Oxidation of Fatty Acids and Ketogenesis

By

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BIOMEDICAL IMPORTANCE

Although fatty acids are both oxidized to acetyl-CoA and synthesized from acetyl-CoA, fatty acid oxidation is not the simple reverse of fatty acid biosynthesis but an entirely different process taking place in a separate compartment of the cell.

Each step in fatty acid oxidation involves acyl-CoA derivatives catalyzed by separate enzymes, utilizes NAD+ and FAD as coenzymes, and generates ATP. It is an aerobic process, requiring the presence of oxygen.

BIOMEDICAL IMPORTANCE

Increased fatty acid oxidation is a characteristic of starvation and of diabetes mellitus, leading to **ketone body production by the liver (ketosis).**

Because gluconeogenesis is dependent upon fatty acid oxidation, any impairment in fatty acid oxidation leads to **hypoglycemia.**

Fatty Acids Are Activated Before Being Catabolized

In the presence of ATP and coenzyme A, the enzyme **acyl-CoA synthetase (thiokinase)** catalyzes the conversion of a fatty acid (or free fatty acid) to an "active fatty acid" or acyl-CoA, which uses one high-energy phosphate with the formation of AMP and PPi (Figure 22–1).

Long-Chain Fatty Acids Penetrate the Inner Mitochondrial Membrane as Carnitine Derivatives

Carnitine (β-hydroxy-γ-trimethylammonium butyrate) is widely distributed and is particularly abundant in muscle.

OXIDATION OF FATTY ACIDS INVOLVES SUCCESSIVE CLEAVAGE WITH RELEASE OF ACETYL-CoA

two carbons at a time are cleaved from acyl-CoA molecules, starting at the carboxyl end. The chain is broken between the α(2)- and β(3)-carbon atoms—hence the name β-oxidation. The two-carbon units formed are acetyl-CoA; thus, palmitoyl-CoA forms eight acetyl-CoA molecules.

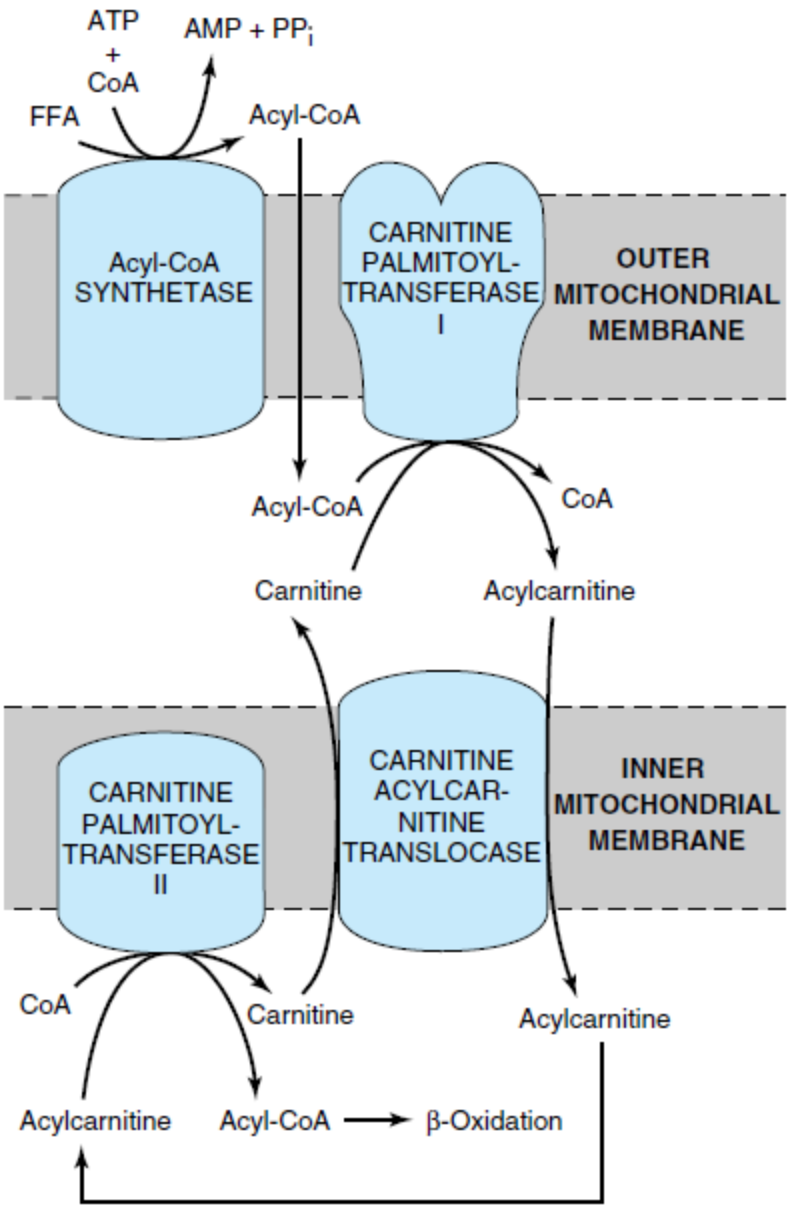

Figure 22–1. Role of carnitine in the transport of

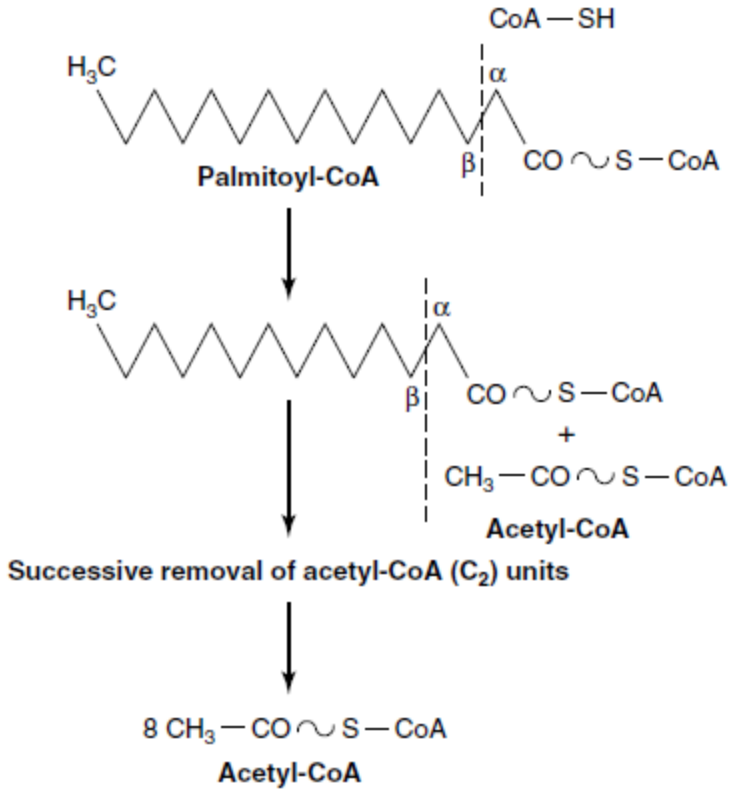

Figure 22–2. Overview of β-oxidation of fatty acids.

The Cyclic Reaction Sequence Generates $FADH_2$ & NADH

Several enzymes, known collectively as "fatty acid oxidase," are found in the mitochondrial matrix or inner membrane adjacent to the respiratory chain. These catalyze the oxidation of acyl-CoA to acetyl-CoA, the system being coupled with the phosphorylation of ADP to ATP (Figure 22–3).

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OXIDATION OF FATTY ACIDS PATHWAY

The first step is the removal of two hydrogen atoms from the 2(α)- and 3(β)-carbon atoms, catalyzed by **acyl-CoA dehydrogenase and requiring FAD. This results** in the formation of Δ2-*trans-enoyl-CoA and* FADH2.

The reoxidation of FADH2 by the respiratory chain requires the mediation of another flavoprotein, termed **electron-transferring flavoprotein** .

OXIDATION OF FATTY ACIDS PATHWAY

Water is added to saturate the double bond and form 3-hydroxyacyl-CoA, catalyzed by **2-enoyl-CoA hydratase. The 3-hydroxy derivative undergoes further** dehydrogenation on the 3-carbon catalyzed by **L(+)-3-hydroxyacyl-CoA dehydrogenase to form the corresponding** 3-ketoacyl-CoA compound.

In this case, NAD+ is the coenzyme involved. Finally, 3-ketoacyl-CoA is split at the 2,3- position by **thiolase (3-ketoacyl-**CoA-thiolase), forming acetyl-CoA and a new acyl-CoA two carbons shorter than the original acyl-CoA molecule

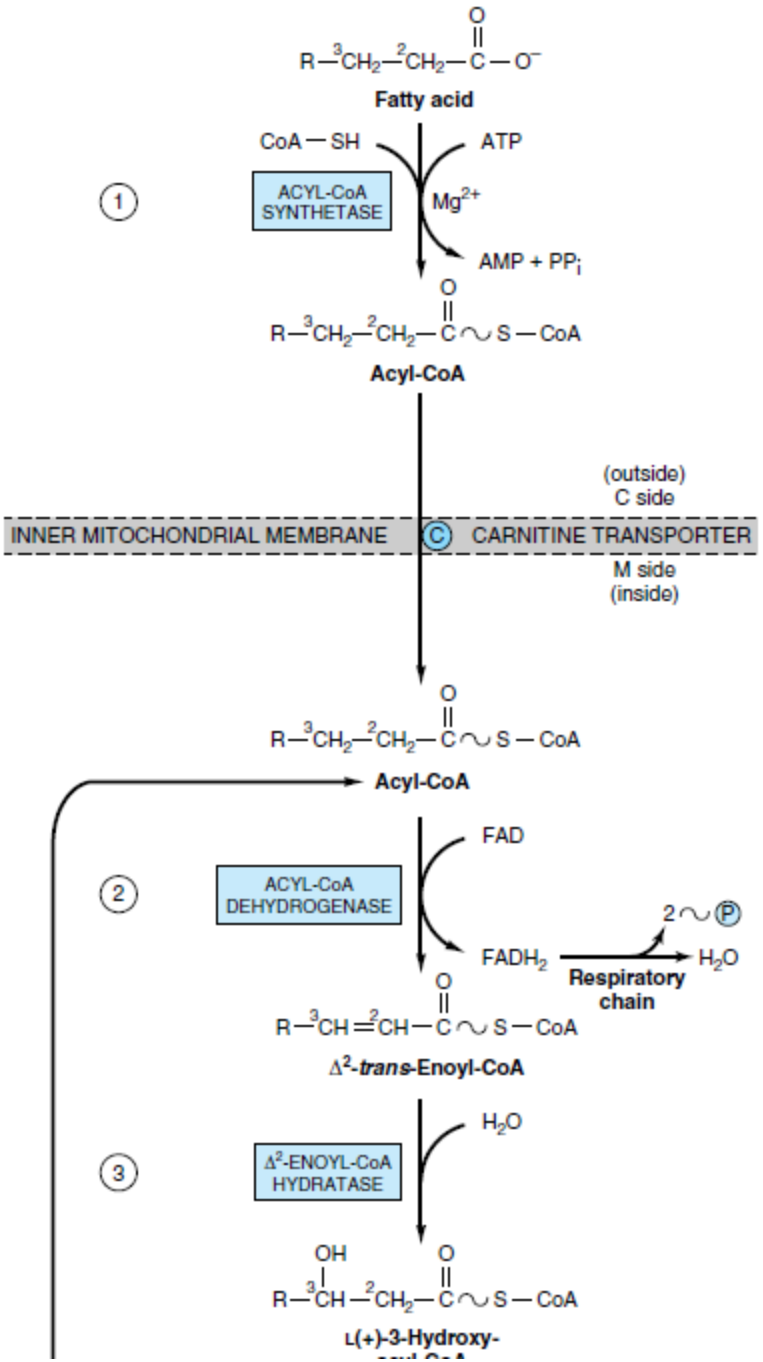


Figure 22–3. β-Oxidation of fatty acids. Long-chain acyl-CoA is cycled through reactions 2–5, acetyl-CoA being split off, each cycle, by thiolase (reaction 5). When the acyl radical is only four carbon atoms in length, two acetyl-CoA molecules are formed in reaction 5.

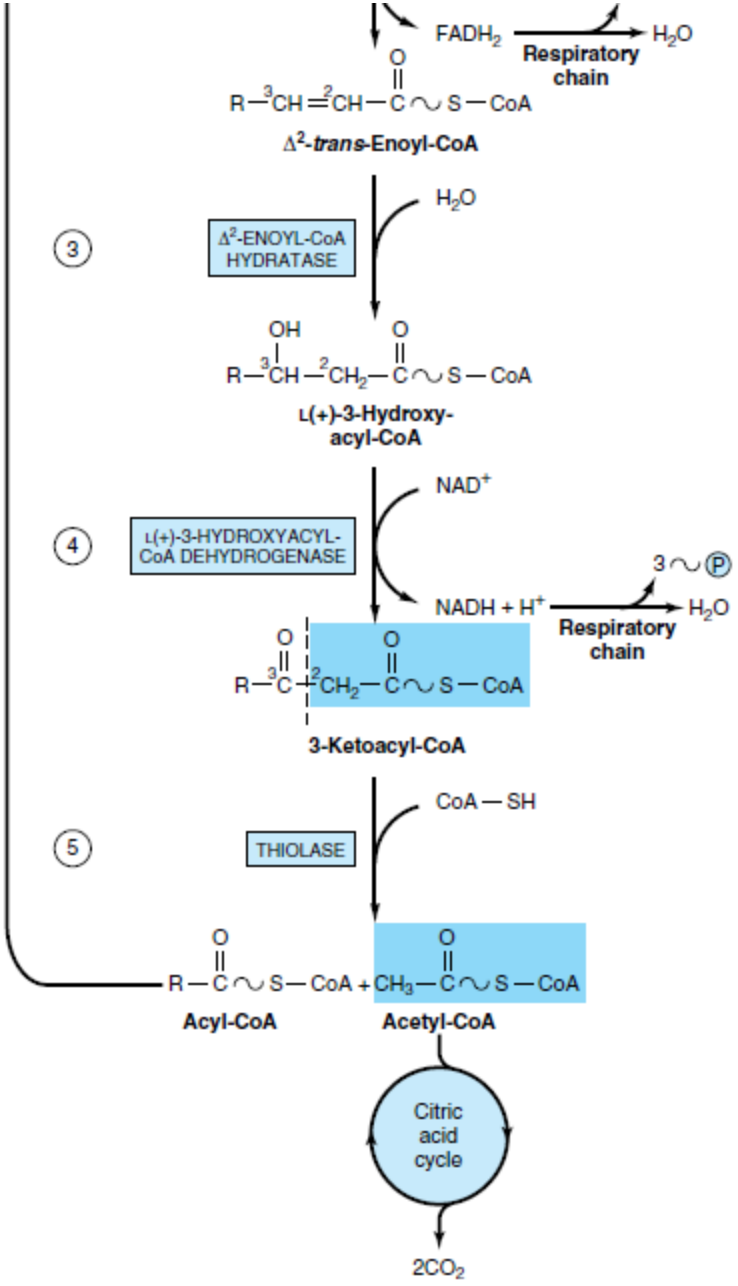
citric acid cycle (which is also found within the mitochondria), the complete oxidation of fatty acids is achieved.

Oxidation of a Fatty Acid With an Odd Number of Carbon Atoms Yields Acetyl-CoA Plus a Molecule of Propionyl-CoA

Fatty acids with an odd number of carbon atoms are oxidized by the pathway of β-oxidation, producing acetyl-CoA, until a three-carbon (propionyl-CoA) residue remains. This compound is converted to succinyl-CoA, a constituent of the citric acid cycle (Figure 19–2). Hence, **the propionyl residue from an odd-chain fatty acid is the only part of a fatty acid that is glucogenic.**

Oxidation of Fatty Acids Produces a Large Quantity of ATP

Transport in the respiratory chain of electrons from $FADH_2$ and NADH will lead to the synthesis of five high-energy phosphates (Chapter 12) for each of the first seven acetyl-CoA molecules formed by β-oxidation of palmitate ($7 \times 5 = 35$). A total of 8 mol of acetyl-CoA is formed, and each will give rise to 12 mol of ATP on oxidation in the citric acid cycle, making $8 \times$



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Peroxisomes Oxidize Very Long Chain Fatty Acids

A modified form of β-oxidation is found in peroxisomes and leads to the formation of acetyl-CoA and H_2O_2 (from the flavoprotein-linked dehydrogenase step), which is broken down by catalase. Thus, this dehydrogenation in peroxisomes is not linked directly to phosphorylation and the generation of ATP. The system facilitates the oxidation of very long chain fatty acids (eg, C_{20}, C_{22}). These enzymes are induced by

* ΔG for the ATP reaction, as explained in Chapter 17.

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KETOGENESIS OCCURS WHEN THERE IS A HIGH RATE OF FATTY ACID OXIDATION IN THE LIVER

Under metabolic conditions associated with a high rate of fatty acid oxidation, the liver produces considerable quantities of **acetoacetate and 3-hydroxybutyrate** (β-hydroxybutyrate). Acetoacetate continually undergoes spontaneous decarboxylation to yield **acetone.**

These three substances are collectively known as the **ketone bodies (also called acetone bodies]** (Figure 22–5).

Acetoacetate and 3-hydroxybtyrate are interconverted by the mitochondrial enzyme **D()-3-hydroxybutyrate dehydrogenase.**

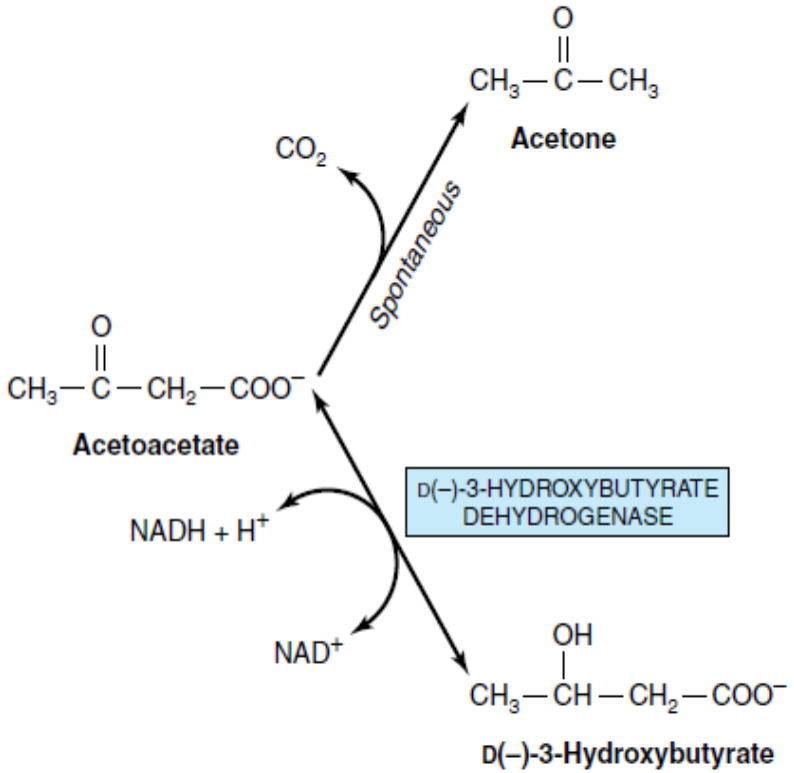

Figure 22–5. Interrelationships of the ketone bodies. D(–)-3-hydroxybutyrate dehydrogenase is a mitochondrial enzyme.

tyrate are interconverted by the mitochondrial enzyme **D(−)-3-hydroxybutyrate dehydrogenase;** the equilibrium is controlled by the mitochondrial [NAD^+]/[NADH] ratio, ie, the **redox state.** The concentration of total ketone bodies in the blood of well-fed mammals does not normally exceed 0.2 mmol/L except in ruminants, where 3-hydroxybutyrate is formed continuously from butyric acid (a product of ruminal fermentation) in the rumen wall. In vivo, the liver appears to be the only organ in nonruminants to add significant quantities of ketone bodies to the blood. Extrahepatic tissues utilize them as respiratory substrates. The net flow of ketone bodies from the liver to the extrahepatic tissues results from active hepatic synthesis coupled with very low utilization. The reverse situation occurs in extrahepatic tissues (Figure 22–6).

3-Hydroxy-3-Methylglutaryl-CoA (HMG-CoA) Is an Intermediate in the Pathway of Ketogenesis

Enzymes responsible for ketone body formation are associated mainly with the mitochondria. Two acetyl-CoA molecules formed in β-oxidation condense with one another to form acetoacetyl-CoA by a reversal of the **thiolase** reaction. Acetoacetyl-CoA, which is the

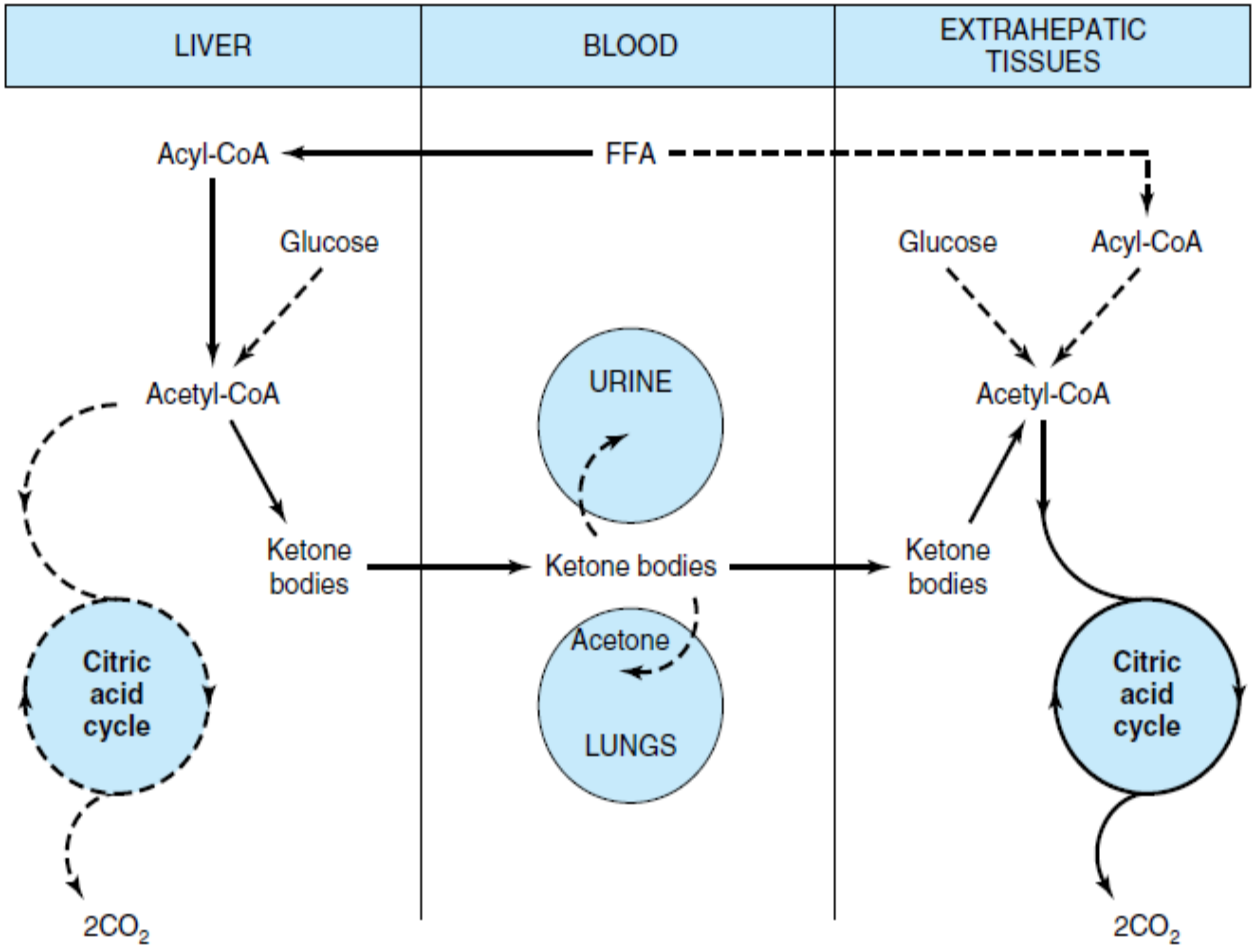

Figure 22–6. Formation, utilization, and excretion of ketone bodies. (The main pathway is indicated by the solid arrows.)

Pathway of Ketogenesis

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Acetoacetyl-CoA, which is the starting material for ketogenesis, also arises directly from the terminal four carbons of a fatty acid during β-oxidation (Figure 22–7).

Pathway of Ketogenesis

Condensation of acetoacetyl-CoA with another molecule of acetyl-CoA by **3-hydroxy-3-methylglutaryl-CoA synthase forms** HMG-CoA. **3-Hydroxy-3-ethylglutaryl-CoA lyase** then causes acetyl-CoA to split off from the HMGCoA, leaving free acetoacetate. The carbon atoms split off in the acetyl-CoA molecule are derived from the original acetoacetyl-CoA molecule.

Both enzymes must be present in mitochondria for ketogenesis to take place. 3-Hydroxybutyrate is quantitatively the predominant ketone body present in the blood and urine in ketosis.

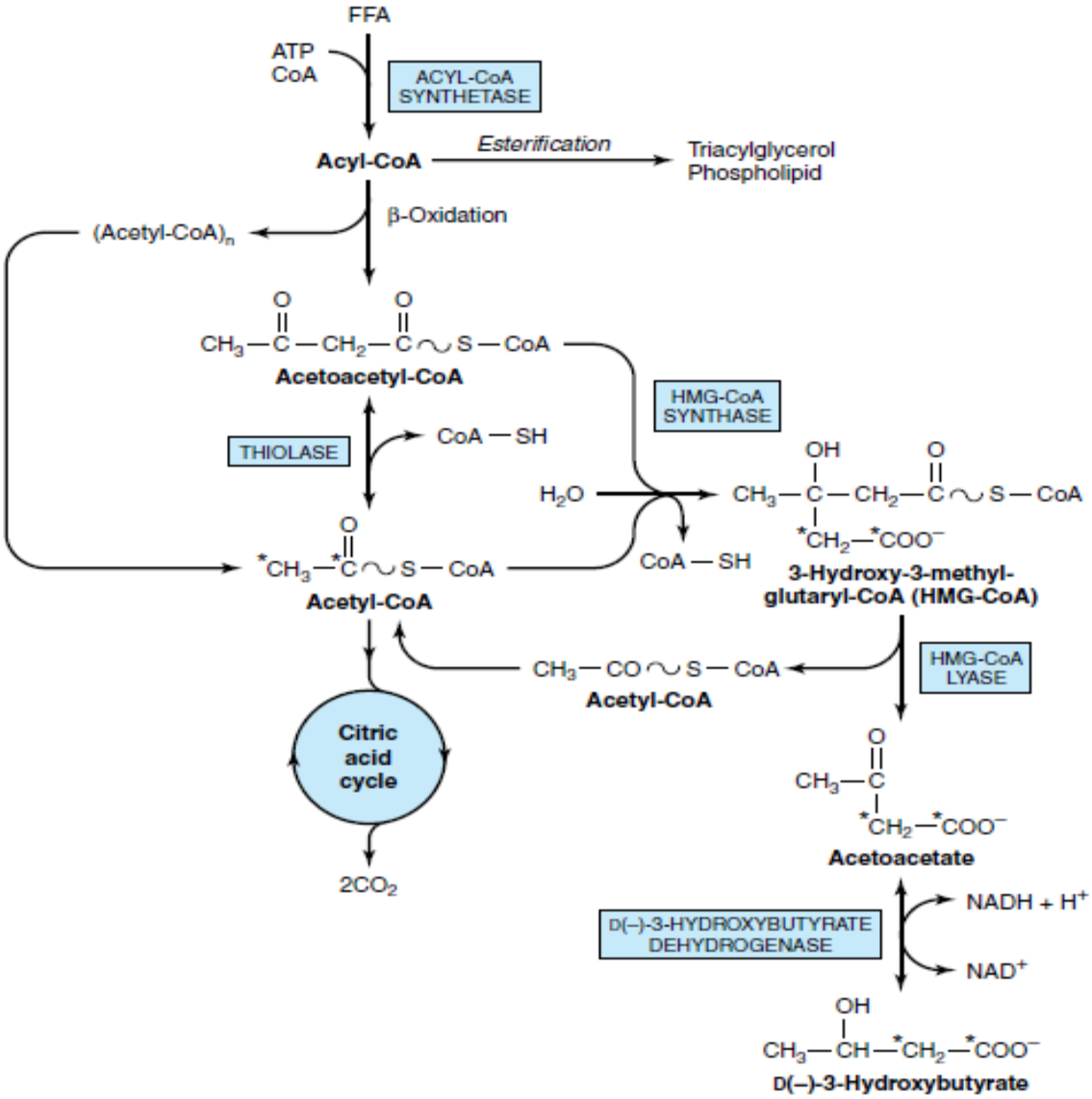

Figure 22–7. Pathways of ketogenesis in the liver. (FFA, free fatty acids; HMG, 3-hydroxy-3-methylglutaryl.)

Ketone Bodies Serve as a Fuel for Extrahepatic Tissues

In extrahepatic tissues, acetoacetate is activated to acetoacetyl-CoA by **succinyl-CoA-acetoacetate CoA transferase. CoA is transferred from succinyl-CoA to** form acetoacetyl-CoA (Figure 22–8).

The acetoacetyl- CoA is split to acetyl-CoA by thiolase and oxidized in the citric acid cycle. In most cases, **ketonemia is due to increased production**

of ketone bodies by the liver rather than to a

deficiency in their utilization by extrahepatic tissues.

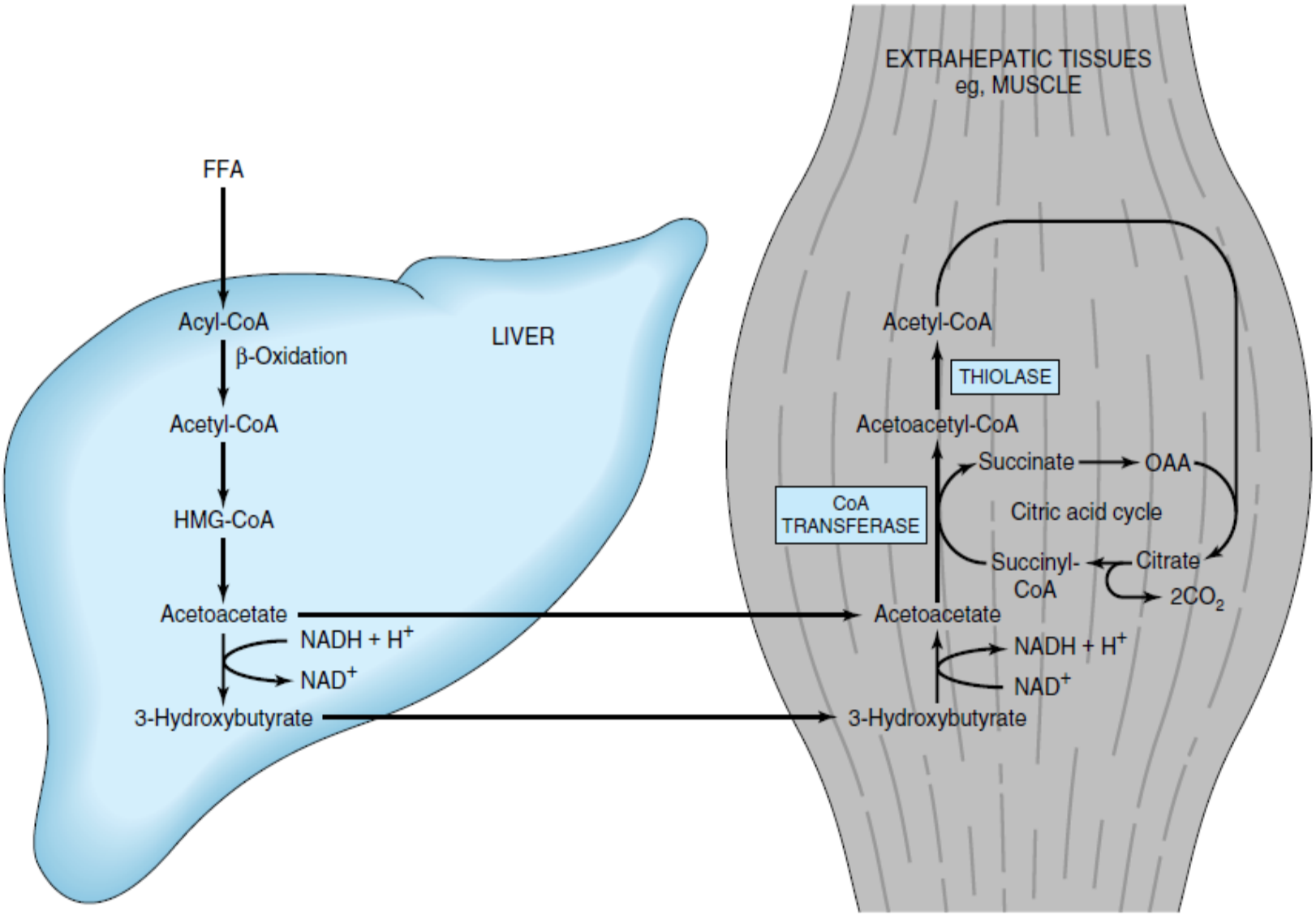

Figure 22–8. Transport of ketone bodies from the liver and pathways of utilization and oxidation in extrahepatic tissues.

KETOGENESIS IS REGULATED AT THREE CRUCIAL STEPS

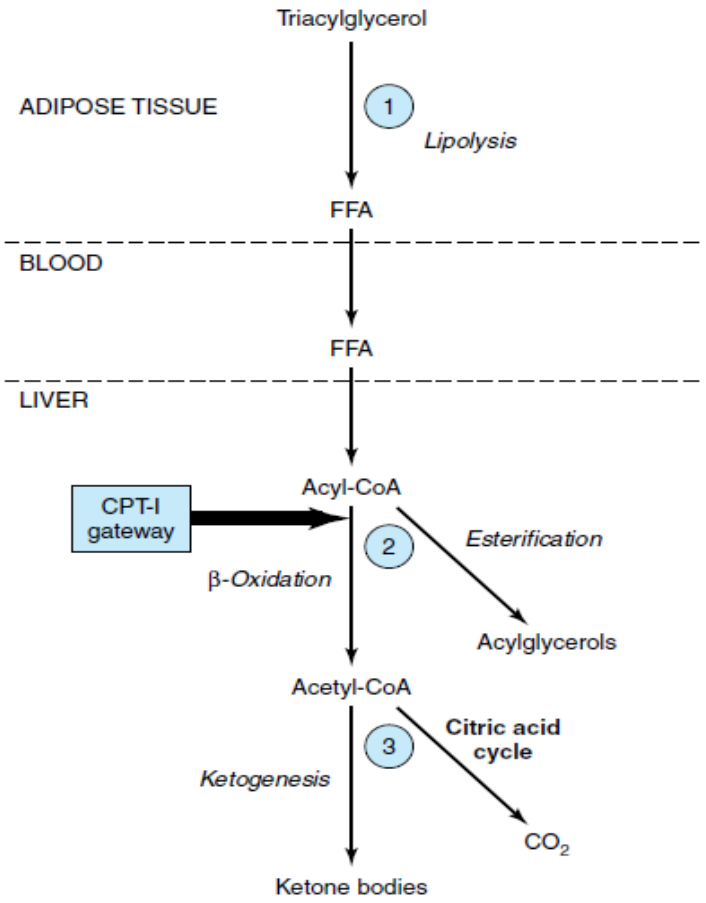

Figure 22–9. Regulation of ketogenesis. ①–③ show three crucial steps in the pathway of metabolism of free fatty acids (FFA) that determine the magnitude of ketogenesis. (CPT-I, carnitine palmitoyltransferase-I.)

(3) In turn, the acetyl-CoA formed in β-oxidation is oxidized in the citric acid cycle, or it enters the pathway of ketogenesis to form ketone bodies. As the level of serum free fatty acids is raised, proportionately more free fatty acid is converted to ketone bodies and less is oxidized via the citric acid cycle to CO_2. The partition of acetyl-CoA between the ketogenic pathway and the pathway of oxidation to CO_2 is so regulated that the total free energy captured in ATP which results from the oxidation of free fatty acids remains constant. This may be appreciated when it is realized that complete oxidation of 1 mol of palmitate involves a net production of 129 mol of ATP via β-oxidation and CO_2 production in the citric acid cycle (see above), whereas only 33 mol of ATP are produced when acetoacetate is the end product and only 21 mol when 3-hydroxybutyrate is the end product. Thus, ketogenesis may be regarded as a mechanism that allows the liver to oxidize increasing quantities of fatty acids within the constraints of a tightly coupled system of oxidative phosphorylation—without increasing its total energy expenditure.

Theoretically, a fall in concentration of oxaloacetate, particularly within the mitochondria, could impair the ability of the citric acid cycle to metabolize acetyl-CoA and divert fatty acid oxidation toward ketogenesis. Such a fall may occur because of an increase in the [NADH]/[NAD^+] ratio caused by increased β-oxidation affecting the equilibrium between oxaloacetate and malate and decreasing the concentration of oxaloacetate. However, pyruvate carboxylase, which catalyzes the conversion of pyruvate to oxaloacetate, is activated by acetyl-CoA. Consequently, when there are significant amounts of acetyl-CoA, there should be sufficient

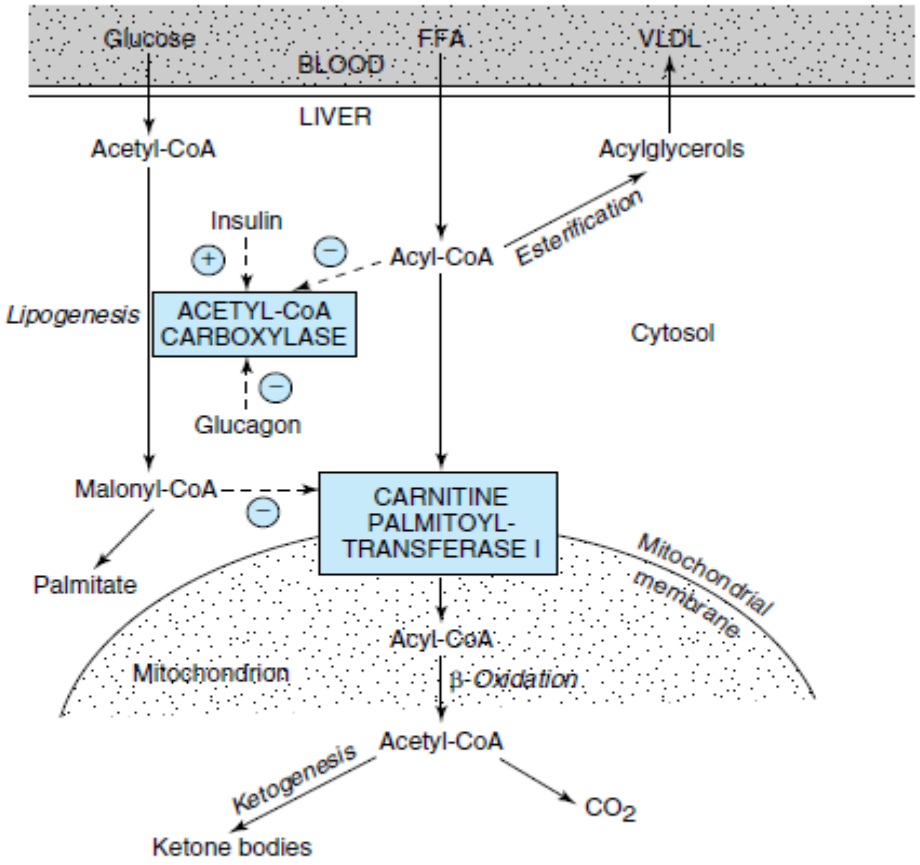

Figure 22–10. Regulation of long-chain fatty acid oxidation in the liver. (FFA, free fatty acids; VLDL, very low density lipoprotein.) Positive (⊕) and negative (⊖) regulatory effects are represented by broken arrows and substrate flow by solid arrows.

marily skeletal muscle and, when severe, the liver. The sulfonylurea drugs (**glyburide** [**glibenclamide**] and **tolbutamide**), used in the treatment of type 2 diabetes mellitus, reduce fatty acid oxidation and, therefore, hyperglycemia by inhibiting CPT-I.

syndrome occurs in individuals with a rare inherited absence of peroxisomes in all tissues. They accumulate C_{26}–C_{38} polyenoic acids in brain tissue and also exhibit a generalized loss of peroxisomal functions, eg, impaired bile acid and ether lipid synthesis.