chapter 32

How Animals Harvest Energy Stored in Nutrients

Outline

Concepts

1. All animals harvest energy from nutrients to fuel their metabolism with energy from ATP. The catabolic processes involved include glycolysis, fermentation, and aerobic respiration.
2. Glycolysis is a specific metabolic pathway that does not require oxygen and involves chemical reactions that transfer chemical energy by rearranging the chemical bonds of glucose to form molecules of pyruvate and to generate two usable molecules of ATP.
3. Animals that live in an anaerobic (low in oxygen) environment utilize fermentation to transfer the electrons and associated hydrogen produced in glycolysis to another atom or molecule. Molecules other than oxygen (e.g., NAD^+) are electron acceptors.
4. In aerobic respiration, the Krebs cycle completes the breakdown of pyruvate to carbon dioxide, water, and H^+ (protons). In the mitochondrion, electrons from hydrogen (H) atoms are channeled to the inner mitochondrial membrane to drive proton pumps and to generate ATP by way of the electron transport chain and chemiosmosis.
5. Fats and proteins can also be nutrients for animals. These molecules break down to intermediates that are eventually fed into the Krebs cycle.

This chapter contains evolutionary concepts, which are set off in this font.

Animals require a constant supply of energy to perform biological work. The energy-rich molecule ATP usually provides this energy. All animals can generate ATP by breaking down organic nutrients (carbohydrates, fats, and proteins). The energy released is used to join ADP and phosphate (P_i) to form ATP.

In animals, the breakdown of organic nutrients, such as glucose, begins in a step-by-step series of chemical reactions called glycolysis. The end product of glycolysis (pyruvate) is then further broken down either in the presence of free oxygen **(aerobic)**—a process called aerobic respiration—or in the absence of free oxygen **(anaerobic)**—a process called fermentation.

Figure 32.1 provides an overview of the catabolic metabolism involved in ATP production. Note that glycolysis and fermentation (anaerobic processes) take place in the cytoplasm of a cell and that aerobic respiration takes place in the mitochondrion.

Glycolysis and fermentation occur in the cytoplasm because during eukaryotic cell evolution, the enzymes that catalyze each reaction remained dissolved in the cytoplasm and did not localize in membranous organelles. This implies an origin prior to the evolution of complex organelles. These reactions are also older in an evolutionary sense than aerobic respiration because they could have occurred in the earliest primitive environment of earth before the atmosphere contained free oxygen.

This chapter presents some of the fundamental biological principles that underlie glycolysis, aerobic respiration, and fermentation in animal cells.

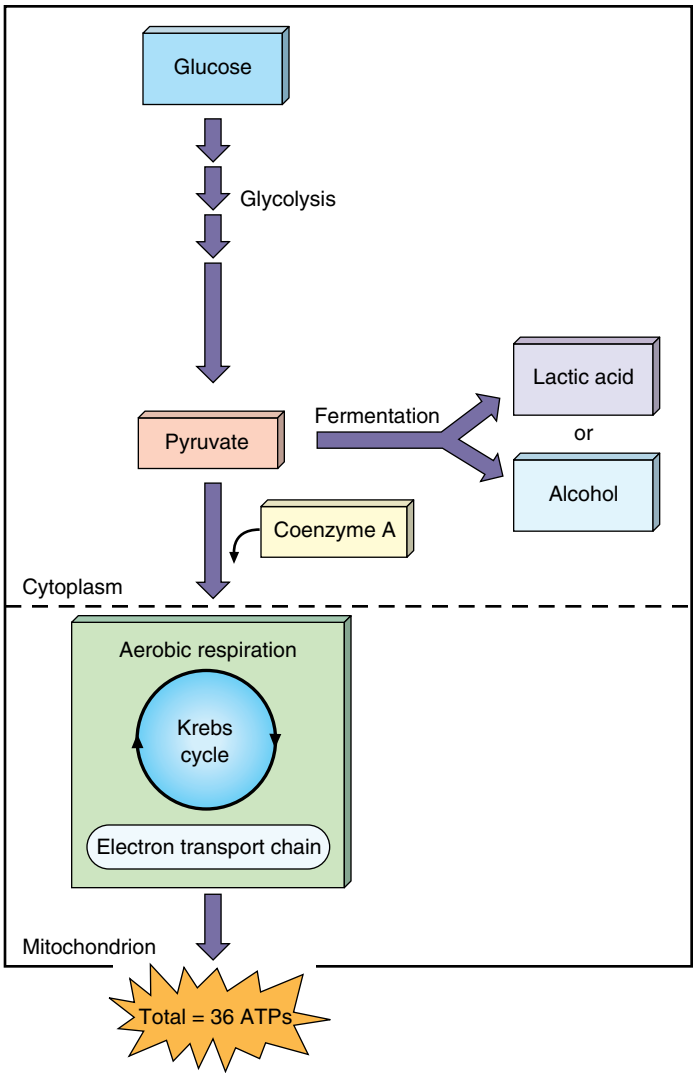


FIGURE 32.1

Overview of the Catabolic Pathways (Glycolysis, Fermentation, Aerobic Respiration) That Generate ATP Molecules. Glycolysis begins in the cytoplasm and causes glucose to be broken down to pyruvate. In the absence of free oxygen, pyruvate undergoes fermentation instead of entering the Krebs cycle. The first step in aerobic respiration is the conversion of pyruvate to a high-energy intermediate by the addition of coenzyme A. The Krebs cycle removes electrons and passes them to the electron transport chain by way of carrier molecules. Both of these processes take place in the mitochondrion. From start (glycolysis) to finish, the aerobic pathway typically has a net energy yield of 36 ATP molecules. Based on fig. 6.19 from Ricki Lewis, *Life*, 2d ed. New York, McGraw-Hill. Reprinted by permission of The McGraw-Hill Companies.

Glycolysis: The First Phase of Nutrient Metabolism

Glycolysis (Gr. *glykys*, sweet + *lyein*, to loosen) is the initial sequence of catabolic chemical reactions that almost all cells use to break the six-carbon glucose molecule into two molecules of a three-carbon compound called pyruvate (pyruvic acid) with the net production of two molecules of ATP (figure 32.2). For each molecule of glucose that enters the glycolytic pathway, four molecules of ATP form. However, because two ATP molecules are used to rearrange the glucose molecule to form new six-carbon compounds, the net energy yield from glycolysis is only two ATP molecules. Although glycolysis does not efficiently harvest all the available energy from glucose, it was the only way most organisms could harvest energy and generate ATP molecules for hundreds of millions of years during the anaerobic stages of early life on earth.

Evolutionary Perspective on Glycolysis

If glycolysis is such an inefficient method of harvesting energy, why has it persisted? One reason might be that evolution is a slow, incremental process involving change based on past events. When glycolysis first evolved, the cells possessing it had a competitive advantage over those that did not. The biochemistry of contemporary organisms indicates that only those organisms capable of glycolysis survived the early competition of life on earth. Obviously, later evolutionary changes in catabolism built on this success. During this building process, glycolysis was not discarded but used as a stepping stone for the evolution of another process for the complete breakdown of glucose. Just as an artist adds successive layers of paint to obtain a final painting, so evolution added another layer of chemical reactions (aerobic respiration) onto the foundation layer (glycolysis) to produce an efficient method of harvesting energy. Looking at glycolysis in another way, all forms of animal life (including humans) carry on glycolysis within their cells—a metabolic memory of an animal's evolutionary past.

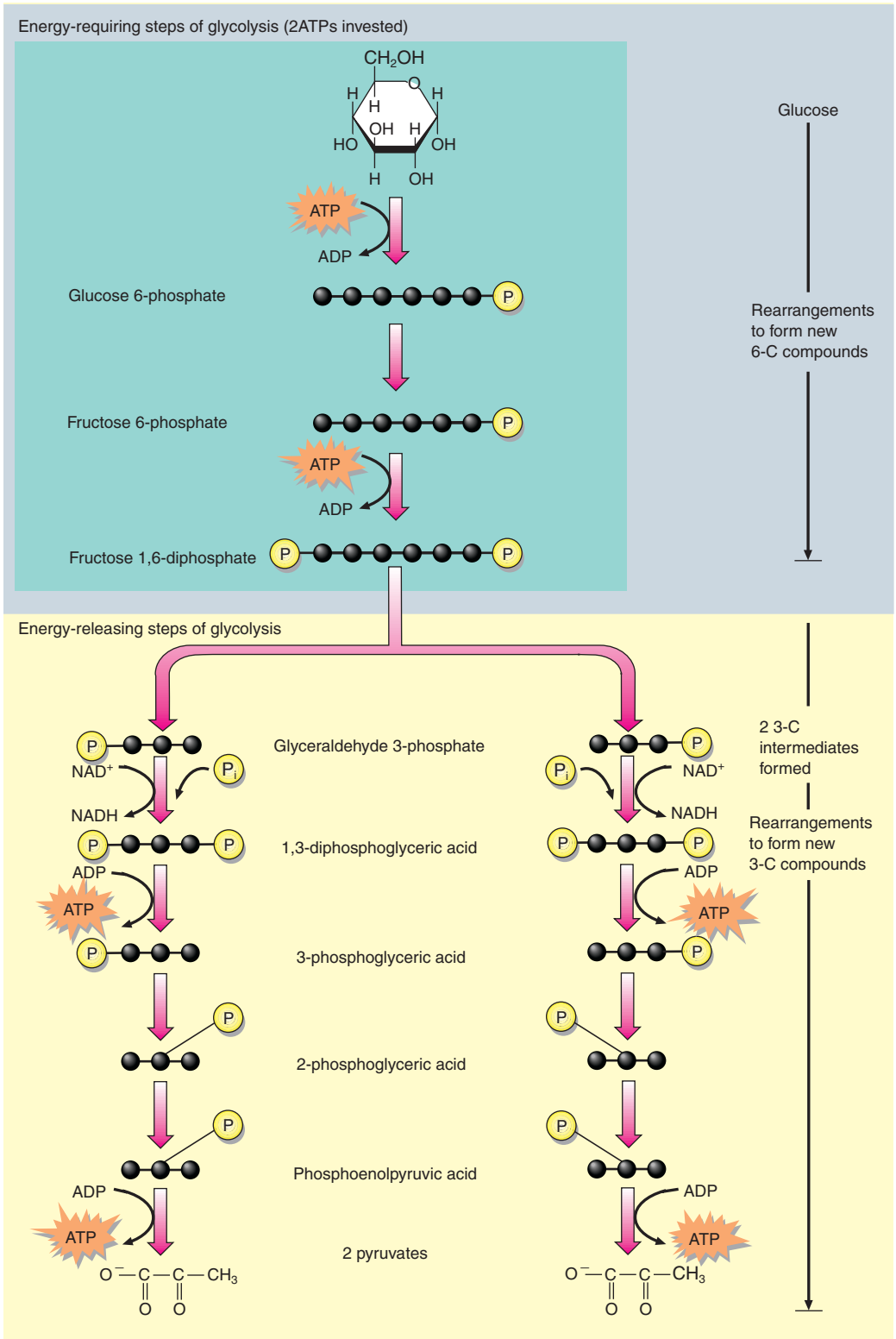


FIGURE 32.2

Glycolysis. In the reactions of glycolysis, glucose is rearranged, split into two three-carbon (3-C) intermediates, then rearranged further to yield two molecules of pyruvate. Along the way, four ATP and two NADH molecules are produced. However, since two ATPs are used in the initial steps of glycolysis, the net yield is only two ATP molecules. From Kathleen Talaro and Arthur Talaro, *Foundations in Microbiology*. New York, McGraw-Hill. Reprinted by permission of The McGraw-Hill Companies.

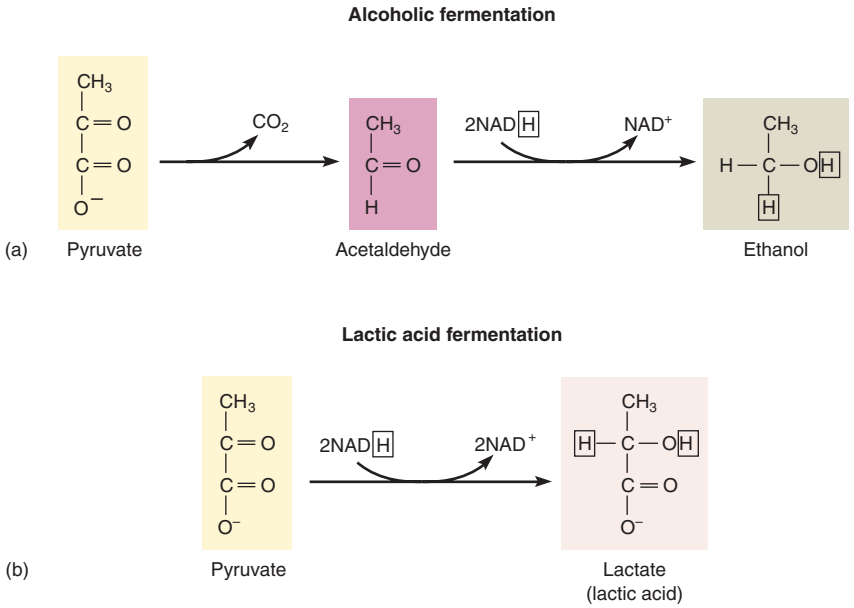


FIGURE 32.3

Fermentation. Fermentation regenerates NAD^+, which is needed to drive glycolysis to ultimately obtain ATP. The boxed hydrogens indicate the hydrogen ions donated by reduced NADH and where the donated hydrogen ions end up after fermentation is complete. *(a)* The pathway from pyruvate to ethanol is called alcoholic fermentation and is catalyzed by specific microbial enzymes. *(b)* The pathway from pyruvate to lactate (lactic acid). Certain animal cells, deprived of oxygen, temporarily carry out lactic acid fermentation.

The Nature of Electron Transfers

Much of the flow of energy through cells involves the transfer of electrons from one molecule to another. This electron transfer is called an **oxidation-reduction reaction,** or **redox reaction.** The molecule that gives up electrons is oxidized; thus, **oxidation** is the loss of electrons. The molecule that accepts electrons is reduced; thus, **reduction** is the gain of electrons. Oxidation-reduction reactions always occur together.

Fermentation: "Life without Oxygen"

Fermentation (L. *fermentum,* leaven) is either an evolutionary bypass that some organisms use to keep glycolysis functioning under anaerobic conditions or, more likely, a biochemical remnant that evolved very early in the history of life, when the earth's atmosphere contained little or no oxygen. As with glycolysis, the ubiquity of fermentation is strong evidence for the common descent of organisms from primitive cells in which glycolysis and fermentation first appeared and still persist.

In fermentation, the hydrogen atoms that glycolysis generates are donated to organic molecules as follows:

$$\text{Pyruvate} + \text{NADH} \rightarrow \text{reduced compound} + \text{NAD}^+$$

The reduced compound can be an organic acid in lactate fermentation (e.g., lactic acid) or an alcohol in alcoholic fermentation (e.g., ethanol; figure 32.3).

The important point to remember about fermentation is that glucose is not completely degraded, so considerable unusable energy still remains in the products. Beyond the two ATP molecules formed during glycolysis, no more ATP is produced. Fermentation serves only to regenerate NAD^+ (the oxidized form of NADH).

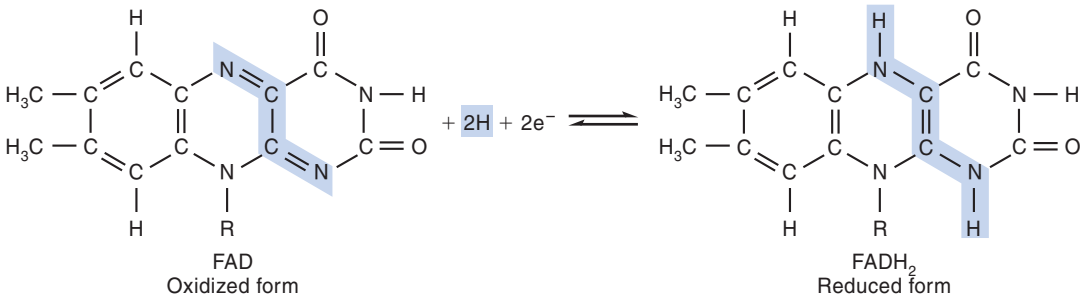
Two types of organisms can carry out fermentation: obligative anaerobic and facultative anaerobic ones. Obligative anaerobic organisms include certain types of bacteria that survive only in the complete absence of molecular oxygen. Facultative anaerobic organisms and tissues include certain bacteria, yeasts, and cells (e.g., animal muscle) that can ferment nutrients when oxygen is absent to generate some ATP by providing NAD^+ for glycolysis. Facultative anaerobic organisms and tissues carry out more efficient energy harvesting when oxygen is present—hence, the term facultative (not obligative).

Aerobic Respiration: The Major Source of ATP

As already noted, the anaerobic generation of ATP through glycolysis and fermentation is relatively inefficient. The end product of glycolysis (pyruvate) still contains a great deal of potential bond energy that can be harvested by further oxidation. The evolution of aerobic respiration in microorganisms and in the mitochondria of eukaryotic cells became possible only after free oxygen had accumulated in the earth's atmosphere as a result of photosynthesis. The addition of an oxygen-requiring stage to the energy-harvesting mechanisms provided cells with a more powerful and efficient way of extracting energy from nutrient molecules. Indeed, without mitochondria's large-scale ATP production, life would have to be at a "snail's pace," and most animals present on earth today would never have evolved.

FIGURE 32.4

The Electron Carrier Flavin Adenine Dinucleotide (FAD). The equation illustrates the oxidized form of FAD being reduced to $FADH_2$. The reactive sites are shaded, and the rest of the molecule is indicated by R.



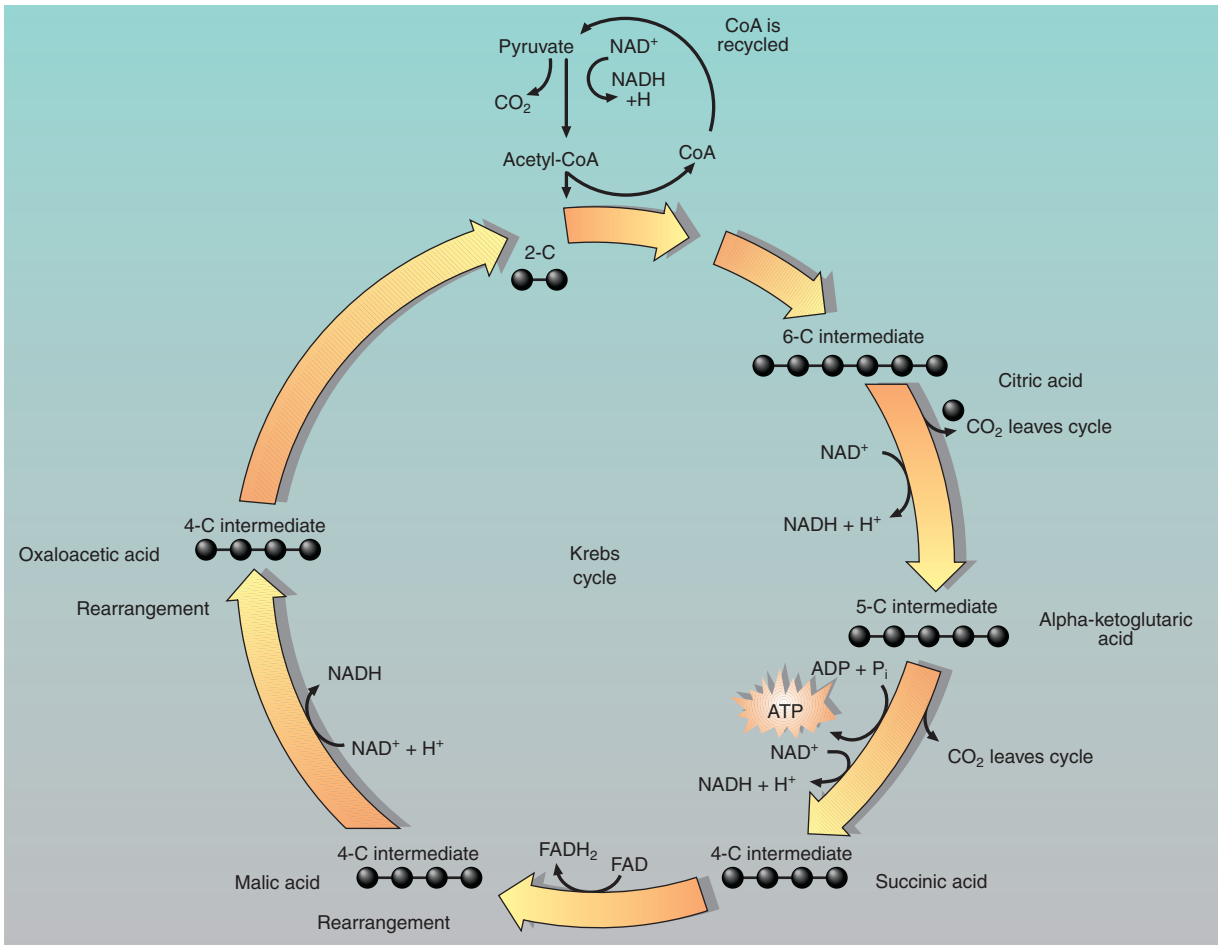


FIGURE 32.5

The Krebs Cycle. For each pyruvate molecule that enters the Krebs cycle by way of acetyl-CoA, two CO_2, one ATP, three NADH, and one $FADH_2$ molecules form. Each of these events occurs twice for each glucose molecule broken down into two molecules of pyruvate. From Ricki Lewis, *Life*, 2d ed. New York, McGraw-Hill. Reprinted by permission of The McGraw-Hill Companies.

In aerobic respiration, the pyruvate that glycolysis produces is shunted into a metabolic pathway called the Krebs cycle or **citric acid cycle;** the NADH goes to the electron transport chain. During this aerobic metabolism, free oxygen accepts electrons and reduces to H_2O as follows:

$$\text{Pyruvate} + O_2 \rightarrow CO_2 + H_2O + 34\text{ATP} + \text{heat energy}$$

During this reaction, 34 molecules of ATP are produced for each molecule of pyruvate consumed.

As in glycolysis, aerobic respiration is organized into a number of reactions, each catalyzed by a specific enzyme and organized into the **Krebs cycle** and the electron transport chain. The Krebs cycle, named after Hans Krebs (who began working out its details in the 1930s), is a series of reactions in which the pyruvate from glycolysis is oxidized to CO_2. Two electron carriers, nicotinamide adenine dinucleotide (NAD) *(see figure 4.8)* and **flavin adenine dinucleotide (FAD)** (figure 32.4), act as hydrogen acceptors and reduce to NADH and $FADH_2$. During this phase of the cycle, three molecules of CO_2 are generated from each pyruvate molecule, and some energy is harvested in the form of ATP (figure 32.5). Most of the remaining energy is in the form of NADH and $FADH_2$. These two molecules are shuttled into the **electron transport chain.** In

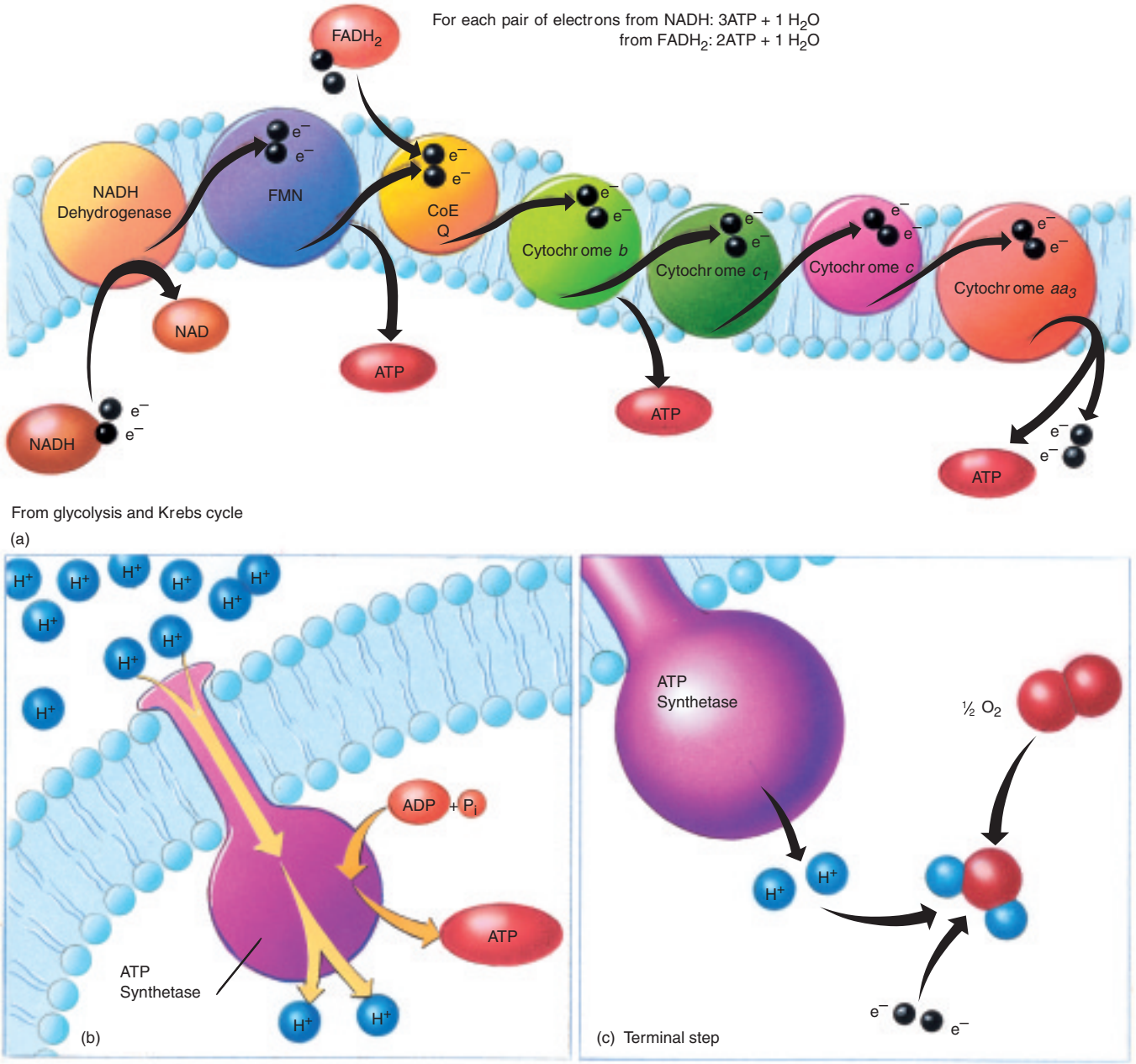


FIGURE 32.6

Electron Transport Chain and Oxidative Phosphorylation. *(a)* Electrons from NADH and $FADH_2$ generated in glycolysis and the Krebs cycle are passed along electron-carrier molecules (colored circles) in the electron transport chain by way of oxidation-reduction reactions. *(b)* The energy released along the way is captured in the high-energy phosphate bonds of ATP by way of oxidative phosphorylation. *(c)* When the electrons reach the end of the chain, an oxygen molecule accepts the electrons and combines with hydrogen to generate a water molecule. From Kathleen Talaro and Arthur Talaro, *Foundations in Microbiology*. New York, McGraw-Hill. Reprinted by permission of The McGraw-Hill Companies.

this chain, the reduced NADH and $FADH_2$ are oxidized, and their electrons are passed along a series of oxidation-reduction reactions to the final acceptor, oxygen (figure 32.6).

As previously mentioned, in eukaryotic cells, aerobic respiration takes place in the mitochondria. The Krebs cycle occurs in the mitochondrial matrix (figure 32.7). The enzymes used to catalyze these reactions are dissolved in the fluid matrix. (In prokaryotic cells, the enzymes occur in the cytoplasm.) The proteins (cytochromes) that bring about the reactions of the electron transport chain are bound to the inner mitochondrial membrane, which is arranged in numerous folds called cristae (sing., crista). (In prokaryotes, cytochromes are bound to the plasma membrane.) Pyruvate, oxygen, ADP, and inorganic phosphate (P_i) continuously diffuse into the mitochondrial matrix. In turn, the

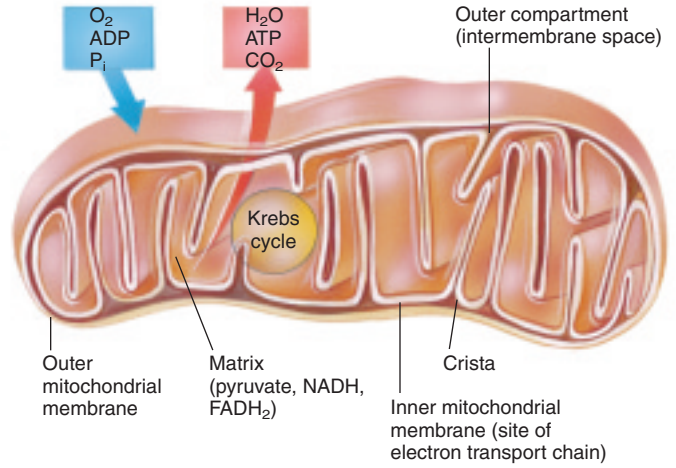


FIGURE 32.7

Mitochondrial Architecture. Reactions of the Krebs cycle occur in the mitochondrial matrix. Molecular complexes that are an integral part of the inner membrane carry out the reactions in the electron transport chain.

end products of aerobic metabolism—ATP, CO_2, and H_2O—diffuse outward into the cytoplasm.

The Energy Score for Aerobic Respiration: A Balance Sheet

The eukaryotic cell obtains a net gain of 36 ATP molecules from the breakdown of each glucose molecule (table 32.1). Glycolysis produces four ATP molecules, but two are used in the glycolytic reactions. The two molecules of NADH formed during glycolysis yield six ATP molecules, but two are used in the reactions that transport the NADH electrons across the inner mitochondrial membrane into the matrix to enter the Krebs cycle. One molecule of NADH is produced for each pyruvate that is converted to acetyl-coenzyme A, and one molecule of CO_2 is released as acetyl-coenzyme A enters the Krebs cycle. Two more ATP molecules are produced in the Krebs cycle, as well as six NADH and two $FADH_2$ molecules. The six NADH from the Krebs cycle and two NADH from the entry of acetyl-coenzyme A into the cycle yield 24 ATP molecules, and the oxidation of the two molecules of $FADH_2$ produced during the Krebs cycle yields four more molecules of ATP. The net gain from all of these reactions is 36 molecules of ATP. As table 32.1 illustrates, the electron transport chain is more efficient than glycolysis at producing ATP for cell activities. Glycolysis, however, can produce ATP in anaerobic conditions, which the Krebs cycle and electron transport chain cannot.

TABLE 32.1 Approximate ATP Yield from the Complete Aerobic Oxidation of One Molecule of Glucose

Process	ATP Produced	NADH, $FADH_2$ Produced	ATP Used
Glycolysis	4 ATP	2 NADH	−2 ATP
Entrance of NADH to Krebs cycle		2 NADH	−2 ATP
Krebs cycle	2 ATP	6 NADH, 2 $FADH_2$	
Electron transport chain:			
3 ATP for each of 2 NADH generated via glycolysis	6 ATP		
3 ATP for each of 8 NADH generated via Krebs cycle and entrance to the cycle	24 ATP		
2 ATP for each of 2 $FADH_2$ generated via Krebs cycle	4 ATP		
Total	40 ATP		−4 ATP
Net ATP	36 ATP		

Metabolism of Fats and Proteins: Alternative Food Molecules

Even though the catabolism of glucose is the most common metabolic pathway in cells, animals also consume fats and proteins, which may be used to harvest energy. Recall that fats built from long-chain fatty acids and glycerol are triglycerides. The initial catabolism of a fat begins with the digestion of the triglycerides (by way of an enzyme called a lipase) to glycerol and three fatty acid molecules (figure 32.8). The glycerol is phosphorylated and can enter the glycolytic pathway at the level of glyceraldehyde 3-phosphate. The free fatty acids move into the mitochondrion, where their carbons are removed, two at a time, to form acetyl-coenzyme A plus additional NADH and $FADH_2$. The acetyl-coenzyme A is then oxidized by the Krebs cycle, and the NADH and $FADH_2$ that are produced are oxidized via the electron transport chain. Interestingly, 1 g of fat provides about 2.5 times more ATP energy than does either 1 g of carbohydrate or protein because the number of hydrogen atoms per unit weight of fat is greater than in carbohydrates or protein. This is why many animals store energy in the form of fat in adipose tissue.

Animals initially digest proteins to yield individual amino acids. Some of these are distributed throughout the body and used to synthesize new proteins. Other amino acids are transported in

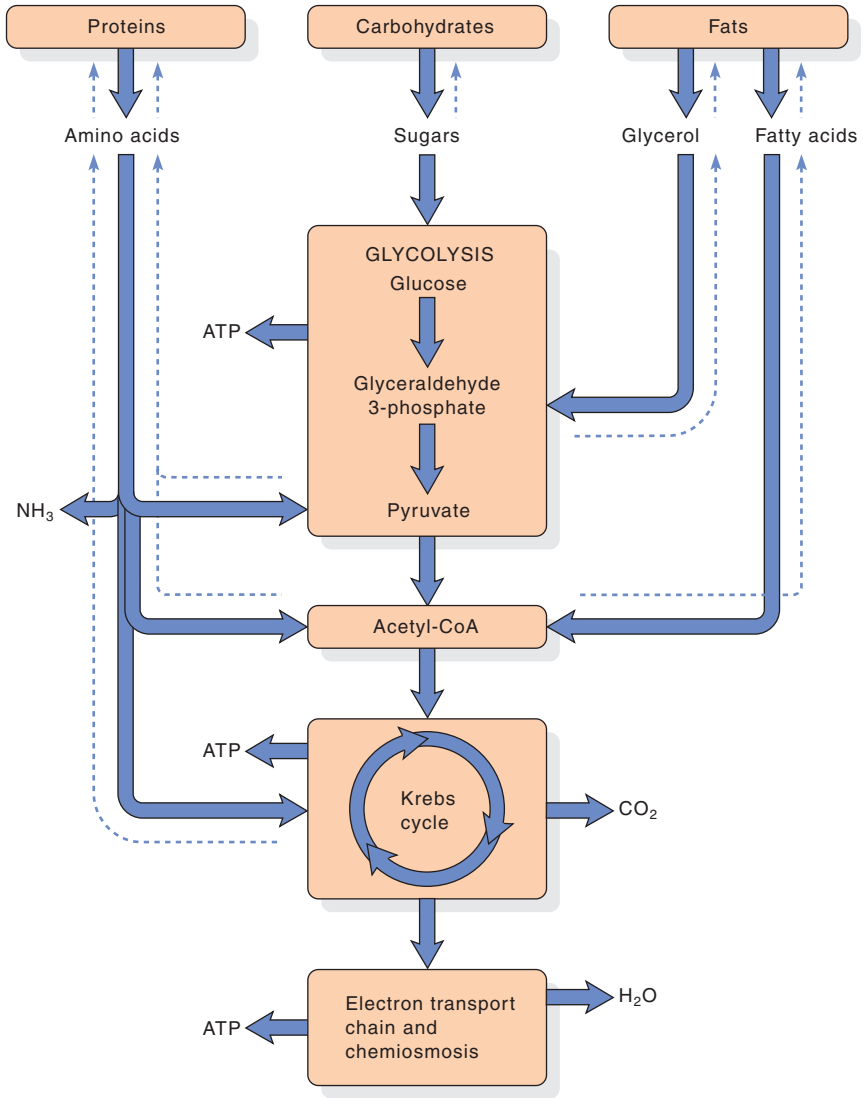
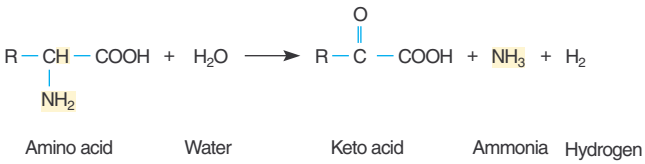


FIGURE 32.8

Catabolism of Various Food Molecules. While only certain molecules can feed directly into the Krebs cycle (e.g., acetyl-CoA), proteins, carbohydrates, and fats can also be broken down into constituent parts and used as fuel for respiration. The dashed arrows indicate that the system also works in anabolic (synthetic) reactions.

the blood or extracellular fluid and comprise the amino acid pool. If needed for fuel, these amino acids can be further degraded by removal of the amine group to yield ammonia. This process is called a **deamination reaction:**



In deamination, an oxygen atom replaces an amine group to form a keto acid. The keto acid can then be funneled into the Krebs cycle (figure 32.8). Eventually, the carbon skeleton of the amino acid is dismantled and oxidized to CO_2. On the average, 1 g of protein yields about the same amount of energy (about 4 kcal) as does 1 g of glucose. The ammonia produced from the complete catabolism of an amino acid is highly toxic and must be excreted. Chapter 38 discusses the various ways in which different animals rid their bodies of toxic wastes.

Control of Metabolism

Cells are very efficient. They do not waste energy by making more of a substance than they need. For example, if a certain amino acid is overabundant in the amino acid pool, the anabolic pathway that synthesizes that amino acid from an intermediate in the Krebs cycle is turned off. The most common mechanism for this control uses **end-product (feedback) inhibition.** In end-product inhibition, the end product of the anabolic pathway inhibits the enzyme that catalyzes a key step in the pathway.

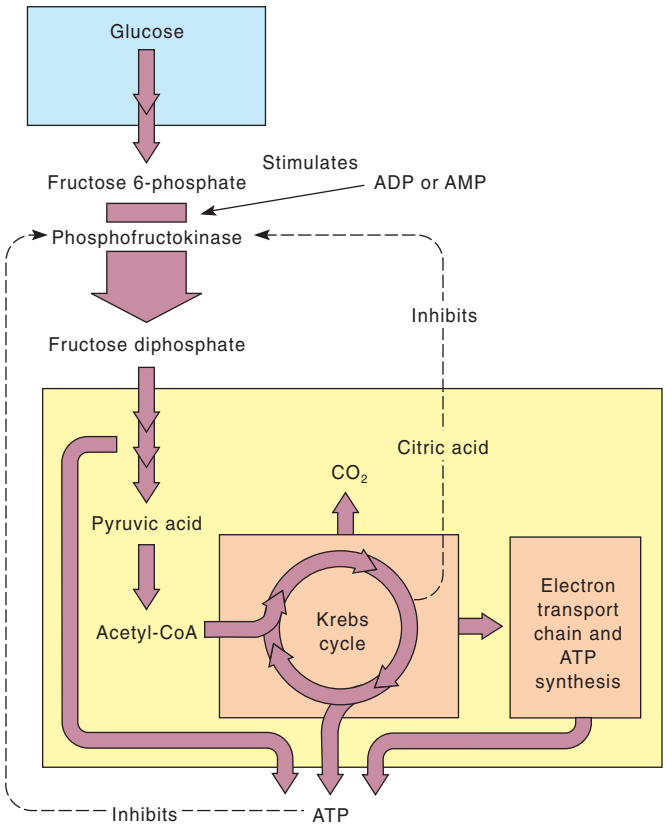


FIGURE 32.9

Control of Cellular Respiration. The enzyme phosphofructokinase responds to activators and inhibitors to regulate the rate of glycolysis and the Krebs cycle. ADP and AMP stimulate the enzyme, but ATP and citric acid inhibit it.

Cells can also control their catabolism. For example, if a cell (e.g., a muscle cell) is working very hard and its ATP concentration begins to decrease, aerobic respiration increases. When ATP is sufficient to meet demand, aerobic respiration slows, sparing valuable organic molecules for other necessary functions. As with anabolism, control is based on regulating enzyme activity at strategic points in the catabolic pathway. As a result, cells are thrifty, expedient, and responsive in their metabolism.

One of the main controlling points in aerobic respiration is the enzyme phosphofructokinase. By controlling how fast or slow this single enzyme functions, a cell can either speed or slow the entire metabolic process. Phosphofructokinase is an enzyme with receptor sites for specific inhibitors and activators. ATP inhibits it, and either ADP or AMP stimulates it. Phosphofructokinase is sensitive to the energy needs of the cell and the ratio of ATP to ADP or AMP (figure 32.9). If ATP begins to accumulate, this enzyme shuts down glycolysis. If ADP or AMP begins to accumulate, phosphofructokinase becomes active and turns on the glycolytic pathway. Citric acid in the cytoplasm also inhibits phosphofructokinase. This control pathway helps synchronize the rates of glycolysis and the Krebs cycle. For example, when citric acid begins to accumulate, glycolysis slows down, reducing the supply of acetyl-coenzyme A to the Krebs cycle. Conversely, if citric acid consumption increases, glycolysis accelerates and meets the needed demand for more acetyl-coenzyme A.

The Metabolic Pool

The degradative chemical reactions (catabolism) of glycolysis and the Krebs cycle do more than just harvest energy for ATP production in animals. They also constitute a metabolic pool that supplies materials for synthesis (anabolism) of many important cellular components. Overall, the balance between catabolism and anabolism is what maintains homeostasis in the cell and, in turn, the whole animal. For example, glycolysis and the Krebs cycle are open systems. An open system has a two-way flow of materials into and out of it. Various compounds enter the pathways at different points so that carbohydrates, fats, and proteins can all be oxidized. At the same time, some of the intermediates of these pathways can be withdrawn from the energy-harvesting machinery and used in synthesis reactions. Thus, the products of glycolysis and the Krebs cycle are all part of a metabolic pool whereby materials are either added or withdrawn.

Summary

1. During glycolysis, glucose breaks down anaerobically to yield two molecules of pyruvate, which are processed further in aerobic respiration. Glycolysis harvests chemical energy by rearranging the chemical bonds of glucose to form two pyruvate molecules and two molecules of ATP.
2. Organisms living in anaerobic environments require a mechanism to dispose of the hydrogen and associated electrons produced in glycolysis. The electrons can be donated to a number of other compounds in a process called fermentation.
3. Each pyruvate molecule formed during glycolysis loses a carbon dioxide molecule and combines with coenzyme A to form acetyl-coenzyme A. Coenzyme A transfers the acetyl group to the Krebs cycle. During one turn of the cycle, the equivalents of the acetyl group's two carbons are removed in the form of carbon dioxide. Some ATP is also produced. During the process, NAD^+ and FAD accept electrons and become NADH and $FADH_2$. They carry these electrons to the electron transport chain.
4. The electron transport chain produces most of the energy harvested during aerobic respiration. The oxidation of one molecule of glucose results in the net production of 36 ATP molecules.
5. Many other metabolic pathways feed into glycolysis and the Krebs cycle from the metabolic pool, enabling cells to use many organic compounds in addition to glucose as food sources to generate usable energy to perform biological work.
6. End-product inhibition helps regulate metabolism and maintain homeostasis within organisms.

Selected Key Terms

aerobic
anaerobic
deamination reaction
electron transport chain
end-product (feedback) inhibition
fermentation
flavin adenine dinucleotide (FAD)
glycolysis

Critical Thinking Questions

1. The aerobic metabolism of glucose generates exactly the same chemical end products and the same amount of energy as when glucose is burned. However, when a cell "burns" glucose, it does so in many small steps. Why has evolution divided glucose catabolism into so many small steps?
2. In anaerobic catabolism of glucose, further conversions of pyruvate to lactate do not yield any more usable energy. What, then, is the advantage of these conversions?
3. Why is anaerobic respiration wasteful and potentially harmful to an animal?
4. Diverse organisms, such as dogs and yeasts, have certain enzymes in common and even share similar metabolic pathways. What are the implications of these similarities in terms of evolution?
5. When an animal cell contains more than enough ATP to carry out its functions, the excess ATP signals a slowing down of the respiratory chain by decreasing the production of acetyl-coenzyme A. When ATP levels fall below what is required for cellular functions, the increased ADP signals increased breakdown of glucose. What general metabolic phenomenon do these relationships demonstrate?