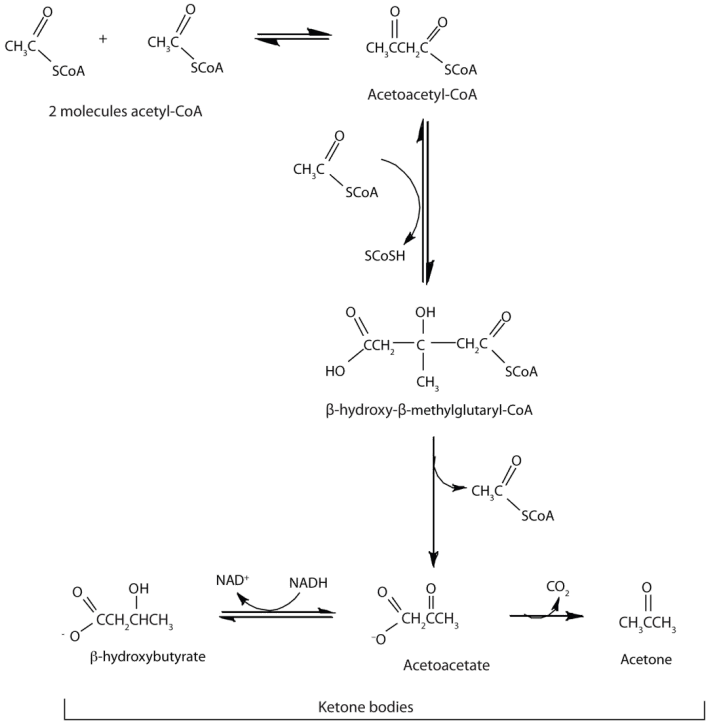
24.6: Ketone Bodies and Ketoacidosis

Learning Objectives

- Describe the structure and function of ketone bodies.

In the liver, most of the acetyl-CoA obtained from fatty acid oxidation is oxidized by the citric acid cycle. However, some of the acetyl-CoA is used to synthesize a group of compounds known as *ketone bodies*: acetoacetate, β-hydroxybutyrate, and acetone. Two acetyl-CoA molecules combine, in a reversal of the final step of β-oxidation, to produce acetoacetyl-CoA. The acetoacetyl-CoA reacts with another molecule of acetyl-CoA and water to form β-hydroxy-β-methylglutaryl-CoA, which is then cleaved to acetoacetate and acetyl-CoA. Most of the acetoacetate is reduced to β-hydroxybutyrate, while a small amount is decarboxylated to carbon dioxide and acetone.



The acetoacetate and β-hydroxybutyrate synthesized by the liver are released into the blood for use as a metabolic fuel (to be converted back to acetyl-CoA) by other tissues, particularly the kidney and the heart. Thus, during prolonged starvation, ketone bodies provide about 70% of the energy requirements of the brain. Under normal conditions, the kidneys excrete about 20 mg of ketone bodies each day, and the blood levels are maintained at about 1 mg of ketone bodies per 100 mL of blood.

In starvation, diabetes mellitus, and certain other physiological conditions in which cells do not receive sufficient amounts of carbohydrate, the rate of fatty acid oxidation increases to provide energy. This leads to an increase in the concentration of acetyl-CoA. The increased acetyl-CoA cannot be oxidized by the citric acid cycle because of a decrease in the concentration of oxaloacetate, which is diverted to glucose synthesis. In response, the rate of ketone body formation in the liver increases further, to a level much higher than can be used by other tissues. The excess ketone bodies accumulate in the blood and the urine, a condition referred to as *ketosis*. When the acetone in the blood reaches the lungs, its volatility causes it to be expelled in the breath. The sweet smell of acetone, a characteristic of ketosis, is frequently noticed on the breath of severely diabetic patients.

Because two of the three kinds of ketone bodies are weak acids, their presence in the blood in excessive amounts overwhelms the blood buffers and causes a marked decrease in blood pH (to 6.9 from a normal value of 7.4). This decrease in pH leads to a serious condition known as *acidosis*. One of the effects of acidosis is a decrease in the ability of hemoglobin to transport oxygen in the blood. In moderate to severe acidosis, breathing becomes labored and very painful. The body also loses fluids and becomes dehydrated as the kidneys attempt to get rid of the acids by eliminating large quantities of water. The lowered oxygen supply and

dehydration lead to depression; even mild acidosis leads to lethargy, loss of appetite, and a generally run-down feeling. Untreated patients may go into a coma. At that point, prompt treatment is necessary if the person's life is to be saved.
