ATP Production III: Fatty Acid Oxidation and Amino Acid Oxidation 2.11

Learning Objectives

- Describe the chemical structure of a triglyceride
- Describe how adipocyte lipolysis is regulated by catecholamines and insulin
- Describe the main route of glycerol oxidation
- Describe the role of carnitine in the import of fatty acids into mitochondria
- List the number of NADH, $FADH_2$, and acetyl CoA produced for each turn of the beta oxidation cycle
- Account for the number of beta oxidation cycles for palmitic acid
- List the number of NADH, $FADH_2$, and GTP produced for oxidation of acetyl CoA
- Account for the total numbers of ATP molecules produced by oxidation of palmitic acid
- List three chemicals that comprise the ketone bodies
- Distinguish between the terms glucogenic and ketogenic for amino acids
- List the amino acids that are exclusively ketogenic
- Recognize the amino acids that are exclusively glucogenic
- Name the amino acid that is required for feed into the urea cycle

FATS AND PROTEINS CONTRIBUTE 50% OF THE ENERGY CONTENT OF MANY DIETS

In the previous chapters, we saw how carbohydrates are metabolized through glycolysis to form pyruvate, producing some energy in the process. Pyruvate is then converted to acetyl CoA, which enters the TCA cycle to produce reducing equivalents. These reduced compounds, NADH and $FADH_2$, are then oxidized by the respiratory chain of the mitochondria to produce a proton electrochemical gradient that is then used to produce ATP. The typical American diet contains only about 49% of its calories as carbohydrates, with another 35% coming from fat and 16% from protein. Thus the fats and proteins must also be used to generate cellular energy. How are fats and proteins used to make ATP?

DEPOT FAT IS STORED AS TRIGLYCERIDES AND BROKEN DOWN TO GLYCEROL AND FATTY ACIDS FOR ENERGY

Most fatty acids in the body are stored as triglycerides (triacylglycerol, TAG; see Figure 2.11.1), the acyl esters of three fatty acids with a glycerol molecule. Blood carries triglycerides in special structures called **lipoproteins**, in which the water-insoluble lipids are coated with special proteins. These lipoproteins are made solely in the intestines and the liver. All tissues can also store triglycerides in lipid droplets in the cytoplasm,

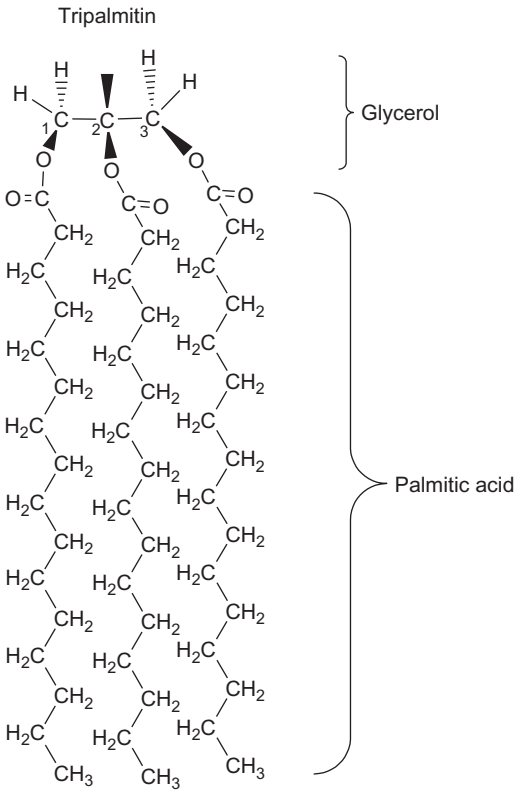

FIGURE 2.11.1 Structure of tripalmitin as an example of a triglyceride. These are stored in adipose tissue and released into the circulation. Lipase breaks down the triglyceride by hydrolyzing the ester bonds between the fatty acids carboxyl group and the glycerol hydroxyl group.

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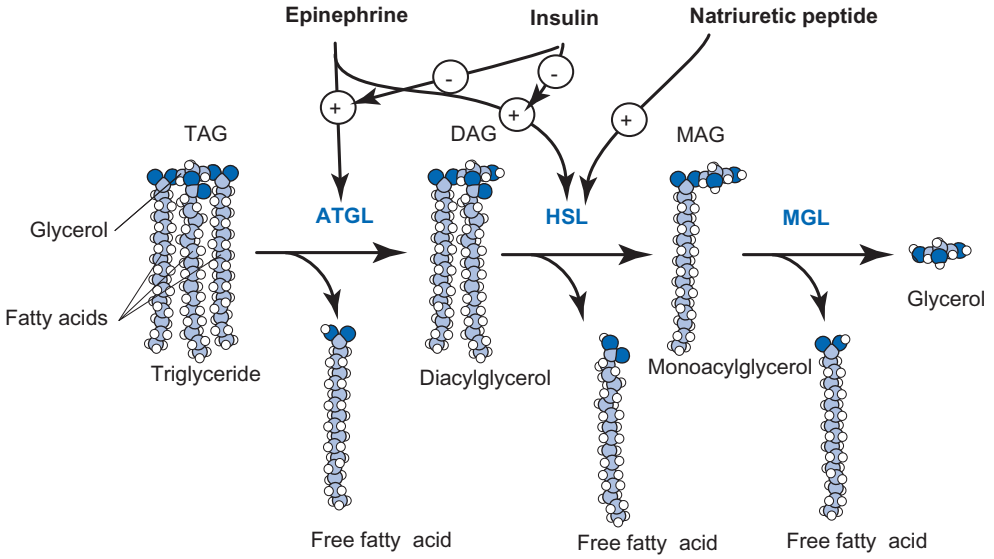

FIGURE 2.11.2 Adipocyte lipolysis. Adipose triglyceride lipase (ATGL) begins lipolysis by converting triglycerides (TAG) in the lipid droplet to diacylglycerol (DAG) and a free fatty acid. Hormone-sensitive lipase (HSL) continues the process by hydrolyzing a second fatty acid, producing monoacylglycerol (MAG). Monoacylglycerol lipase (MGL) then hydrolyzes the last fatty acid ester bond to produce glycerol and a third free fatty acid. Hormones and nerves control lipolysis by activating or inhibiting ATGL and HSL. Epinephrine can activate ATGL and HSL through β receptors and this action is blocked by insulin. Epinephrine can inhibit ATGL and HSL through α_2 receptors. Natriuretic peptides also can activate lipolysis through independent mechanisms.

but adipocytes contain very large lipid droplets that may occupy most of the cell. The adipocytes are specialized for storage and release of lipids for energy. The circulating triglycerides can be hydrolyzed to form glycerol and three fatty acids through the action of lipoprotein **lipase** that both hydrolyzes the lipid and acts as a bridge in lipoprotein uptake. Lipid droplets can also be hydrolyzed for energy within the cell, but the adipocyte alone can export the glycerol and free fatty acids derived from the lipid store.

Lipid droplets are surrounded by a phospholipid monolayer to which is absorbed the protein **perilipin**, which has five members (PLIN1-5) that are distributed in different tissues. In adipose tissue, the major form is PLIN1. PLIN1 stabilizes the lipid droplet against lipolysis. Lipolysis begins by **ATGL, adipose triglyceride lipase**, that converts tricacylglycerides (TAG) into diacylglycerol (DAG) and a free fatty acid (FA). **Hormone-sensitive lipase** (HSL) then converts the DAG into monoacylglycerol (MAG) and a free fatty acid. The MAG is further converted to glycerol and an FA by the enzyme **monoglycerol lipase**. Control of this process is hormonal and neural, as shown in Figures 2.11.2 and 2.11.3. The catecholamines, derived either from circulating epinephrine or from sympathetic nervous stimulation, can either activate or inhibit lipolysis. Insulin inhibits lipolysis, and natriuretic peptide stimulates it.

In Chapter 2.9, we learned that epinephrine mobilizes liver glycogen stores by activating glycogenolysis through a G_s mechanism. Epinephrine can also mobilize lipid stores by activating lipolysis through a G_s mechanism, as shown in Figure 2.11.3. Binding of catecholamines to β_1 or β_2 receptors on the adipocyte is followed by the activation of adenylyl cyclase and an increase in 3′,5′-cyclic AMP in the adipocyte cytosol. This activates protein kinase A (PKA) that phosphorylates a number of targets including perilipin, PLIN1, and HSL (hormone-sensitive lipase). PLIN1 binds ABHD5 (α/β hydrolase domain containing 5) that activates ATGL. Phosphorylation of PLIN1 releases the ABHD5 to activate ATGL. Simultaneously, HSL that was previously located in the cytosol binds to the lipid droplet where it participates in lipolysis.

Adipocytes also have α_2 receptors that are coupled to a G_i mechanism that inhibits adenylyl cyclase activity. Occupancy of these receptors has the opposite effect, an inhibition of lipolysis, as occupancy of the β receptors. Insulin inhibits lipolysis by activating cAMP phosphodiesterase, type 3B, by phosphorylation by PKB. This activated PDE-3B decreases the cAMP concentration, leading to inactivation of lipolysis.

Natriuretic peptide increases lipolysis by activation of HSL through phosphorylation by PKG, a cGMP-activated protein kinase.

GLYCEROL IS CONVERTED TO AN INTERMEDIATE OF GLYCOLYSIS

Plasma glycerol is taken up by tissues and converted to α-glycerophosphate by an enzyme called **glycerol kinase**, by phosphorylating the glycerol with the terminal phosphate group of ATP. The glycerophosphate is converted to **dihydroxyacetone phosphate**

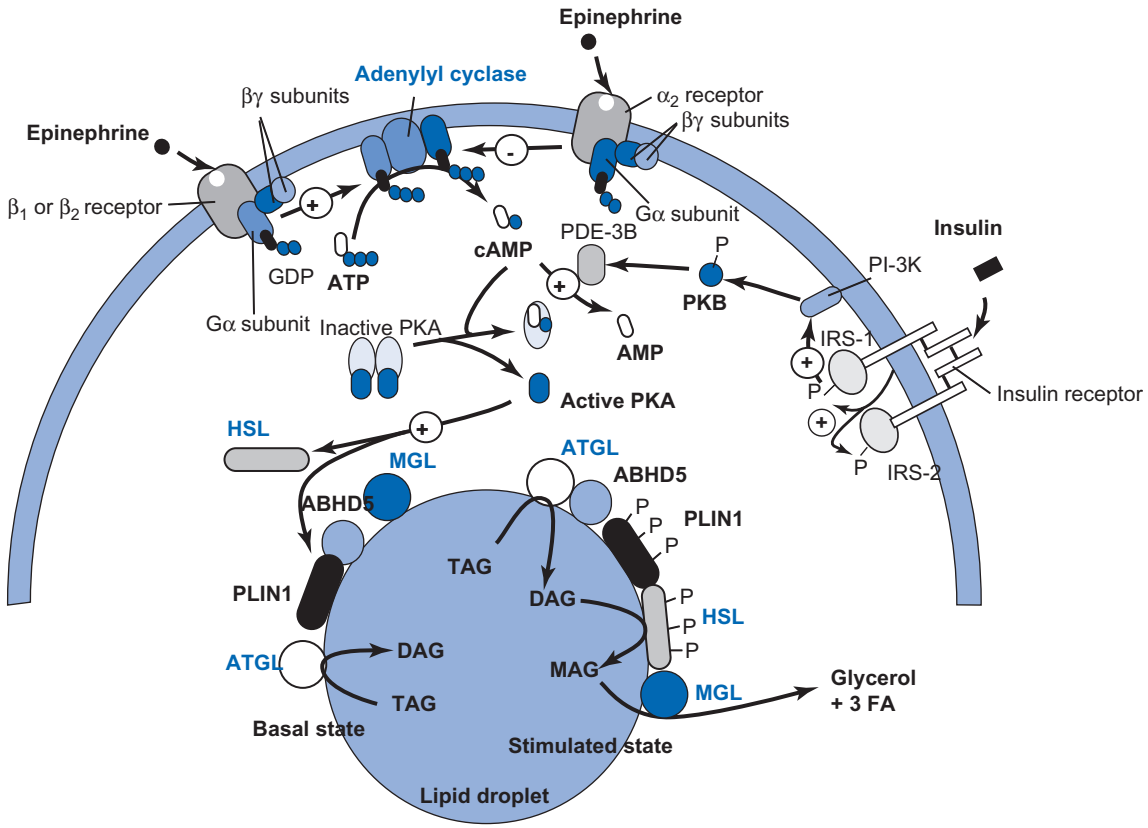

FIGURE 2.11.3 Control of lipolysis by hormones. Binding of epinephrine to β_1 or β_2 receptors activates adenylyl cyclase by the $G_{\alpha s}$ subunit. This increases formation of cAMP and therefore increases the concentration of cAMP in the cell. Increased cAMP activates protein kinase A that phosphorylates PLIN1 and HSL. Phosphorylation of PLIN1 releases ABHD5 that then binds to ATGL and activates it. PKA phosphorylation of HSL results in its translocation from the cytosol to the lipid droplet surface. In this position, the enzymes completely hydrolyze TAG to glycerol and 3 fatty acids, which are exported out of the adipocyte. Lipolysis is inhibited by binding of epinephrine to α_2 receptors that inhibit adenylyl cyclase. Insulin binding to its receptor results in a cascade that activates PKB that phosphorylates cAMP phosphodiesterase. This lowers the cAMP concentration and inhibits lipolysis.

by another enzyme, α-glycerophosphate dehydrogenase, requiring NAD^+, and thus the glycerol can enter into glycolysis and the TCA cycle to be fully oxidized to CO_2 and H_2O to provide energy as ATP to the cell (see Figure 2.11.4).

FATTY ACIDS ARE METABOLIZED IN THE MITOCHONDRIA AND PEROXISOMES

Free fatty acids are formed in the cytoplasm by the action of lipase on stored triglycerides, but the fatty acids themselves are degraded and oxidized only in the mitochondria and peroxisomes. The fatty acids have surface activity (they lower the surface tension) and can impair membrane integrity. Therefore, the fatty acids are carried in solution by **fatty acid binding proteins**. These are low-molecular-weight proteins (about 14,000 Da) that probably have a dual function of decreasing the concentration of the free fatty acids and of enhancing the diffusion through the cytoplasm by carrying the fatty acids.

The first step in the metabolism of free fatty acids is their import into the inner mitochondrial matrix by combining with a carrier substance, **carnitine** (see Figure 2.11.5). First, the fatty acid is combined with coenzyme A by the enzyme **thiokinase**, which hydrolyzes ATP to AMP and PPi. This fatty acyl CoA is then transferred to carnitine by the enzyme **carnitine fatty acyl transferase**. Once the fatty acyl carnitine is transferred to the mitochondrial matrix, it is once again combined with CoA to form fatty acyl CoA. In this form and in this place, the fatty acid can be oxidized in a systematic way to produce energy.

BETA OXIDATION CLEAVES TWO CARBON PIECES OFF FATTY ACIDS

Beta oxidation is the process by which fatty acids are processed progressively to release two-carbon segments in the form of acetyl CoA. This series of reactions is summarized in Figure 2.11.6. These reactions produce acetyl CoA and 1 $FADH_2$ and 1 NADH per turn of the beta oxidation cycle.

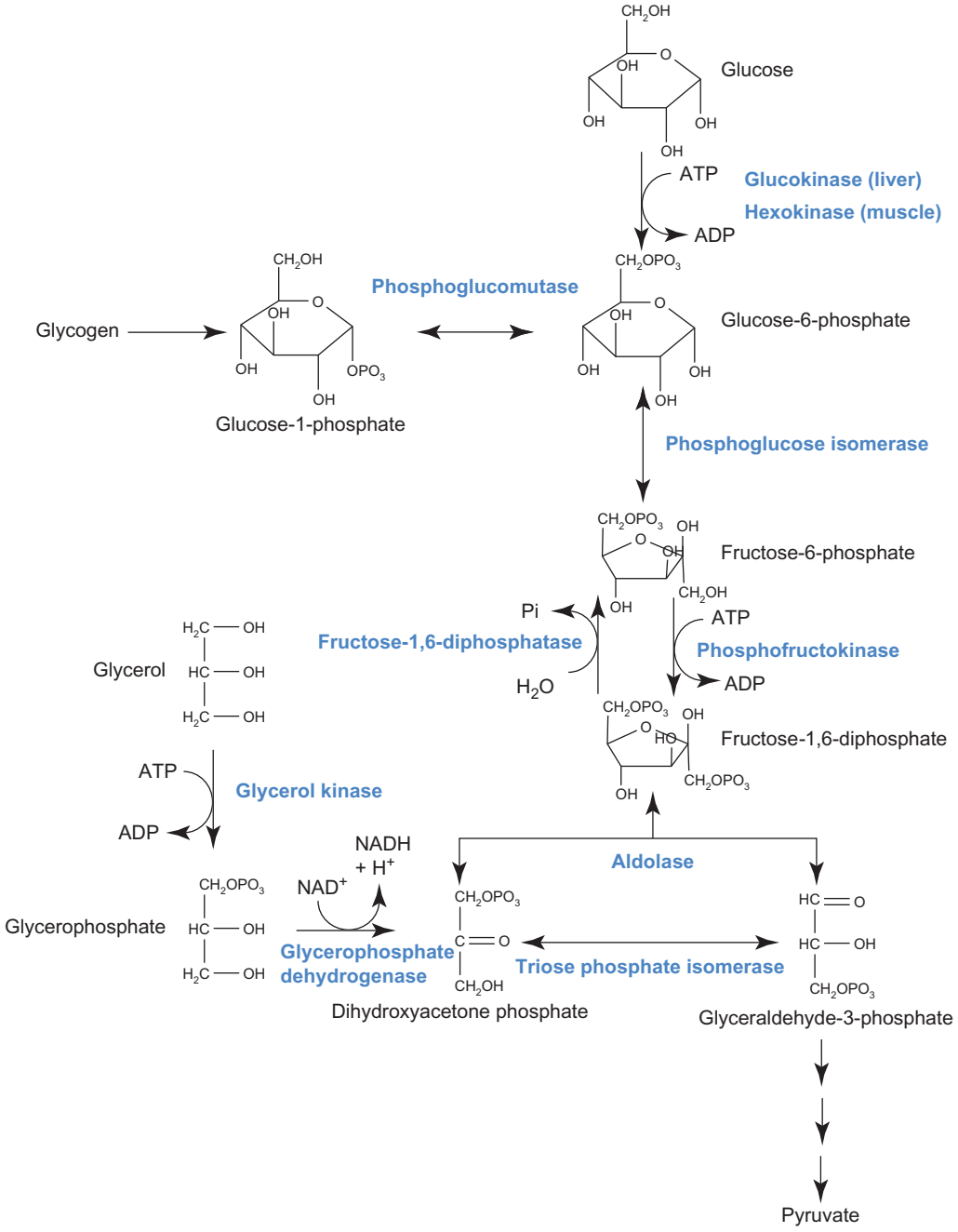

FIGURE 2.11.4 Metabolism of glycerol. Glycerol is phosphorylated and then converted into dihydroxyacetone phosphate, an intermediate in glycolysis.

EXAMPLE 2.11.1 ATP Yield from Glycerol

How much ATP is made from glycerol, under optimal conditions?

Glycerol requires 1 ATP per molecule for the conversion into glycerol phosphate. The glycerol phosphate is then converted to dihydroxyacetone phosphate with the production of 1 molecule of NADH. The dihydroxyacetone phosphate can then be oxidized fully to CO_2 through glycolysis and the TCA cycle as outlined in Chapters 2.9 and 2.10.

In the conversion to pyruvic acid, dihydroxyacetone phosphate generates 1 NADH and 2 ATP molecules per molecule of glycerol. The net effect of converting glycerol to pyruvic acid is -1 ATP + 2 ATP + 2 NADH = 1 ATP + 2 NADH = 6 ATP, assuming that the NADH are both oxidized with the generation of 2.5 ATP per NADH. The complete oxidation of pyruvate produces 4 NADH, 1 $FADH_2$, and 1 GTP. When the reducing equivalents are oxidized through the electron transport chain, this produces

$$4\ \text{NADH} \times 2.5\ \text{ATP/NADH} + 1\ \text{FADH}_2 \times 1.5\text{ATP/FADH}_2 + 1\ \text{GTP} \times 1\ \text{ATP/GTP} = 12.5\ \text{ATP}$$

Each glycerol molecule liberated from a triglyceride thus produces at most 18.5 **molecules ATP per molecule glycerol**. Glycerol has a gram molecular weight of 92 g mol^{-1}. It produces 18.5 moles ATP/92 g mol^{-1} = **0.20 mol g^{-1}**.

This is a little more than the energy derived from glucose: 32 moles ATP/180 g mol^{-1} = 0.18 mol g^{-1}.

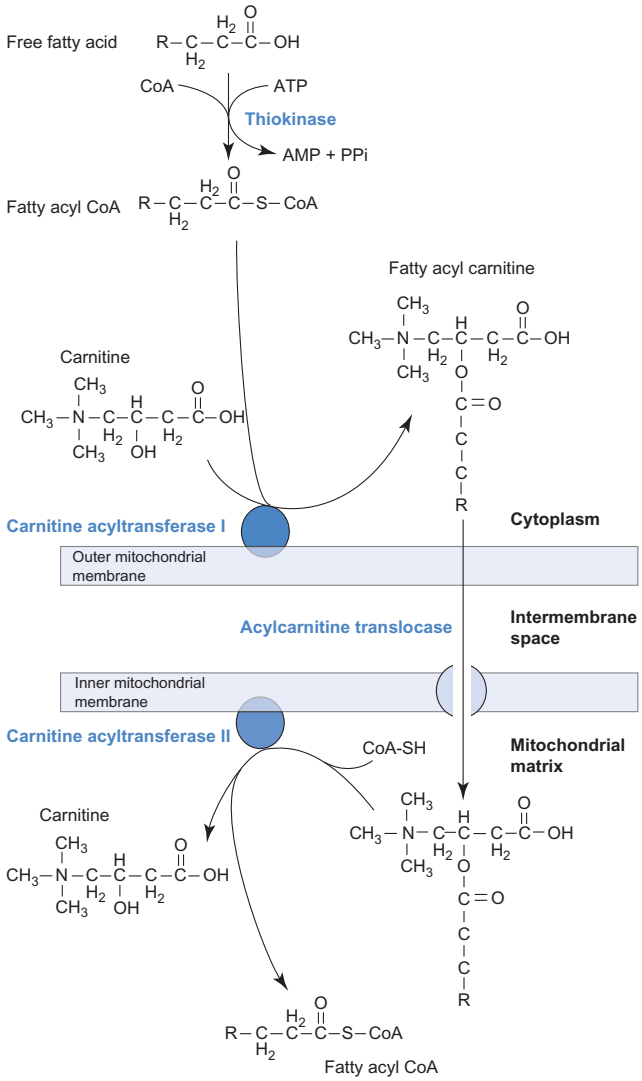

FIGURE 2.11.5 Involvement of carnitine in the entry of free fatty acids into the inner mitochondrial space. Fatty acids are combined with coenzyme A in a reaction that effectively costs 2 ATP molecules per reaction. The fatty acyl CoA is then converted to fatty acyl carnitine, which can penetrate the inner mitochondrial membrane. In the mitochondrial matrix, the carnitine is removed by a second, different carnitine acyl transferase.

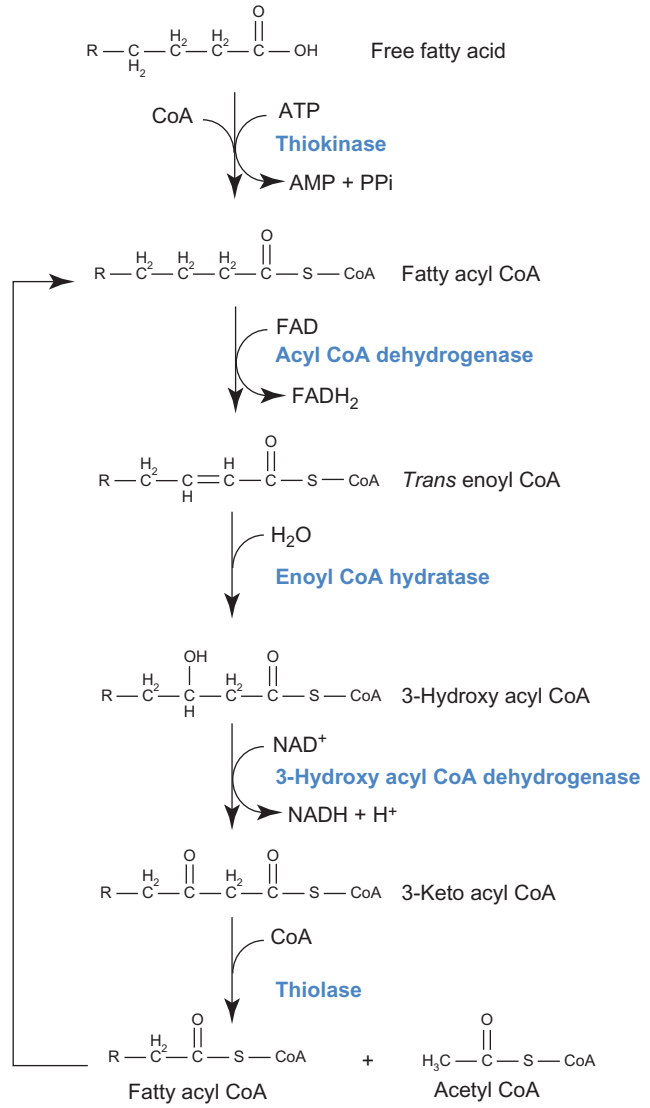

FIGURE 2.11.6 Beta oxidation of free fatty acid.

Once coupled with coenzyme A, the fatty acyl chain is oxidized, producing $FADH_2$. The fatty acyl chain is further oxidized by adding water and then removing two more hydrogens by the 3-hydroxy acyl CoA dehydrogenase, this time producing NADH. The final step in each turn of the beta oxidation cycle is the production of acetyl CoA and the regeneration of fatty acyl CoA, shortened by two carbon atoms. This shorter fatty acyl CoA reenters the beta oxidation cycle until, at the end, all of the chain is converted to acetyl CoA. In this way, palmitic acid, for example, will produce 8 acetyl CoA molecules and 7 $FADH_2$ molecules and 7 NADH molecules (there are only 7 because the last turn of the cycle produces two acetyl CoA molecules and so the last two carbons do not enter the cycle again to produce $FADH_2$ and NADH).

THE LIVER PACKAGES SUBSTRATES FOR ENERGY PRODUCTION BY OTHER TISSUES

During exercise, when fatty oxidation occurs rapidly, the liver packages acetyl CoA in a form that can be readily used by other tissues for the generation of energy. In the liver, two molecules of acetyl CoA combine to form acetoacetate. The acetoacetate that forms can then be converted to β-hydroxybutyric acid and, to a lesser extent, to acetone. All three of these compounds, **acetoacetate**, **β-hydroxybutyric acid**, and **acetone**, are referred to as **ketone bodies** (see Figure 2.11.7). They leave the liver cell and travel in the blood to the peripheral tissues, which take up the compounds and metabolize them for energy.

The combined concentration of the ketone bodies is typically less than about 3 mg%. Despite these low

EXAMPLE 2.11.2 ATP Yield from Fatty Acids

Each turn of the beta oxidation cycle produces NADH and $FADH_2$. For palmitic acid, $C_{16}H_{32}O_2$, a total of eight acetyl CoA molecules are produced from seven turns of the beta oxidation cycle. The NADH and $FADH_2$ feed into the electron transport chain to produce ATP. The total ATP produced from beta oxidation is thus

$$7\ \text{NADH/palmitate} \times 2.5\ \text{ATP/NADH} + 7\ \text{FADH}_2\text{/palmitate} \times 1.5\ \text{ATP/FADH}_2 = 28\ \text{ATP/palmitate}$$

Each acetyl CoA produced by beta oxidation enters the TCA cycle where it is further oxidized to CO_2 and produces reducing equivalents that are used by the ETC to make ATP. Each acetyl CoA molecule produces 3 NADH, 1 $FADH_2$, and 1 GTP molecule during a single turn of the TCA cycle. These are eventually used by the ETC to produce

$$3\ \text{NADH/acetyl CoA} \times 2.5\ \text{ATP/NADH} + 1\ \text{FADH}_2\text{/acetylCoA} \times 1.5\ \text{ATP/FADH}_2 + 1\ \text{GTP/acetyl} \times 1\ \text{ATP/GTP} = 10\ \text{ATP/acetyl CoA}$$

Since there are eight acetyl CoA molecules per palmitic acid produced from beta oxidation, the total ATP produced from acetyl CoA from palmitic acid is

$$10\ \text{ATP/acetyl CoA} \times 8\ \text{acetyl CoA/palmitate} = 80\ \text{ATP/palmitate}$$

We add this to the ATP produced from beta oxidation and subtract the two ATP needed to start beta oxidation from the initial thiokinase reaction to get

$$28\ \text{ATP from beta oxidation} + 80\ \text{ATP from TCA cycle} - 2\ \text{ATP from thiokinase reaction} = \mathbf{106\ ATP/palmitic\ acid}$$

EXAMPLE 2.11.3 Compare ATP Yield from Glucose to that of Tripalmitin

In Chapter 2.10, we found that the maximum yield of ATP from the complete oxidation of glucose was 32 ATP per glucose. This corresponds to 7 ATP per glucose from the oxidation of glucose to pyruvate, and 25 ATP from the complete oxidation of pyruvate to CO_2 and H_2O. The gram molecular weight of glucose is 180 g mol^{-1}, so the ATP production is

$$32\ \text{moles ATP/mol glucose} = 32\ \text{moles ATP}/180\ \text{g} = \mathbf{0.18\ mol\ ATP\ per\ g\ of\ glucose}$$

The gram molecular weight of tripalmitin is 807.3 g mol^{-1}, tripalmitin consisting of three palmitic acid molecules and one glycerol. We have calculated that glycerol gives rise to at most 18.5 ATP per glycerol, and each palmitic acid produces at most 106 ATP per palmitic. The total for tripalmitin is thus

$$336.5\ \text{moles ATP/mole tripalmitin} = 336.5\ \text{moles}/807.3\ \text{g} = \mathbf{0.42\ ATP\ per\ g\ of\ tripalmitin}$$

Thus fat has about 2.3 times as much energy stored per unit weight.

concentrations, the flux of energy to the metabolizing tissues can be great because the ketone bodies are taken up so quickly. The concentrations of the ketone bodies can occasionally rise to very high levels, a condition known as **ketosis**. This condition occurs whenever metabolism of fats is emphasized such as in starvation and in diabetes mellitus. In this case, the urine can contain ketones and the presence of acetone is sometimes detectable by its odor in the exhaled air.

In the peripheral tissues, acetoacetic acid is taken up and converted in the mitochondria to acetoacetyl CoA by the transfer of a CoA moiety from succinyl CoA, an intermediate in the TCA cycle. Since succinyl CoA is usually converted to succinate with the formation of 1 molecule of GTP, conversion of succinyl CoA to succinate in this reaction removes the potential synthesis of 1 molecule of GTP. So, although no energy in the form of ATP is directly involved in this transfer, it has a net cost of 1 molecule of ATP. The acetoacetyl CoA can then be converted to two molecules of acetyl CoA by **thiolase**, the same enzyme involved in the production of acetyl CoA from fatty acyl CoA during the beta oxidation pathway of fatty acids.

AMINO ACIDS CAN BE USED TO GENERATE ATP

Amino acids can be used to build body proteins and they can be broken down to yield energy. In the steady state of the adult, the body store of proteins remains constant and there is a constant throughput of amino acids, equal to the dietary intake, that is converted to metabolic energy. In the typical American diet, about 16% of the calories are provided by dietary protein.

Because the hepatic portal blood leaves the intestines and travels to the liver, the liver has the first opportunity to metabolize all the nutrients, including the amino acids absorbed from digested proteins in the intestinal lumen. The liver does several things: it catabolizes a

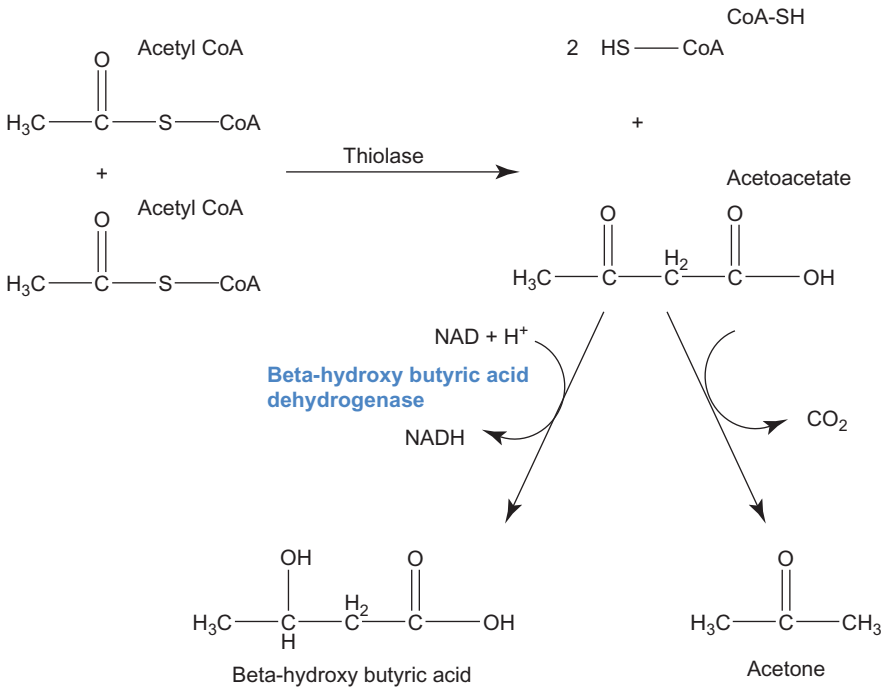

FIGURE 2.11.7 Formation of ketone bodies by the liver. During rapid lipid metabolism, when production of acetyl CoA outstrips the liver's ability to oxidize it, acetyl CoA coalesces to form acetoacetate, beta-hydroxybutyric acid, and acetone.

large fraction of the amino acids (57%), releases some unchanged into the general circulation (23%), and utilizes some 20% for synthesis of proteins that either remain in the liver or are released into the blood.

Catabolism of amino acids can be broadly categorized into two processes: the breakdown of amino acids to carbohydrate precursors and potentially leading to the formation of glucose; and transformations leading to acetyl CoA that result in the potential formation of ketone bodies. Amino acids that break down into carbohydrate precursors are called **glucogenic**; those leading to acetyl CoA are called **ketogenic**.

- **Leucine** and **lysine** are the only exclusively ketogenic amino acids.
- **Isoleucine, threonine, phenylalanine, tyrosine, and tryptophan** are both glucogenic and ketogenic.
- **Aspartatic acid, asparagine, glutamic acid, glutamine, alanine, arginine, histidine, glycine, serine, proline, valine, methionine**, and **cysteine** are glucogenic.

Because each amino acid has a different side chain, each amino acid is catabolized differently to produce energy and waste products. We will not go through all of these reactions for each of the amino acids. The overall fate of the amino acids is shown in Figure 2.11.8.

AMINO ACIDS ARE DEAMINATED TO ENABLE OXIDATION

Many amino acids share a common mechanism for the removal of the amino group to form intermediates in the TCA cycle or glycolytic cascade. This is a **transamination** reaction followed by a **dehydrogenation** reaction, as shown in Figure 2.11.9. The α-ketoglutarate formed in the transamination reaction in the mitochondria can then enter the TCA cycle. The deamination results in the liberation of ammonia. The reaction sequence shown is one of many such involved in the deamination of a variety of amino acids including phenylalanine, tyrosine, aspartate, cysteine, lysine, arginine, alanine, isoleucine, leucine, and valine. The reactions differ only in the α-keto acid formed following the transamination.

UREA IS PRODUCED DURING DEAMINATION AND IS ELIMINATED AS A WASTE PRODUCT

The ammonia released during deamination is removed from the blood almost entirely by conversion into **urea** in the **liver**. This occurs through another metabolic process called the **urea cycle** (see Figure 2.11.10). In this process, the ammonia is combined with bicarbonate ion to form **carbamoyl phosphate**. **The complete operation of the cycle requires continual input of aspartate**. This can be derived from transamination of oxaloacetic acid by glutamic acid, the reverse of the process shown in Figure 2.11.9. Since glutamate is the product of transamination with several amino acids, it can be replenished. Thus one of the amino groups of urea is derived from ammonia and the other is derived from amino groups on various amino acids, transaminated to glutamate.

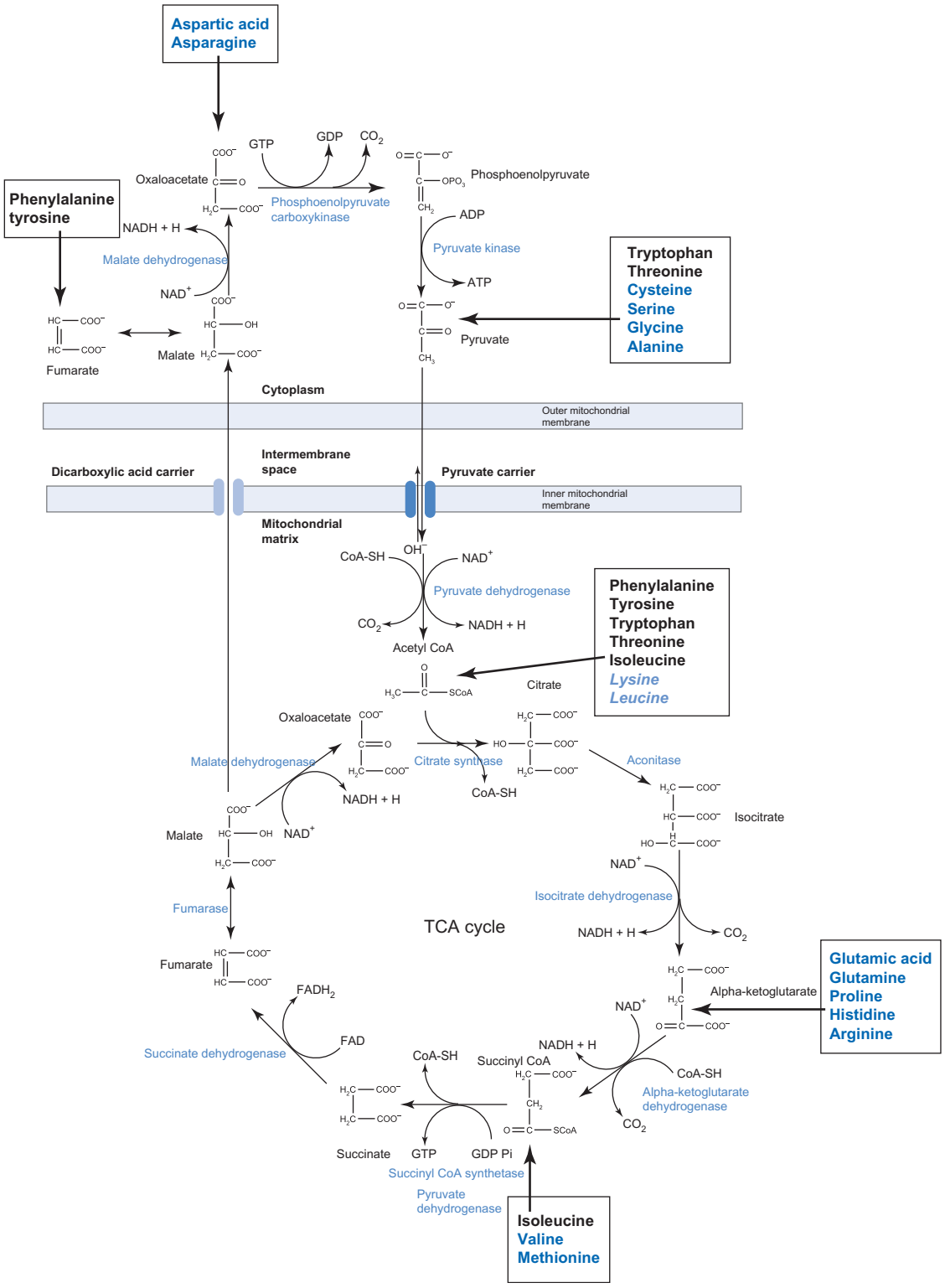

FIGURE 2.11.8 Metabolic entry points for the catabolism of the amino acids. Those amino acids that produce acetyl CoA are called ketogenic. These include leucine, lysine, phenylalanine, tyrosine, tryptophan, and isoleucine. Those amino acids that produce carbohydrate precursors that can be converted to glucose are called glucogenic. These include aspartic acid, asparagine, phenylalanine, tyrosine, tryptophan, alanine, cysteine, serine, threonine, glycine, glutamic acid, glutamine, proline, histidine, arginine, isoleucine, valine, and methionine. Only lysine and leucine are exclusively ketogenic. Exclusively ketogenic amino acids are in light blue italic; exclusively glucogenic are in dark blue; both ketogenic and glucogenic are in black.

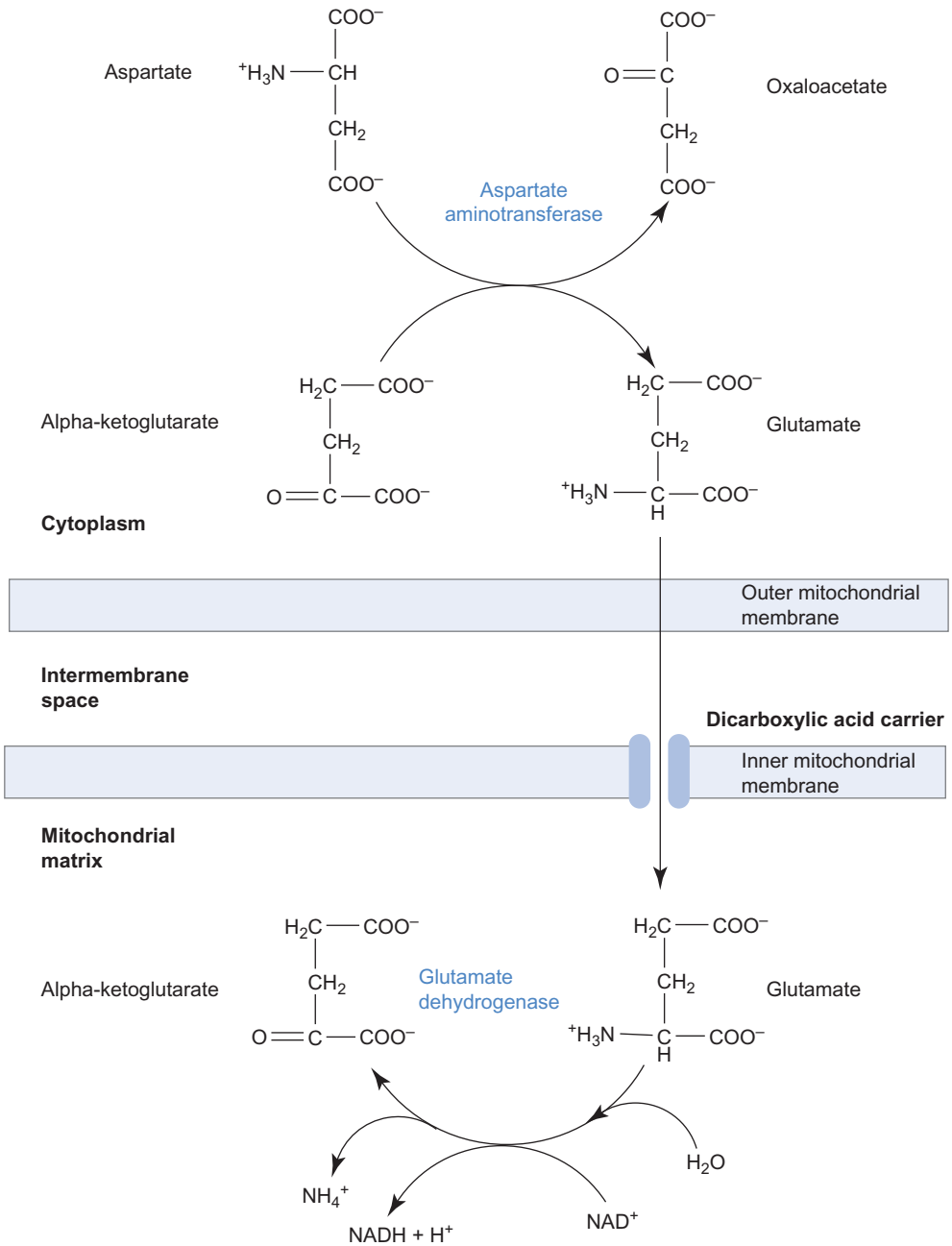

FIGURE 2.11.9 Deamination of amino acids by aminotransferase and glutamate dehydrogenase action.

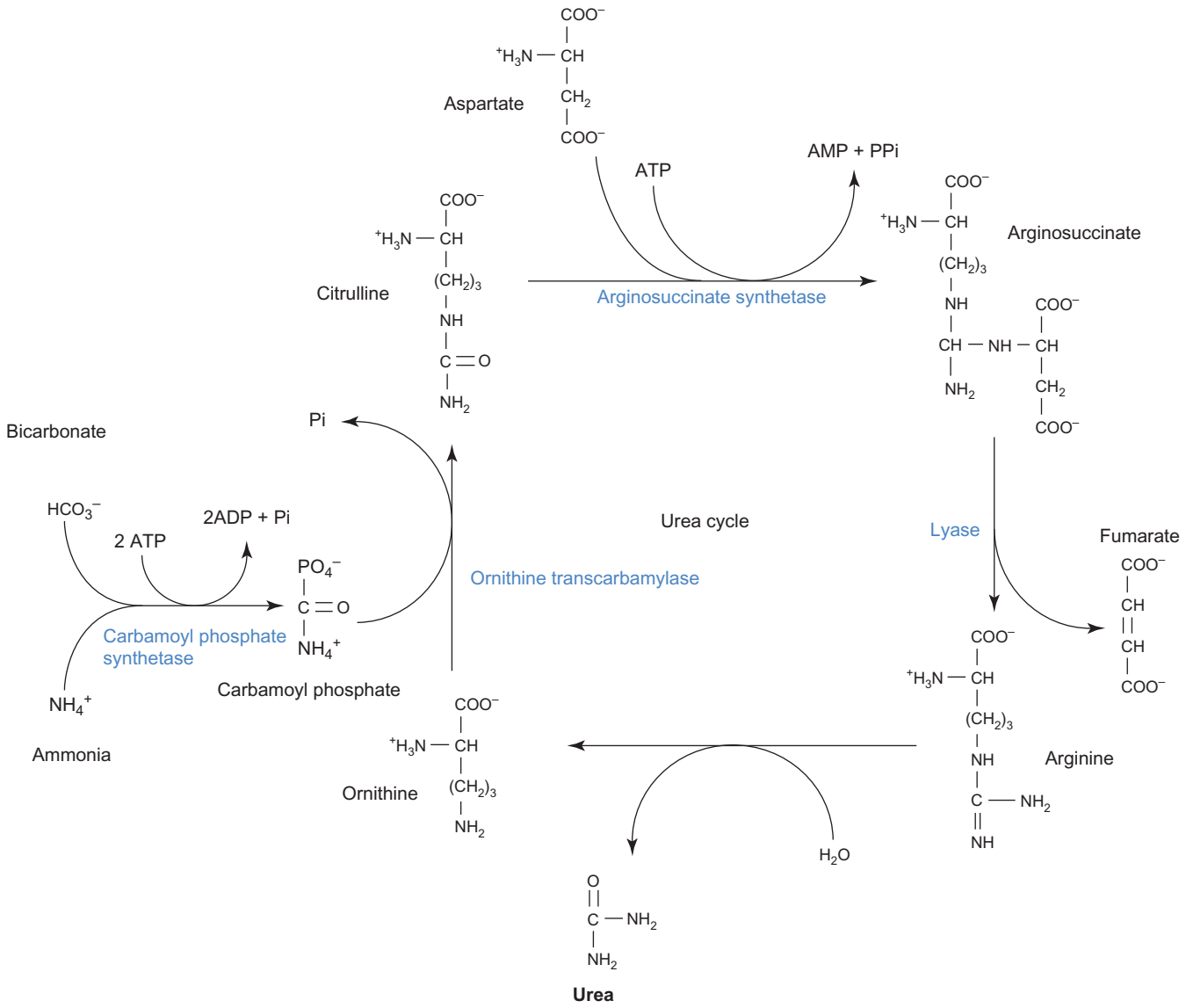

FIGURE 2.11.10 Formation of urea from the urea cycle.

Clinical Applications: Nonshivering Thermogenesis

Immediately after birth, the baby is thrust into a cool and dry environment. It loses heat rapidly by evaporation. Even when its skin dries, the baby continues to lose heat because it has a large surface area relative to its small body mass, it cannot put on warmer clothes, it has poor thermal insulation in the form of fat, and it has limited ability to generate heat by muscular contractions. However, the baby is able to generate heat by nonshivering thermogenesis, also called metabolic thermogenesis.

Babies have specialized fat tissue called brown fat, located mainly in the neck and in the midline of the back. Mitochondria contain cytochromes that contain iron, giving the mitochondria a reddish-brown color. Brown fat contains lots of mitochondria so it takes on a brownish color from mitochondrial pigments. The mitochondria in this fat make ATP primarily from the oxidation of fatty acids that are produced by hydrolysis of stored triglycerides. Under certain circumstances, these mitochondria can become **uncoupled**. Uncoupling of oxidative phosphorylation in brown fat mitochondria generates heat.

Oxidative phosphorylation couples an **exothermic** reaction, one that releases heat, to an **endothermic** reaction, one that requires heat. Pumping of H^+ ions out of the mitochondrial matrix couples the exothermic oxidation reactions to the energy of the H^+ electrochemical gradient. This in turn is coupled to the endothermic synthesis of ATP. The oxidation of foodstuffs (carbohydrates, fats, and amino acids) reduces NAD^+ to NADH, whose oxidation powers the H^+ pumping by the electron transport chain. The ATP synthase couples the energy stored in the electrochemical potential of H^+ to ATP synthesis. This coupling can never be 100% efficient, so that cellular respiration releases some energy

as heat. Under certain circumstances a special protein, called the **uncoupling protein**, short-circuits the synthesis of ATP by allowing H^+ ions to cross the inner mitochondrial membrane without making ATP. Then more of the energy stored in the H^+ gradient is dissipated as heat and less is captured by ATP. The exothermic reactions are uncoupled from ATP synthesis and the mitochondria generate heat proportionate to the number of mitochondria and the rate of oxygen consumption.

UCP1, a 32-kDa protein isolated from brown fat mitochondria, was the first uncoupling protein to be described. UCP1 is located mainly in brown fat, whereas UCP2 is expressed in many tissues and UCP3 is found mainly in skeletal muscle. BMCP1 is specific to the brain. UCP1 is activated by fatty acids and inhibited by purine nucleotides (ATP, ADP, GTP, and GDP). Exposure to cold increases UCP1 content in brown fat, and increased caloric content of the diet increases the tissue content of UCP2. Thus these proteins are believed to participate in basal or regulatory thermogenesis, but their exact functions are not yet worked out.

The mechanism of brown fat thermogenesis in response to cold is shown in Figure 2.11.11. Adipose tissue is supplied by sympathetic nerves that release noradrenaline onto the fat cells. This stimulates the breakdown of stored triglycerides to fatty acids, which in turn activate UCP1. The effect depends on the tissue content of UCP1, which is also increased by cold exposure. How UCP1 increases the H^+ flux across the membrane is also not yet known. UCP1 may form a H^+-specific pore or it may transport H^+ ions by cycling an H^+ carrier, most likely fatty acids. Current work favors the H^+ carrier mechanism because some carboxylic acid groups can activate transport without being transported.

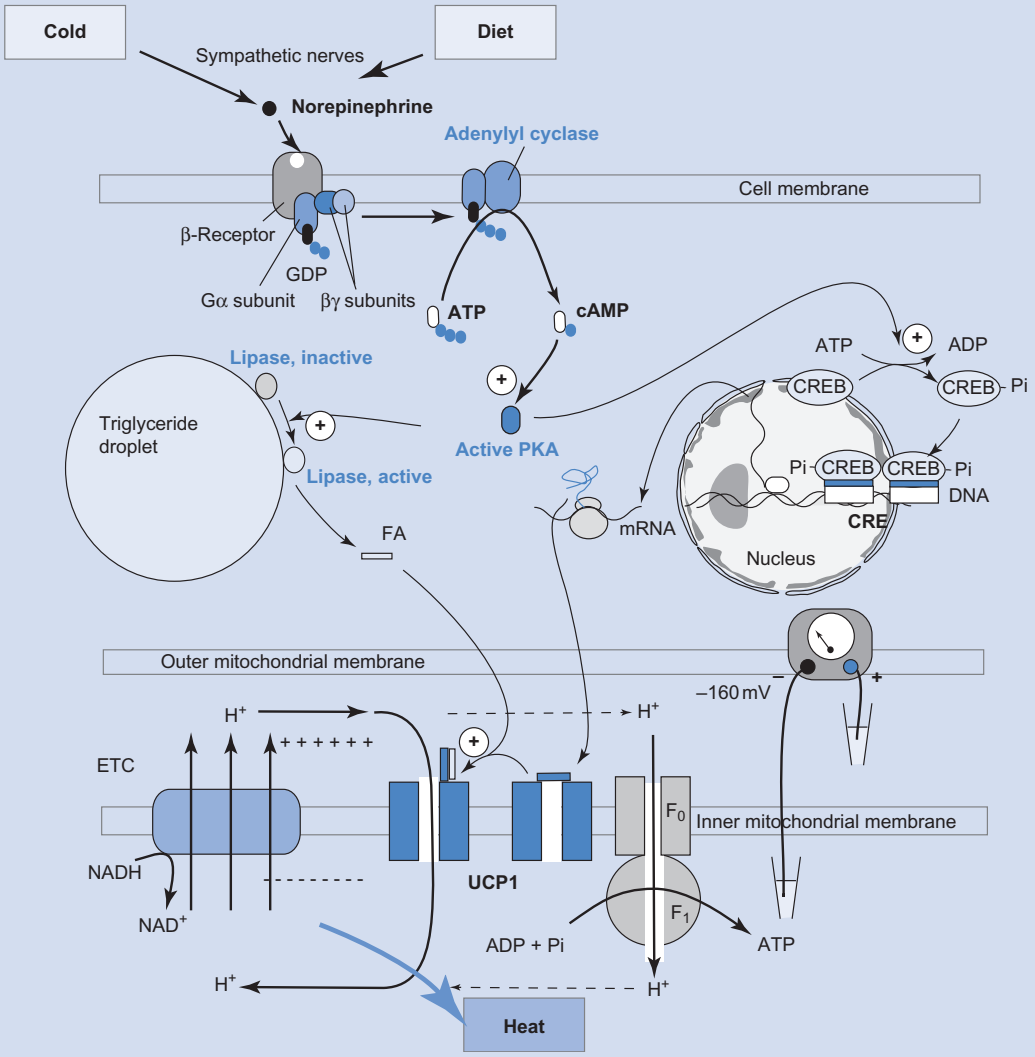

FIGURE 2.11.11 Postulated mechanisms for nonshivering thermogenesis in brown adipose tissue. Noradrenaline released from sympathetic nerve terminals in adipose tissue binds to β receptors on the surface of the adipocytes, leading to increased cytosolic cAMP by activating adenylyl cyclase. cAMP activates protein kinase A (PKA), which phosphorylates several targets, thereby changing their activity. PKA activates hormone-sensitive lipase that increases triglyceride breakdown and increases cytoplasmic fatty acid concentration. The increased fatty acids activate UCP1, short-circuiting the H^+ electrochemical gradient and reducing the synthesis of ATP from ADP and Pi. This uncouples oxidative phosphorylation and the energy of oxidation of fats appears as heat. PKA also phosphorylates a transcription factor, CREB (cyclic AMP response element binding protein), that binds to specific regions of the DNA (CRE—cAMP response element) and activates their transcription into mRNA. This leads to increased numbers of UCP1 protein in the mitochondria, which adapts the body to exposure to cold or some other stress. Diet-induced thermogenesis probably involves increased expression of UCP2.

SUMMARY

The oxidation of fatty acids and amino acids produces ATP through some of the same reactions used to produce ATP by the oxidation of carbohydrates. Fatty acids are released from triglycerides by hormone-sensitive lipase. The fatty acids are bound in the cytoplasm by fatty acid binding protein and carried into the mitochondria by being complexed with carnitine. Inside the mitochondria, fatty acids undergo beta oxidation in which two carbons at a time are cleaved off the carboxyl end and converted into acetyl Coenzyme A. Each turn of the beta oxidation cycle produces one NADH and one $FADH_2$. These feed reducing equivalents into the electron transport chain, which pumps H^+ ions out of the mitochondrial matrix and produces the electrochemical gradient of H^+ that drives ATP synthesis through the F_0F_1ATPase. Beta oxidation also produces acetyl CoA that enters the TCA cycle by combining with oxaloacetate to form citric acid. Each turn of the TCA cycle converts the acetyl CoA into 2 molecules of CO_2, 3 NADH, 1 $FADH_2$, and 1 GTP. Thus palmitic acid (16:0) produces 7 NADH and 7 $FADH_2$ from beta oxidation, and 24 NADH, 8 $FADH_2$, and 8 GTP from the complete oxidation of acetyl CoA. Since NADH produces 2.5 ATP molecules and $FADH_2$ produces 1.5, the ATP count from palmitic acid is 28 from beta oxidation and 80 from the TCA cycle. Two ATP molecules are used to prime the palmitic acid in the thiokinase reaction that converts palmitic acid to palmitoyl CoA.

The liver packages lipid metabolites into ketone bodies, which collectively consist of acetoacetic acid, beta-hydroxybutyric acid, and acetone. Build-up of these ketone bodies during starvation or other metabolic conditions such as diabetes is called ketosis.

Each amino acid has its own metabolic pathway because they all differ chemically. However, they feed into the main metabolic pathways in a limited number of places. Those amino acids that can be used to make glucose are called glucogenic. Those that can be used to make ketone bodies by producing acetyl CoA are called ketogenic. Many amino acids are both glucogenic and ketogenic. Only leucine and lysine are exclusively ketogenic.

Many amino acids are deaminated by a combination of transamination and dehydrogenation. In this reaction, the amino group is transferred from the amino acid to alpha-ketoglutaric acid, forming glutamic acid. The glutamic acid is then converted back to alpha-ketoglutaric acid by glutamate dehydrogenase, resulting in release of ammonia and formation of NADH. The ammonium formed in this way is converted to urea through the urea cycle. The urea cycle begins with the formation of carbamoyl phosphate by condensing ammonium with HCO_3^-. Carbamoyl phosphate then combines with ornithine to form citrulline. Citrulline combines with aspartic acid to form arginosuccinate and arginine in sequence. Arginine gives rise to urea and ornithine to begin the cycle again.

REVIEW QUESTIONS

1. What components make up a triglyceride? Where are triglycerides found in the body? Can they be metabolized as is? What enzyme breaks triglycerides down into components? What activates this enzyme? What inhibits the enzyme?
2. How is glycerol oxidized? How much ATP is produced from glycerol, mole per mole?
3. How are fatty acids carried in the cytosol? Where does oxidation of fatty acids take place? How do the fatty acids get into the mitochondria?
4. What is meant by beta oxidation? What are the main products? How many beta oxidation cycles are there for palmitic acid? Stearic acid? Oleic acid?
5. How much ATP is produced from the complete oxidation of palmitic acid, mole per mole?
6. What are the ketone bodies? Where are they produced?
7. What is a glucogenic amino acid? Which amino acids are glucogenic?
8. What is a ketogenic amino acid? Which amino acids are exclusively ketogenic?
9. What is transamination? What are the major receptors for transamination?
10. What is urea? Where is it produced?