cycle only if fat and carbohydrate degradation are appropriately balanced. The reason is that the entry of acetyl CoA into the citric acid cycle depends on the availability of oxaloacetate for the formation of citrate, but the concentration of oxaloacetate is lowered if carbohydrate is unavailable or improperly utilized. Recall that oxaloacetate is normally formed from pyruvate, the product of glycolysis, by pyruvate

carboxylase (Section 16.3.1). This is the molecular basis of the adage that *fats burn in the flame of carbohydrates*. In fasting or diabetes, oxaloacetate is consumed to form glucose by the gluconeogenic pathway and

hence is unavailable for condensation with acetyl CoA. Under these conditions, acetyl CoA is diverted to the formation

of acetoacetate and d-3-hydroxybutyrate. Acetoacetate, d-3-hydroxybutyrate, and acetone are often referred to as *ketone*

bodies. Abnormally high levels of ketone bodies are present in the blood of untreated diabetics (Section 22.3.6).

Acetoacetate is formed from acetyl CoA in three steps (Figure 22.19). Two molecules of acetyl CoA condense to form

acetoacetyl CoA. This reaction, which is catalyzed by thiolase, is the reverse of the thiolysis step in the oxidation of fatty

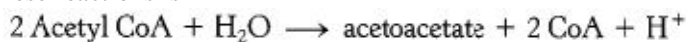
acids. Acetoacetyl CoA then reacts with acetyl CoA and water to give 3-hydroxy-3-methylglutaryl CoA (HMG-CoA)

and CoA. This condensation resembles the one catalyzed by citrate synthase (Section 17.1.3). This reaction, which has a

favorable equilibrium owing to the hydrolysis of a thioester linkage, compensates for the unfavorable equilibrium in the

formation of acetoacetyl CoA. 3-Hydroxy-3-methylglutaryl CoA is then cleaved to acetyl CoA and acetoacetate. The

sum of these reactions is

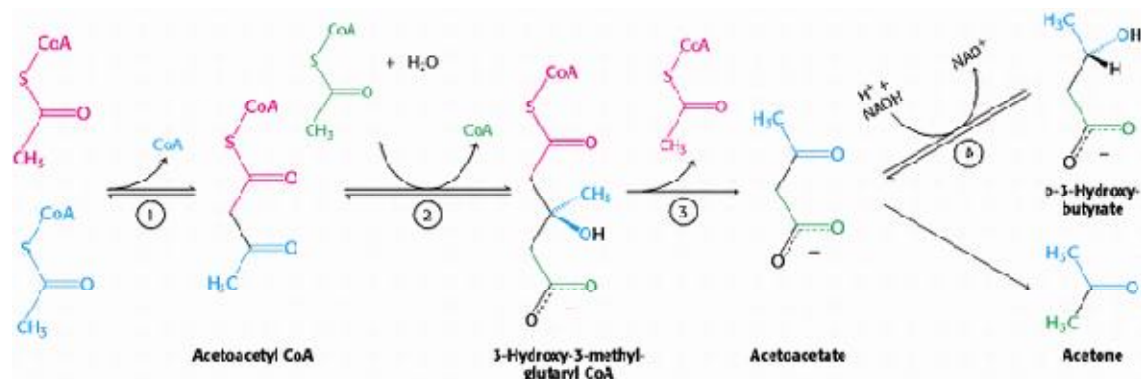


d-3-Hydroxybutyrate is formed by the reduction of acetoacetate in the mitochondrial matrix by d-3-hydroxybutyrate

dehydrogenase. The ratio of hydroxybutyrate to acetoacetate depends on the NADH/NAD⁺ ratio inside mitochondria.

Because it is a β -ketoacid, acetoacetate also undergoes a slow, spontaneous decarboxylation to acetone. The odor of

acetone may be detected in the breath of a person who has a high level of acetoacetate in the blood.



Formation of Ketone Bodies. The Ketone bodies-acetoacetate, d-3-hydroxybutyrate, and acetone from

acetyl CoA are formed primarily in the liver. Enzymes catalyzing these reactions are (1) 3-ketothiolase, (2)

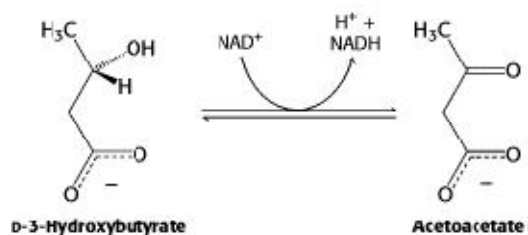
hydroxymethylglutaryl CoA synthase, (3) hydroxymethylglutaryl CoA cleavage enzyme, and (4) d-3-hydroxybutyrate

dehydrogenase. Acetoacetate spontaneously decarboxylates to form acetone.

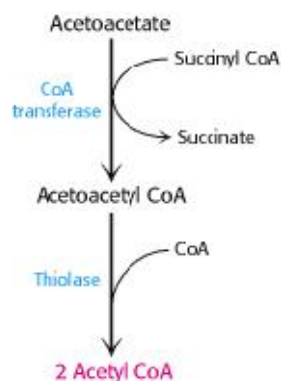
22.3.6. Ketone Bodies Are a Major Fuel in Some Tissues

The major site of production of acetoacetate and 3-hydroxybutyrate is the liver. These substances diffuse from the liver

mitochondria into the blood and are transported to peripheral tissues. These ketone bodies were initially regarded as degradation products of little physiological value. However, the results of studies by George Cahill and others revealed that these derivatives of acetyl CoA are important molecules in energy metabolism. *Acetoacetate and 3-hydroxybutyrate are normal fuels of respiration and are quantitatively important as sources of energy.* Indeed, heart muscle and the renal cortex use acetoacetate in preference to glucose. In contrast, glucose is the major fuel for the brain and red blood cells in well-nourished people on a balanced diet. However, the brain adapts to the utilization of acetoacetate during starvation and diabetes (Sections 30.3.1 and 30.3.2). In prolonged starvation, 75% of the fuel needs of the brain are met by ketone bodies. 3-Hydroxybutyrate is oxidized to produce acetoacetate as well as NADH for use in oxidative phosphorylation.



Acetoacetate can be activated by the transfer of CoA from succinyl CoA in a reaction catalyzed by a specific CoA transferase. Acetoacetyl CoA is then cleaved by thiolase to yield two molecules of acetyl CoA, which can then enter the citric acid cycle.



Utilization of Acetoacetate as a Fuel. Acetoacetate can be converted into two molecules of acetyl CoA, which then enter the citric acid cycle.

The liver has acetoacetate available to supply to other organs because it lacks this particular CoA transferase.

Ketone bodies can be regarded as a water-soluble, transportable form of acetyl units. Fatty acids are released by adipose tissue and converted into acetyl units by the liver, which then exports them as acetoacetate. As might be expected, acetoacetate also has a regulatory role. *High levels of acetoacetate in the blood signify an abundance of acetyl units and lead to a decrease in the rate of lipolysis in adipose tissue.*

Certain pathological conditions can lead to a life-threatening rise in the blood levels of the ketone bodies. Most common of these conditions is diabetic ketosis in patients with insulin-dependent diabetes mellitus. The absence of insulin has two major biochemical consequences. First, the liver cannot absorb glucose and consequently cannot provide oxaloacetate to process fatty acid-derived acetyl CoA. Second, insulin normally curtails fatty acid mobilization by adipose tissue. The liver thus produces large amounts of ketone bodies, which are moderately strong acids. The result is severe acidosis. The decrease in pH impairs tissue function, most importantly in the central nervous system.