Triathlete racing past photosynthesizing trees and vegetation.

8

Cellular Respiration

A triathlete racing a bike, a bacterium with undulating flagella, an ocelot climbing a tree, or a snail moving slowly to hide under a rock—each, including the tree, are making and using ATP. ATP is an ancient "molecular fossil." Its molecular structure, plus its presence in the first cell or cells that arose on planet Earth, accounts for its being the universal energy currency of cells.

ATP is unique among the cell's storehouse of chemicals; amino acids join to make a protein, and nucleotides join to make DNA or RNA, but ATP is singular and works alone. Whether you go skiing, take an aerobics class, or just hang out, ATP molecules provide the energy needed for nerve conduction, muscle contraction, and any other cellular process that requires energy. Cellular respiration, by which cells harvest the energy of organic compounds and convert it to ATP molecules, is the topic of this chapter. It's a process that requires many steps and involves the cytoplasm and the mitochondria, the powerhouses of the cell.

As you read through the chapter, think about the following questions:

1. How does the ATP molecule store chemical energy needed to run biological processes?
2. How are enzymes involved in regulating energy metabolism?
3. If nearly all life on Earth uses ATP, what does that indicate about its origins and biological importance?

Chapter Outline

Before You Begin

Before beginning this chapter, take a few moments to review the following discussions.

Figure 6.3 How does an ATP molecule store energy?

Figure 7.5 Where does the glucose that we metabolize come from?

Section 6.4 How are high energy electrons used to make energy for cellular work?

Following *the* Big Ideas

CHAPTER 8 CELLULAR RESPIRATION

Energy and Homeostasis	Chemical energy in the bonds of food molecules can be released in small, regulated steps through cellular respiration, transferring the free energy to create ATP molecules.
Interactions and Systems	The energy for life typically originates with sunlight, whose solar energy passes to the chloroplast where some is stored in the chemical energy of carbohydrates which are passed to mitochondria where some is stored in the chemical energy of ATP molecules.

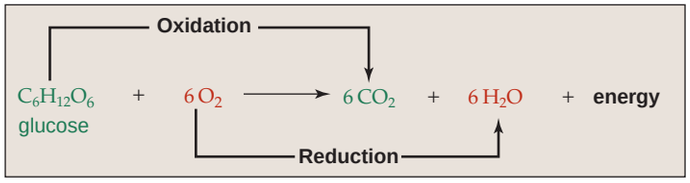
8.1 Cellular Respiration

Learning Outcomes

Upon completion of this section, you should be able to

1. Describe the overall reaction for glucose breakdown and show that it is a redox reaction.
2. Examine the role of NADH and $FADH_2$ redox reactions in cellular respiration.
3. Evaluate where each carbon molecule goes during cellular respiration for a 6-carbon glucose molecule.

Cellular respiration is the process by which cells acquire energy by breaking down nutrient molecules produced by photosynthesizers. Cellular respiration requires oxygen (O_2) and gives off carbon dioxide (CO_2), which, in effect, is the opposite of photosynthesis. In fact, it is the reason any animal, such as an ocelot or human, breathes (Fig. 8.1) and why plants also require a supply of oxygen. This chemical interaction between animals and plants is important because animals, like humans, breathe the oxygen made by photosynthesizers. Most often, cellular respiration involves the complete breakdown of glucose to carbon dioxide and water (H_2O):



This equation shows that cellular respiration is an oxidation-reduction reaction. Recall that oxidation is the loss of electrons, and reduction is the gain of electrons; therefore, glucose has been oxidized and O_2 has been reduced. Also remember that a hydrogen atom consists of a hydrogen ion plus an electron ($H^+ + e^-$). Therefore, when hydrogen atoms are removed from glucose, so are electrons, and similarly, when hydrogen atoms are added to oxygen, so are electrons.

Glucose is a high-energy molecule, and its breakdown products, CO_2 and H_2O, are low-energy molecules. Therefore, as the equation shows, energy is released. This is the energy that will be used to produce ATP molecules. The cell carries out cellular respiration in order to build up ATP molecules.

The pathways of cellular respiration allow the energy within a glucose molecule to be released slowly so that ATP can be produced gradually. Cells would lose a tremendous amount of energy if glucose breakdown occurred all at once—most of the energy would become nonusable heat. The step-by-step breakdown of glucose to CO_2 and H_2O usually makes a maximum yield of 36 or 38 ATP molecules, dependent on conditions to be discussed later. The energy in these ATP molecules is equivalent to about 39% of the energy that was available in glucose. Even though it might seem less efficient, this conversion is more efficient than many others; for example, only between 20% and 30% of the energy within gasoline is converted to the motion of a car.

NAD^+ and FAD

Cellular respiration involves many individual metabolic reactions, each one catalyzed by its own enzyme. Enzymes of particular significance are those that use **NAD^+**, a coenzyme of oxidation-reduction (sometimes called a redox coenzyme). When a metabolite is oxidized, NAD^+ accepts two electrons plus a hydrogen ion (H^+), and NADH results. The electrons received by NAD^+ are high-energy electrons that are usually carried to the electron transport chain (see Fig. 6.12):

$$NAD^+ + 2\,e^- + H^+ \longrightarrow NADH$$

NAD^+ can oxidize a metabolite by accepting electrons and can reduce a metabolite by giving up electrons. Only a small amount of NAD^+ needs to be present in a cell, because each NAD^+ molecule is used over and over again. **FAD,** another coenzyme of oxidation-reduction, is sometimes used instead of NAD^+. FAD

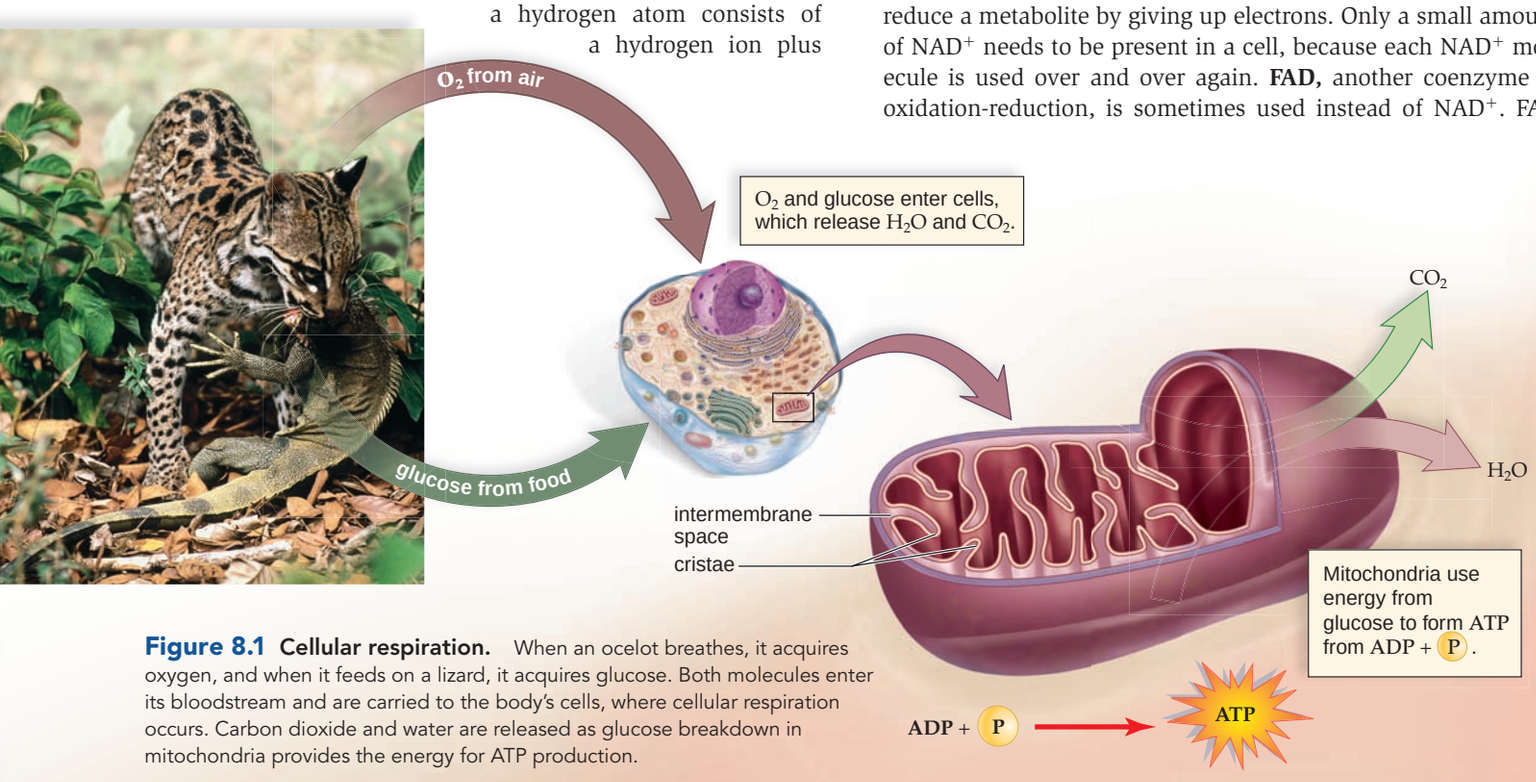


Figure 8.1 Cellular respiration. When an ocelot breathes, it acquires oxygen, and when it feeds on a lizard, it acquires glucose. Both molecules enter its bloodstream and are carried to the body's cells, where cellular respiration occurs. Carbon dioxide and water are released as glucose breakdown in mitochondria provides the energy for ATP production.

accepts two electrons and two hydrogen ions (H^+) to become $FADH_2$.

Animation How the NAD⁺Works

Phases of Cellular Respiration

Cellular respiration involves four phases: glycolysis, the preparatory reaction, the citric acid cycle, and the electron transport chain (Fig. 8.2). Glycolysis takes place outside the mitochondria and does not require the presence of oxygen. Therefore, glycolysis is **anaerobic.** The other phases of cellular respiration take place inside the mitochondria, where oxygen is the final acceptor of electrons. Because they require oxygen, these phases are called **aerobic.**

During these phases, notice where CO_2 and H_2O, the end products of cellular respiration, and ATP, the main outcome of respiration, are produced.

- **Glycolysis** [Gk. *glycos*, sugar, and *lysis,* splitting] is the breakdown of glucose (a 6-carbon molecule) to two molecules of pyruvate (two 3-carbon molecules). Oxidation results in NADH and provides enough energy for the net gain of two ATP molecules.
- The **preparatory (prep) reaction** takes place in the matrix of the mitochondrion. Pyruvate is broken down from a 3-carbon (C_3) to a 2-carbon (C_2) acetyl group, and a 1-carbon CO_2 molecule is released. Since glycolysis ends with two molecules of pyruvate, the prep reaction occurs twice per glucose molecule.
- The **citric acid cycle** also takes place in the matrix of the mitochondrion. Each 2-carbon acetyl group matches up with a 4-carbon molecule, forming two 6-carbon citrate molecules. As citrate bonds are broken and oxidation occurs, NADH and $FADH_2$ are formed, and two CO_2 per citrate are released. The citric acid cycle is able to produce one ATP per turn. Because two acetyl groups enter the cycle per glucose molecule, the cycle turns twice.
- The **electron transport chain (ETC)** is a series of carriers on the cristae of the mitochondria. NADH and $FADH_2$ give up their high-energy electrons to the chain. Energy is released and captured as the electrons move from a higher-energy to a lower-energy state during each redox reaction. Later, this energy is used for the production of ATP by chemiosmosis. After oxygen receives electrons at the end of the chain, it combines with hydrogen ions (H^+) and becomes water (H_2O).

Pyruvate, the end product of glycolysis, is a pivotal metabolite; its further treatment depends on whether oxygen is available. If oxygen is available, pyruvate enters a mitochondrion and is broken down completely to CO_2 and H_2O as shown in the cellular respiration equation (p. 136). If oxygen is not available, pyruvate is further metabolized in the cytoplasm by an anaerobic process called **fermentation.** Fermentation results in a net gain of only two ATP per glucose molecule.

MP3 Cellular Respiration

Check Your Progress 8.1

1. Explain the benefit of slow glucose breakdown rather than rapid breakdown during cellular respiration.
2. Describe the four phases of complete glucose breakdown, including which release CO_2 and which produce H_2O.

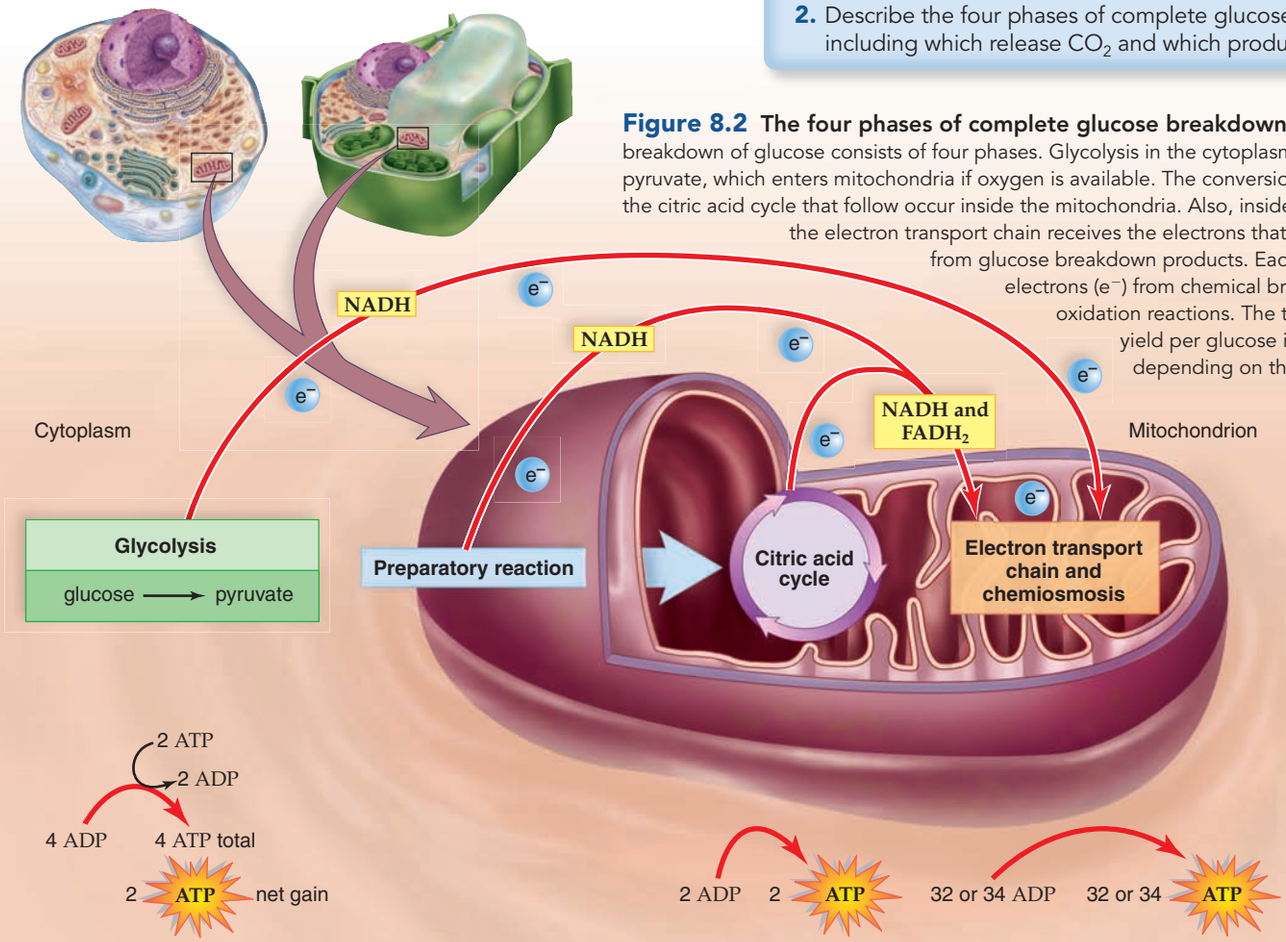


Figure 8.2 The four phases of complete glucose breakdown. The complete breakdown of glucose consists of four phases. Glycolysis in the cytoplasm produces pyruvate, which enters mitochondria if oxygen is available. The conversion reaction and the citric acid cycle that follow occur inside the mitochondria. Also, inside mitochondria, the electron transport chain receives the electrons that were removed from glucose breakdown products. Each stage generates electrons (e^-) from chemical breakdown and oxidation reactions. The theoretical yield per glucose is 36 to 38 ATP, depending on the particular cell.

8.2 Outside the Mitochondria: Glycolysis

Learning Outcomes

Upon completion of this section, you should be able to

1. Describe the location where glycolysis occurs in the cell.
2. Compare the amount of carbon between input and output of glycolysis.
3. Explain how energy-investment and energy-harvesting steps of glycolysis result in 2 net ATP.

Glycolysis, which takes place within the cytoplasm outside the mitochondria, is the breakdown of C_6 (6-carbon) glucose to two C_3 (3-carbon) pyruvate molecules. Since glycolysis occurs universally in organisms, it most likely evolved before the citric acid cycle and the electron transport chain. This may be why glycolysis occurs in the cytoplasm and does not require oxygen. There was no free oxygen in the early atmosphere of the Earth.

Glycolysis is series of ten reactions, and just as you would expect for a metabolic pathway, each step has its own enzyme. The pathway can be conveniently divided into the energy-investment step and the energy-harvesting steps. During the energy-investment step, ATP is used to "jump-start" glycolysis. During the energy-harvesting steps, four total ATP are made, producing 2 net ATP overall.

Energy-Investment Step

As glycolysis begins, two ATP are used to activate glucose by adding phosphate. Glucose eventually splits into two C_3 molecules known as G3P, the same molecule produced during photosynthesis. Each G3P has a phosphate group, each of which is acquired from an ATP molecule. From this point on, each C_3 molecule undergoes the same series of reactions.

Energy-Harvesting Step

Oxidation of G3P now occurs by the removal of electrons accompanied by hydrogen ions. In duplicate reactions, electrons are picked up by coenzyme NAD^+, which becomes

$$\text{NADH: } 2\ NAD^+ + 4\ e^- + 2\ H^+ \longrightarrow 2\ NADH$$

When O_2 is available, each NADH molecule carries two high-energy electrons to the electron transport chain and becomes NAD^+ again. In this way, NAD^+ is recycled and used again.

The addition of inorganic phosphate results in a high-energy phosphate group on each C_3 molecule. These phosphate groups are used to directly synthesize two ATP in the later steps of glycolysis. This is called **substrate-level ATP synthesis** (sometimes called substrate-level phosphorylation) because an enzyme passes a high-energy phosphate to ADP, and ATP results (Fig. 8.3). Notice that this is an example of coupling: An energy-releasing reaction is driving forward an energy-requiring reaction on the surface of the enzyme.

Oxidation occurs again, but by the removal of H_2O. Substrate-level ATP synthesis occurs again per each C_3, and two molecules of pyruvate result. Subtracting the two ATP that were used to get started, and the four ATP produced overall, there is a net gain of two ATP from glycolysis (Fig. 8.4).

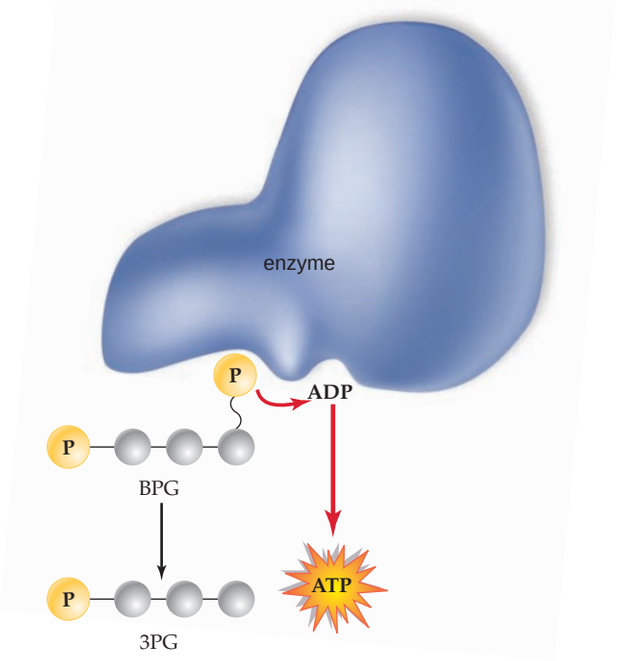
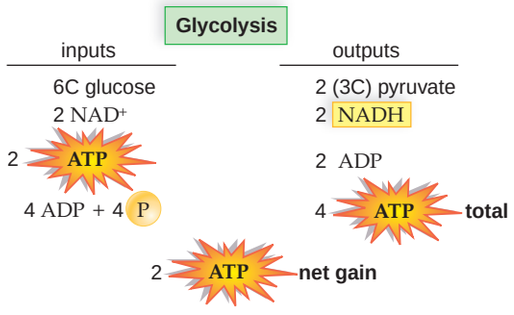


Figure 8.3 Substrate-level ATP synthesis. Substrates participating in the reaction are oriented on the enzyme. A phosphate group is transferred to ADP, producing one ATP molecule. During glycolysis (see Fig. 8.4), BPG is a C_3 substrate (each gray ball is a carbon atom) that gives up a phosphate group to ADP. This reaction occurs twice per glucose molecule.

Animation How Glycolysis Works

Inputs and Outputs of Glycolysis

All together, the inputs and outputs of glycolysis are as follows:



Notice that, so far, we have accounted for only two of the 36 to 38 ATP molecules that are theoretically possible when glucose is completely broken down to CO_2 and H_2O. When O_2 is available, the end product of glycolysis, pyruvate, enters the mitochondria, where it is metabolized. If O_2 is not available, fermentation, which is discussed next, occurs.

3D Animation Glycolysis

Check Your Progress 8.2

1. Examine where ATP is used and is produced in glycolysis.
2. Explain how ATP is produced from ADP and phosphate during glycolysis.

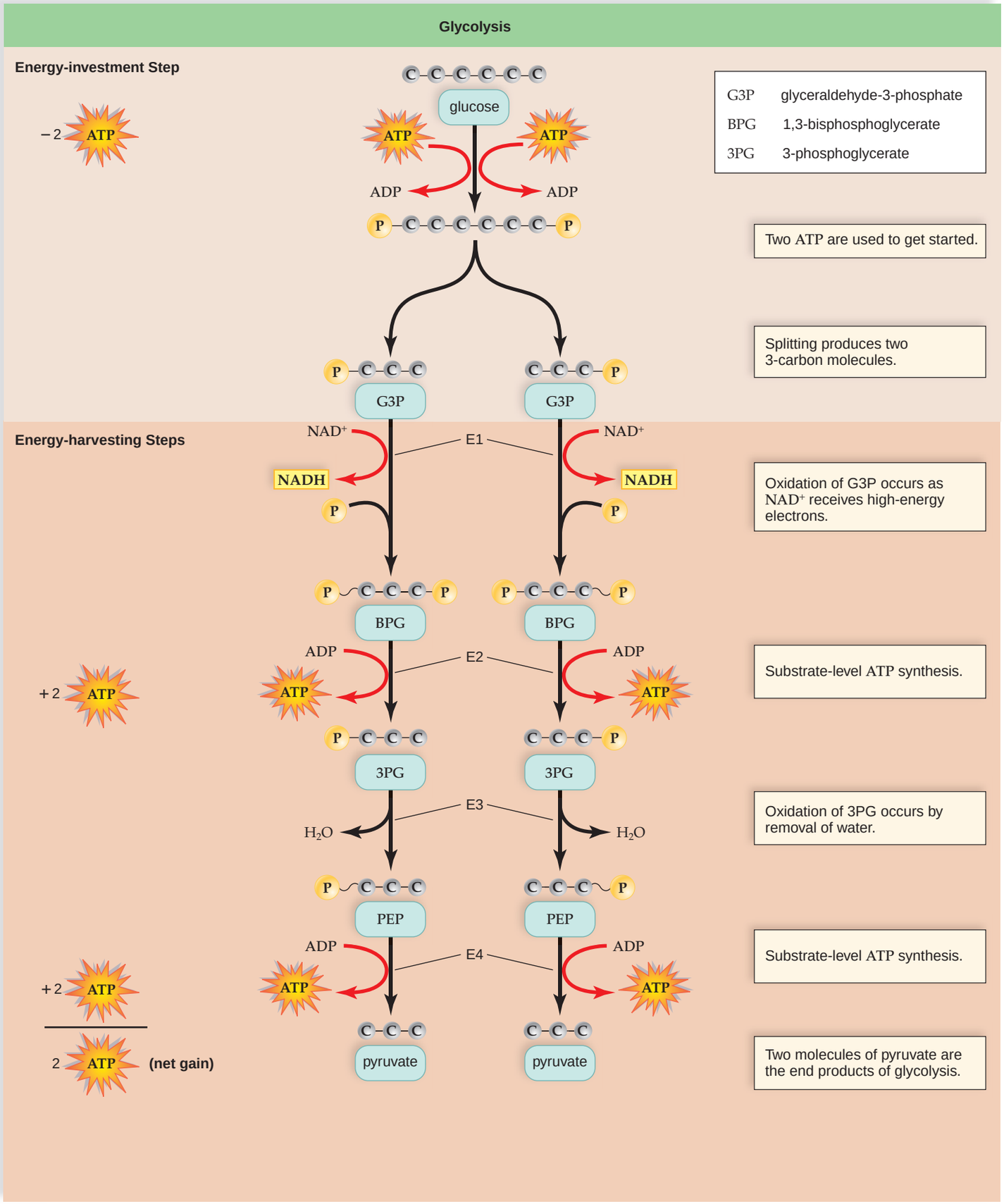


Figure 8.4 Glycolysis. This metabolic pathway begins with C_6 glucose (each gray ball is a carbon atom) and ends with two C_3 pyruvate molecules. Net gain of two ATP molecules can be calculated by subtracting those expended during the energy-investment step from those produced during the energy-harvesting steps. Each step is catalyzed by a specialized enzyme (E).

8.3 Outside the Mitochondria: Fermentation

Learning Outcomes

Upon completion of this section, you should be able to

1. Explain how ATP can continue to be produced in the absence of oxygen.
2. Compare the benefits and drawbacks of fermentation.

Complete glucose breakdown requires an input of oxygen to keep the electron transport chain working. So how does the cell produce energy if oxygen is limited? **Fermentation** is an anaerobic process that produces a limited amount of ATP in the absence of oxygen. In animal cells, including human cells, pyruvate, the end product of glycolysis, is reduced by NADH to lactate (Fig. 8.5). Depending on their particular enzymes, bacteria vary as to whether they produce an organic acid, such as lactate, or an alcohol and CO_2. Yeasts are good examples of organisms that generate ethyl alcohol and CO_2 as a result of fermentation.

Why is it beneficial for pyruvate to be reduced when oxygen is not available? Because the cell still needs energy when oxygen is absent. The fermentation reaction regenerates NAD^+, which is required for the first step in the energy-harvesting phase of glycolysis. This NAD^+ is now "free" to return to the earlier reaction (see return arrow in Fig. 8.5) and become reduced once more. Although this process generates much less ATP than when oxygen is present and glucose is fully metabolized into CO_2 and H_2O in the ETC, glycolysis and substrate-level ATP synthesis produce enough energy for the cell to continue working.

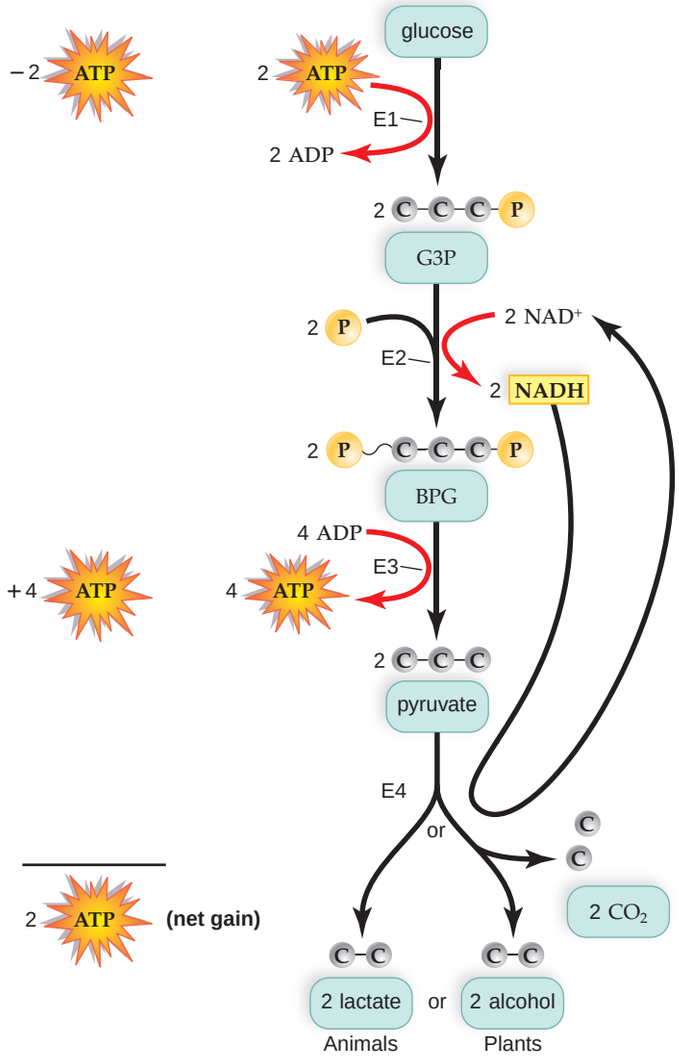


Figure 8.5 Fermentation. Fermentation consists of glycolysis followed by a reduction of pyruvate. This "frees" NAD^+ and it returns to the glycolytic pathway to pick up more electrons. As with glycolysis, each step is catalyzed by a specialized enzyme (E).

Advantages and Disadvantages of Fermentation

As discussed in the Nature of Science feature in this chapter, people have long used anaerobic bacteria that produce lactate to create cheese, yogurt, and sauerkraut—even before we knew that bacteria were responsible! Other bacteria produce chemicals of industrial importance, including isopropanol, butyric acid, propionic acid, and acetic acid when they ferment. Yeasts, of course, are used to make breads rise. In addition, alcoholic fermentation is utilized to produce wine, beer, and other alcoholic beverages.

Despite its low yield of only two ATP made by substrate-level ATP synthesis, lactic acid fermentation is essential to certain animals and/or tissues. Typically, animals use lactic acid fermentation for a rapid burst of energy, such as a cheetah chasing a gazelle. Also, when muscles are working vigorously over a short period of time, lactic acid fermentation provides them with ATP, even though oxygen is temporarily in limited supply.

Efficiency of Fermentation

The two ATP produced per glucose during alcoholic fermentation and lactic acid fermentation are equivalent to 14.6 kcal. Complete glucose breakdown to CO_2 and H_2O represents a possible energy yield of 686 kcal per molecule. Therefore, the efficiency of fermentation is only 14.6 kcal/686 kcal × 100, or 2.1% of the total possible for the complete breakdown of glucose. The inputs and outputs of fermentation are shown here:

Fermentation

inputs	outputs
glucose	2 lactate or 2 alcohol and 2 CO_2
2 ADP + 2 P	2 ATP net gain

The two ATP produced by fermentation fall far short of the theoretical 36 or 38 ATP molecules that may be produced by cellular respiration. To achieve this number of ATP per glucose molecule, it is necessary to move on to the reactions and pathways that occur with oxygen in the mitochondria.

Check Your Progress 8.3

1. Describe the role of NADH in fermentation.

Nature of Science

Fermentation Helps Produce Numerous Food Products

At the grocery store, you will find such items as bread, yogurt, soy sauce, pickles, and maybe even beer or wine (**Fig. 8A**). These are just a few of the many foods that are produced when microorganisms ferment (break down sugar in the absence of oxygen). Foods produced by fermentation last longer because the fermenting organisms have removed many of the nutrients that would attract other organisms. The products of fermentation can even be dangerous to the very organisms that produced them, as when yeasts are killed by the alcohol they produce.

Yeast Fermentation

Baker's yeast, *Saccharomyces cerevisiae*, is added to bread for the purpose of leavening—the dough rises when the yeasts give off CO_2. The ethyl alcohol produced by the fermenting yeast evaporates during baking. The many different varieties of sourdough breads obtain their leavening from a starter

composed of fermenting yeasts along with bacteria from the environment. Depending on the community of microorganisms in the starter, the flavor of the bread may range from sour and tangy, as in San Francisco–style sourdough, to a milder taste, such as that produced by most Amish friendship bread recipes.

Ethyl alcohol in beer and wine is produced when yeasts ferment carbohydrates. When yeasts ferment fruit carbohydrates, the end result is wine. If they ferment grain, beer results. A few specialized varieties of beer, such as traditional wheat beers, have a distinctive sour taste because they are produced with the assistance of lactic acid–producing bacteria, such as those of the genus *Lactobacillus.* Stronger alcoholic drinks (e.g., whiskey and vodka) require distillation to concentrate the alcohol content.

Bacteria that produce acetic acid, including *Acetobacter aceti*, spoil wine. These bacteria convert the alcohol in wine or cider to acetic acid (vinegar). Until the renowned nineteenth-century scientist Louis Pasteur invented the process of pasteurization, acetic acid bacteria commonly caused wine to spoil. Although today we generally associate the process of pasteurization with making milk safe to drink, it was originally developed to reduce bacterial contamination in wine so that limited acetic acid would be produced. The discovery of pasteurization is another example of how the pursuit of scientific knowledge can positively affect our lives.

Bacterial Fermentation

Yogurt, sour cream, and cheese are produced through the action of various lactic acid bacteria that cause milk to sour. Milk contains lactose, which these bacteria use as a carbohydrate source for fermentation. Yogurt, for example, is made by adding lactic acid bacteria, such as *Streptococcus thermophilus* and *Lactobacillus bulgaricus,* to milk and then incubating it to encourage the bacteria to convert the lactose. During the production of cheese, an enzyme called rennin must also be added to the milk to cause it to coagulate and become solid.

Old-fashioned brine cucumber pickles, sauerkraut, and kimchi are pickled vegetables produced by the action of acid-producing, fermenting bacteria that can survive in high-salt environments. Salt is used to draw liquid out of the vegetables and aid in their preservation. The bacteria need not be added to the vegetables, because they are already present on the surfaces of the plants.

Soy Sauce Production

Soy sauce is traditionally made by adding a mold, *Aspergillus,* and a combination of yeasts and fermenting bacteria to soybeans and wheat. The mold breaks down starch, supplying the fermenting microorganisms with sugar they can use to produce alcohol and organic acids.

As you can see from each of these examples, fermentation is a biologically and economically important process that scientists use for the betterment of our lives.

Questions to Consider:

1. How many products of fermentation do you consume daily?
2. What might everyday life be like without fermentation?

Figure 8A Products from fermentation. *Fermentation of different carbohydrates by microorganisms like bacteria and yeast helps produce the products shown.*

8.4 Inside the Mitochondria

Learning Outcomes

Upon completion of this section, you should be able to

1. Explain the fate of each carbon during the complete aerobic metabolism of glucose.
2. Contrast substrate-level phosphorylation and chemiosmosis as methods of ATP synthesis.
3. Describe how electron energy from redox reactions is used to create a proton gradient.

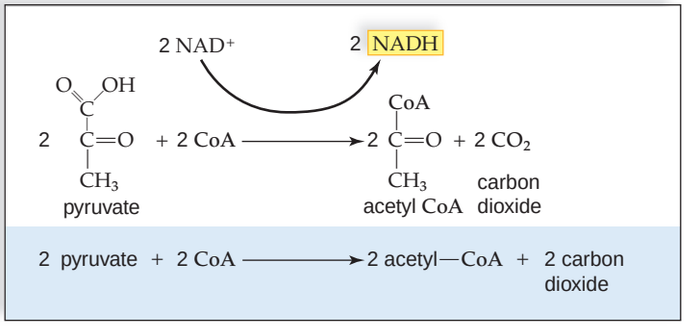
The preparatory (prep) reaction, the citric acid cycle, and the electron transport chain, which are needed for the complete breakdown of glucose, take place within the mitochondria. A **mitochondrion** has a double membrane with an intermembrane space (between the outer and inner membrane). Cristae are folds of inner membrane that jut out into the matrix, the innermost compartment, which is filled with a gel-like fluid (Fig. 8.6). Like a chloroplast, a mitochondrion is highly structured, and as such we would expect reactions to be located in particular parts of this organelle.

The enzymes that speed the prep reaction and the citric acid cycle are arranged in the matrix, and the electron transport chain is located in the cristae in a very organized manner.

Most of the ATP from cellular respiration is produced in mitochondria; therefore, mitochondria are often called the powerhouses of the cell.

The Preparatory Reaction

The **preparatory (prep) reaction** is so called because it converts products from glycolysis into products that enter the citric acid cycle. In this reaction, the C_3 pyruvate is converted to a C_2 acetyl group and CO_2 is given off. This is an oxidation-reaction in which electrons are removed from pyruvate by NAD^+, and NADH is formed. One prep reaction occurs per pyruvate, so altogether, the prep reaction occurs twice per glucose molecule:



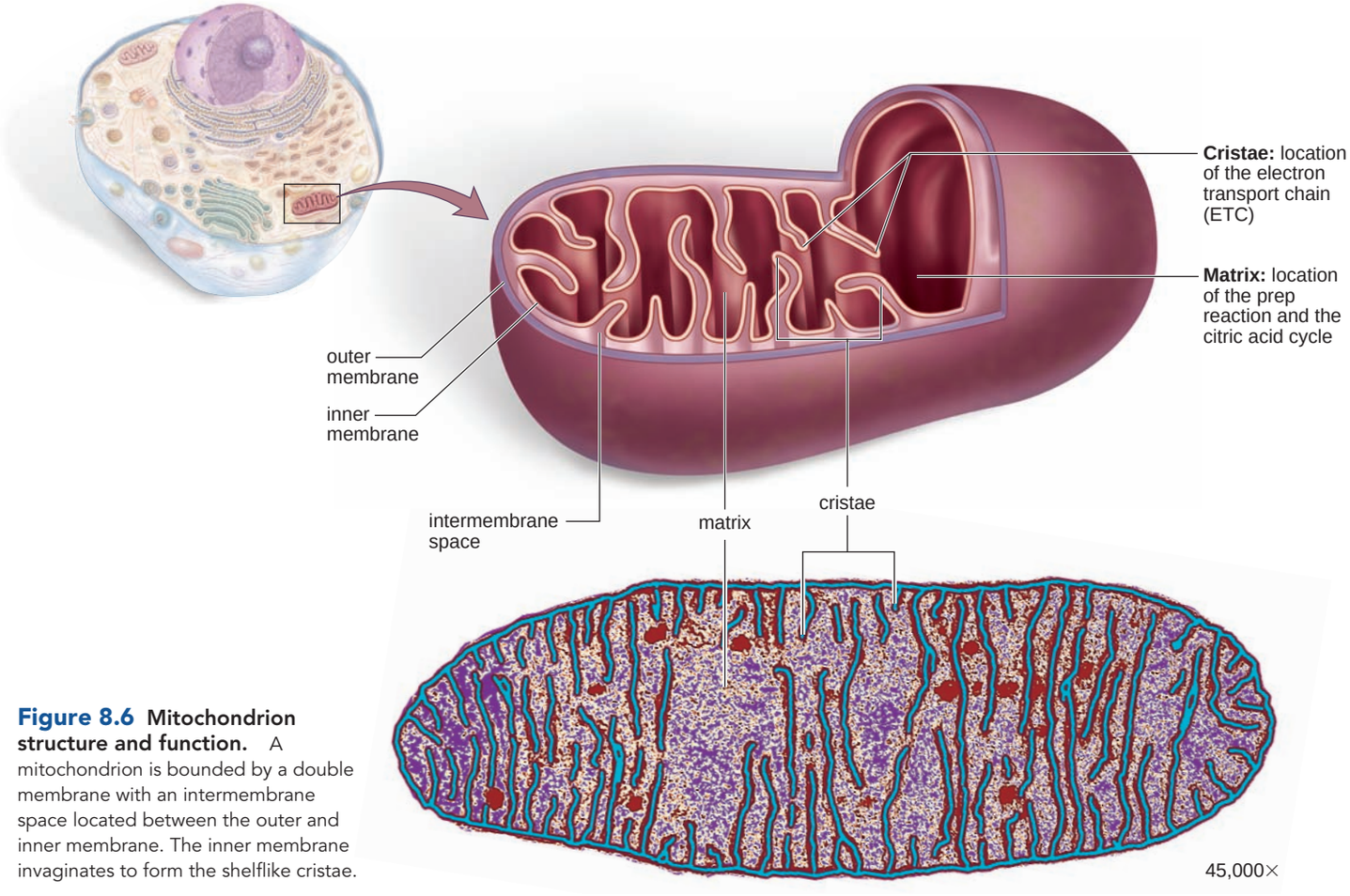


Figure 8.6 Mitochondrion structure and function. A mitochondrion is bounded by a double membrane with an intermembrane space located between the outer and inner membrane. The inner membrane invaginates to form the shelflike cristae.

The C_2 acetyl group is combined with a molecule known as CoA. CoA will carry the acetyl group to the citric acid cycle in the mitochondrial matrix. The two NADH carry electrons to the electron transport chain. What about the CO_2? In vertebrates, such as ourselves, CO_2 freely diffuses out of cells into the blood, which transports it to the lungs where it is exhaled.

Citric Acid Cycle

The **citric acid cycle** is a cyclical metabolic pathway located in the matrix of mitochondria (Fig. 8.7). The citric acid cycle is also known as the Krebs cycle, after Hans Krebs, the chemist who worked out the fundamentals of the process in the 1930s.

Animation
How the Krebs Cycle Works

At the start of the citric acid cycle, the (C_2) acetyl group carried by CoA joins with a C_4 molecule, and a C_6 citrate molecule results. During the cycle, oxidation occurs when electrons are accepted by NAD^+ in three instances and by FAD in one instance. Therefore, three NADH and one $FADH_2$ are formed as a result of one turn of the citric acid cycle. Also, the acetyl group received from the prep reaction is oxidized to two CO_2 molecules. Substrate-level ATP synthesis is also an important event of the citric acid cycle. In substrate-level ATP synthesis, you will recall, an enzyme passes a high-energy phosphate to ADP, and ATP results.

Because the citric acid cycle turns twice for each original glucose molecule, the inputs and outputs of the citric acid cycle per glucose molecule are as follows:

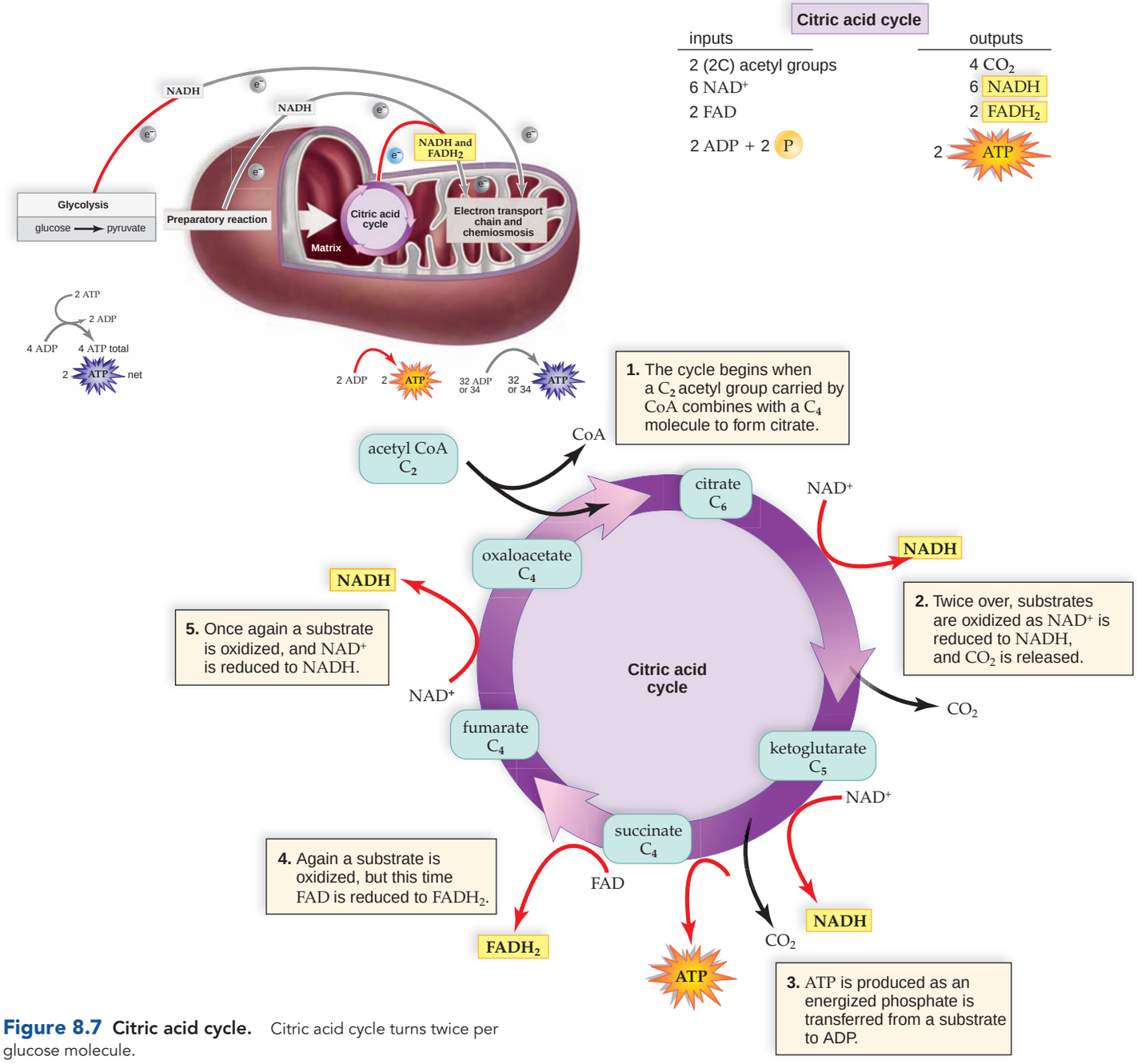


Figure 8.7 Citric acid cycle. Citric acid cycle turns twice per glucose molecule.

Production of CO_2

The six carbon atoms originally located in a glucose molecule have now become CO_2. The prep reaction produces the first two CO_2, and the citric acid cycle produces the last four CO_2 per glucose molecule. We have already mentioned that this is the CO_2 humans and other animals breathe out.

Thus far, we have broken down glucose to CO_2 and hydrogen atoms. Recall that, as bonds are broken and glucose gets converted to CO_2, energy in the form of high energy electrons is released. NADH and $FADH_2$ capture those high-energy electrons and carry them to the electron transport chain, as discussed next.

Electron Transport Chain

The **electron transport chain (ETC),** located in the cristae of the mitochondria and the plasma membrane of aerobic prokaryotes, is a series of carriers that pass electrons from one to the other. The high-energy electrons that enter the electron transport chain are carried by NADH and $FADH_2$. Figure 8.8 is arranged to show that high-energy electrons enter the chain, and low-energy electrons leave the chain.

Members of the Chain

When NADH gives up its electrons, it becomes oxidized to NAD^+, and when $FADH_2$ gives up its electrons, it becomes oxidized to FAD. The next carrier gains the electrons and is reduced. This oxidation-reduction reaction starts the process, and each of the carriers, in turn, becomes reduced and then oxidized as the electrons move down the chain.

Many of the redox carriers are cytochrome molecules. A **cytochrome** is a protein that has a tightly bound heme group with a central atom of iron, the same as hemoglobin does. When the iron accepts electrons, it becomes reduced, and when iron gives them up, it becomes oxidized. As the pair of electrons is passed from carrier to carrier, energy is captured and eventually used to form ATP molecules. A number of poisons, such as cyanide, cause death by binding to and blocking the function of cytochromes.

What is the role of oxygen in cellular respiration and the reason we breathe to take in oxygen? Oxygen is the final acceptor of electrons from the electron transport chain. Oxygen receives the energy-spent electrons from the last of the carriers (i.e., cytochrome oxidase). After receiving electrons, oxygen combines with hydrogen ions, and water forms:

$$\tfrac{1}{2}O_2 + 2e^- + 2H^+ \longrightarrow H_2O$$

The critical role of oxygen as the final acceptor of electrons during cellular respiration is exemplified by noting that if oxygen is not present, the chain does not function, and no ATP is produced by mitochondria. The limited capacity of the body to form ATP in a way that does not involve the electron transport chain means that death eventually results if oxygen is not available.

Cycling of Carriers

When NADH delivers high energy electrons to the first carrier of the electron transport chain, enough energy is captured by the time the electrons are received by O_2 to permit the production of three ATP molecules. When $FADH_2$ delivers high-energy electrons to the electron transport chain, two ATP are produced.

Once NADH has delivered electrons to the electron transport chain and becomes NAD^+, it is able to return and pick up more hydrogen atoms. The reuse of coenzymes increases cellular efficiency because the cell does not have to constantly make new NAD^+; it simply recycles what is already there.

The Cristae of a Mitochondrion and Chemiosmosis

The carriers of the electron transport chain and the proteins involved with ATP synthesis are spatially arranged on the cristae of mitochondria. Their sequential arrangement on the cristae allows the production of ATP to occur.

The ETC Pumps Hydrogen Ions. Essentially, the electron transport chain consists of three protein complexes and two carriers. The three protein complexes include NADH-Q reductase complex, the cytochrome reductase complex, and cytochrome oxidase complex. The two other carriers that transport electrons between the complexes are coenzyme Q and cytochrome *c* (Fig. 8.8).

We have already seen that the members of the electron transport chain accept electrons, which they pass from one to the other via redox reactions. So what happens to the hydrogen ions (H^+) carried by NADH and $FADH_2$? The complexes of the electron transport chain use the energy released during redox reactions to pump these hydrogen ions from the matrix into the intermembrane space of a mitochondrion.

The vertical arrows in Figure 8.8 show that the protein complexes of the electron transport chain all pump H^+ into the intermembrane space. Energy obtained from electron passage is needed because H^+ ions are pumped and actively transported against their gradient. This means the few H^+ ions in the matrix will be moved to the intermembrane space, where there are already many H^+ ions. Just as the walls of a dam hold back water, allowing it to collect, so do cristae hold back hydrogen ions. Eventually, a strong electrochemical gradient develops; about ten times as many H^+ are found in the intermembrane space as are present in the matrix.

The ATP Synthase Complex Produces ATP. The ATP synthase complex can be likened to the gates of a dam. When the gates of a hydroelectric dam are opened, water rushes through, and electricity (energy) is produced. Similarly, when H^+ flows down a gradient from the intermembrane space into the matrix, the enzyme ATP synthase synthesizes ATP from ADP +Ⓟ. This process

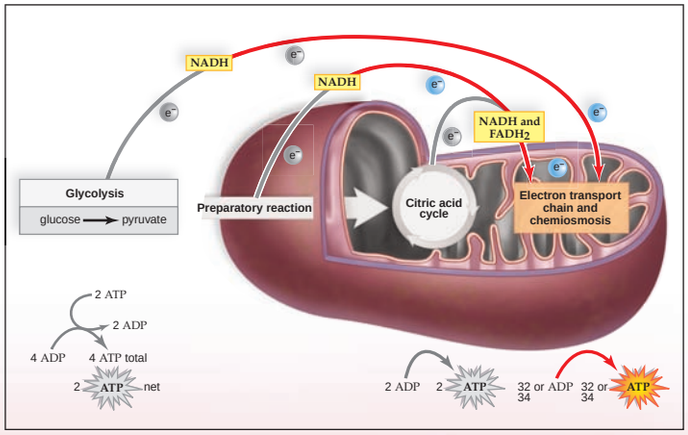
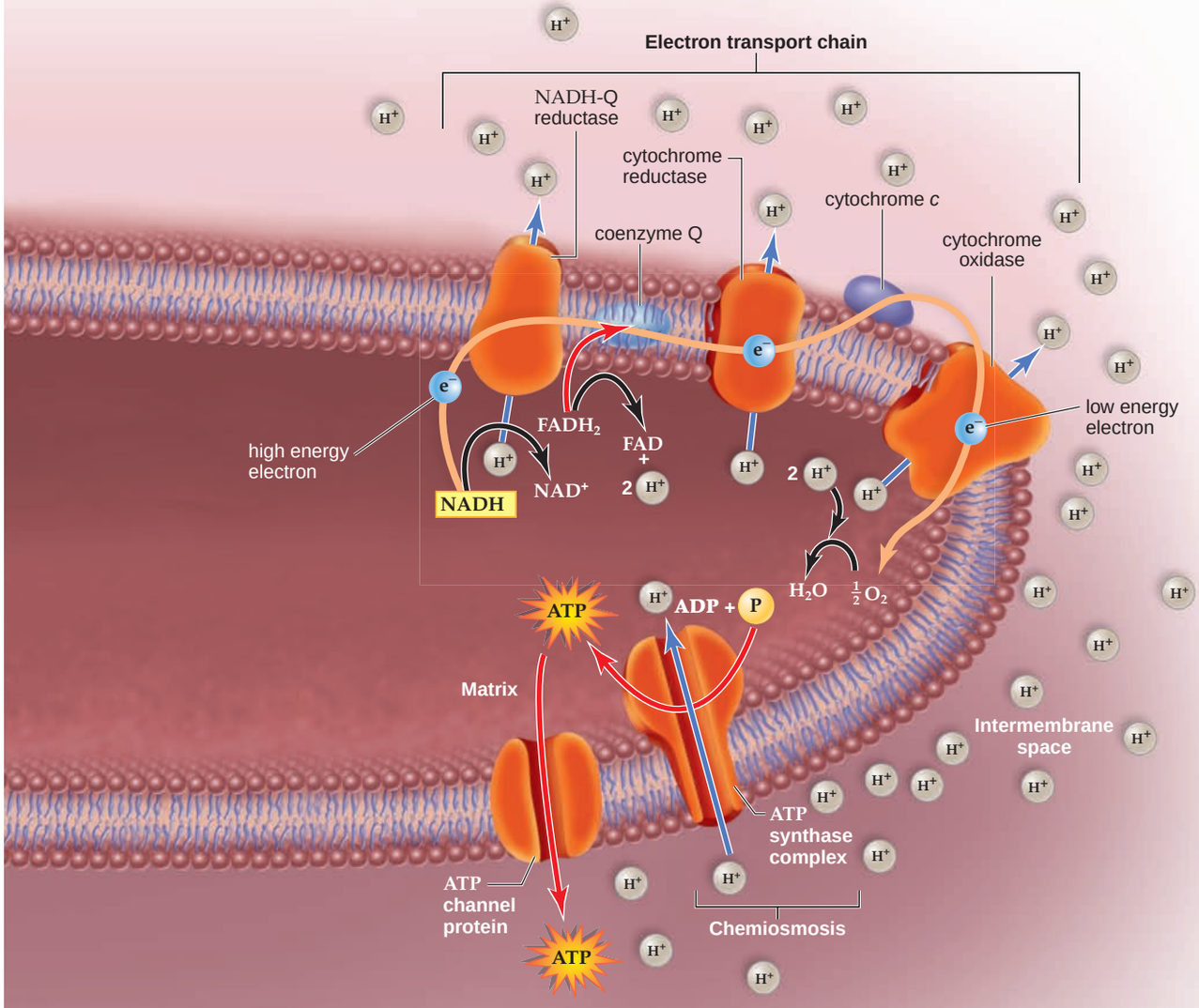


Figure 8.8 Organization and function of the electron transport chain. The electron transport chain is located in the mitochondrial cristae. NADH and $FADH_2$ bring electrons to the electron transport chain. As electrons move from one protein complex to the other via redox reactions, energy is used to pump hydrogen ions (H^+) from the matrix into the intermembrane space. As hydrogen ions flow down a concentration gradient from the intermembrane space into the mitochondrial matrix, ATP is synthesized by the enzyme ATP synthase. For every pair of electrons that enters by way of NADH, three ATP result. For every pair of electrons that enters by way of $FADH_2$, two ATP result. Oxygen, the final acceptor of the electrons, becomes a part of water. ATP leaves the matrix by way of a channel protein.



is called **chemiosmosis** because ATP production is tied to the establishment of an H^+ gradient.

Once formed, ATP moves out of mitochondria and is used to perform cellular work, during which it breaks down to ADP and Ⓟ. These molecules are then returned to mitochondria for recycling. At any given time, the amount of ATP in a human would sustain life for only about a minute; therefore, ATP synthase must constantly produce ATP. It is estimated that mitochondria produce our body weight in ATP every day.

Active Tissues Contain More Mitochondria. Active tissues, such as muscles, require greater amounts of ATP and have more mitochondria than less active cells. When a burst of energy is required, however, muscles still utilize fermentation.

As an example of the relative amounts of ATP, consider that the dark meat of chickens, namely the thigh meat, contains more mitochondria than the white meat of the breast. This suggests that chickens mainly walk or run, rather than fly, about the barnyard.

Energy Yield from Glucose Metabolism

Figure 8.9 calculates the theoretical ATP yield for the complete breakdown of glucose to CO_2 and H_2O during cellular respiration. Notice that the diagram includes the number of ATP produced directly by glycolysis and the citric acid cycle (to the left), as well as the number produced as a result of electrons passing down the electron transport chain (to the right). A maximum of between 32 to 34 ATP molecules may be produced by the electron transport chain.

Substrate-Level ATP Synthesis

Per glucose molecule, there is a net gain of two ATP from glycolysis, which takes place in the cytoplasm. The citric acid cycle, which occurs in the matrix of mitochondria, accounts for two ATP per glucose molecule. This means that a total of four ATP are formed by substrate-level ATP synthesis outside the electron transport chain.

ETC and Chemiosmosis

Most ATP is produced by the electron transport chain and chemiosmosis. Per glucose molecule, ten NADH and two $FADH_2$ take electrons to the electron transport chain. For each NADH formed *inside* the mitochondria by the citric acid cycle, three ATP result, but for each $FADH_2$, only two ATP are produced. Figure 8.8 explains the reason for this difference: $FADH_2$ delivers its electrons to the transport chain after NADH, and therefore these electrons do not participate in as many redox reactions and don't pump as many H^+ as NADH. Therefore, $FADH_2$ cannot account for as much ATP production.

What about the ATP yield per NADH generated *outside* the mitochondria by the glycolytic pathway? In some cells, NADH cannot cross mitochondrial membranes, but a "shuttle" mechanism allows its electrons to be delivered to the electron transport chain inside the mitochondria. The cost to the cell is one ATP for each NADH that is shuttled to the ETC. This reduces the overall count of ATP produced as a result of glycolysis, in some cells, to four instead of six ATP.

Efficiency of Cellular Respiration

It is interesting to calculate how much of the energy in a glucose molecule eventually becomes available to the cell. The difference in energy content between the reactants (glucose and O_2) and the products (CO_2 and H_2O) is 686 kcal. An ATP phosphate bond has an energy content of 7.3 kcal, and 36 of these are potentially produced during glucose breakdown; 36 phosphates are equivalent to a total of 263 kcal. Therefore, 263/686, or 39%, of the available energy is usually transferred from glucose to ATP. The rest of the energy is lost in the form of heat.

In the next section, we consider how cellular respiration fits into metabolism as a whole.

Check Your Progress 8.4

1. Explain when carbon is converted from glucose into carbon dioxide during cellular respiration.
2. Examine which processes during glucose breakdown produce the most ATP.
3. Compare the function of the mitochondrial inner membrane to a hydroelectric dam.

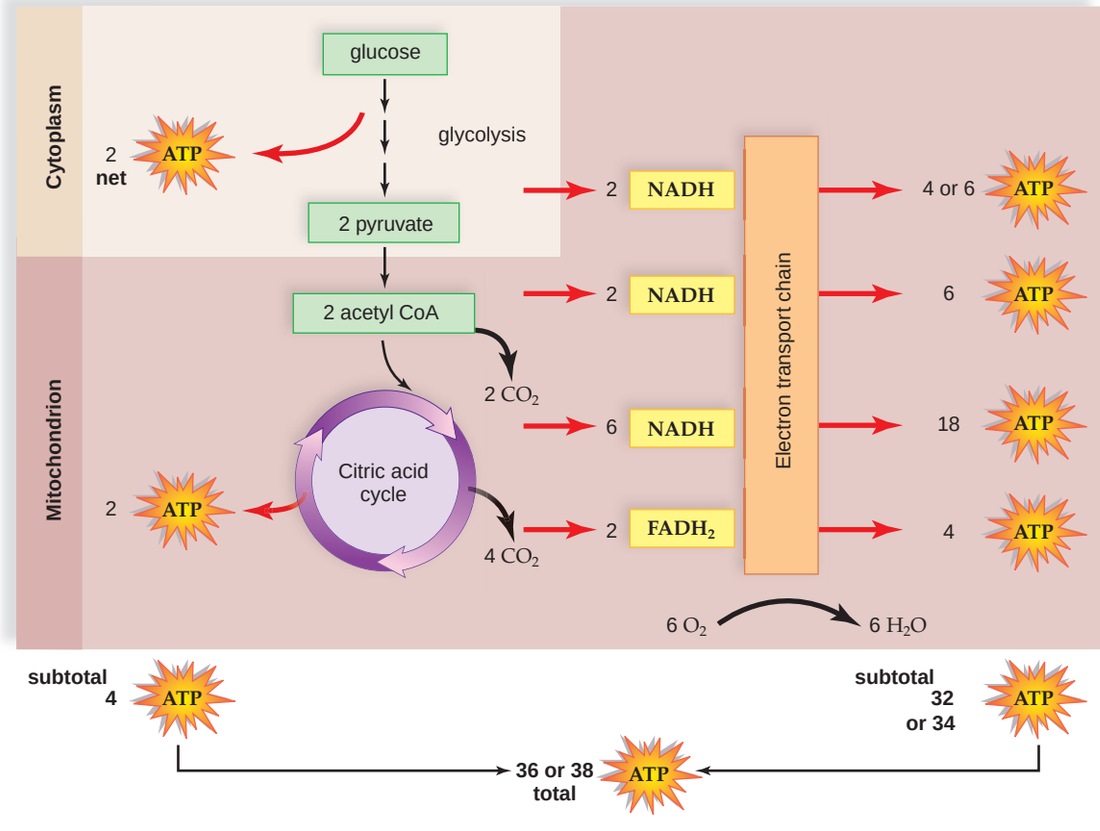


Figure 8.9 Accounting of energy yield per glucose molecule breakdown. Substrate-level ATP synthesis during glycolysis and the citric acid cycle accounts for 4 ATP. The electron transport chain accounts for 32 or 34 ATP, making the theoretical grand total of ATP between 36 and 38 ATP. Other factors may reduce the efficiency of cellular respiration. For example, cells differ as to the delivery of the electrons from NADH generated outside the mitochondria. If they are delivered by a shuttle mechanism to the start of the electron transport chain, 6 ATP result; otherwise, 4 ATP result.

8.5 Metabolic Pool

Learning Outcomes

Upon completion of this section, you should be able to

1. Compare the pathways of carbohydrate, fat, and protein catabolism.
2. Explain how the structure of mitochondria and chloroplasts enable a flow of energy through living things.

Key metabolic pathways routinely draw from pools of particular substrates needed to synthesize or degrade larger molecules. Substrates like the end product of glycolysis, pyruvate, exist as a pool that is continuously affected by changes in cellular and environmental conditions (Fig. 8.10). Degradative reactions, termed **catabolism,** that break down molecules must be dynamically balanced with constructive reactions, or **anabolism.** For example, catabolic breakdown of fats will occur when insufficient carbodyrate is present; this breakdown adds to the **metabolic pool** of pyruvate. When energy needs to be stored as fat, pyruvate is taken from the pool. This dynamic balance of catabolism and anabolism is essential to optimal cellular function.

Catabolism

We already know that glucose is broken down during cellular respiration. However, other molecules like fats and proteins can also be broken down as necessary. When a fat is used as an energy source, it breaks down to glycerol and three fatty acids. As Figure 8.10 indicates, glycerol can be converted to pyruvate and enter glycolysis. The fatty acids are converted to 2-carbon acetyl CoA that enters the citric acid cycle. An 18-carbon fatty acid results in nine acetyl CoA molecules. Calculation shows that respiration of these can produce a total of 108 ATP molecules. This is why fats are an efficient form of stored energy—the three long fatty acid chains per fat molecule can produce considerable ATP when needed.

Proteins are less frequently used as an energy source, but are available as necessary. The carbon skeleton of amino acids can enter glycolysis, be converted to acetyl groups, or enter the citric acid cycle at some other juncture. The carbon skeleton is produced in the liver when an amino acid undergoes **deamination,** or the removal of the amino group. The amino group becomes ammonia (NH_3), which enters the urea cycle and becomes part of urea, the primary excretory product of humans. Just where the carbon skeleton begins degradation depends on the length of the *R* group, since this determines the number of carbons left after deamination.

Anabolism

We have already mentioned that the building of new molecules requires ATP produced during breakdown of molecules. These catabolic reactions also provide the basic components used to build new molecules. For example, excessive carbohydrate intake can result in the formation of fat. Extra G3P from glycolysis can be converted to glycerol, and acetyl groups from glycolysis can be joined to form fatty acids, which in turn are used to synthesize fat. This explains why you gain weight from eating too much candy, ice cream, or cake.

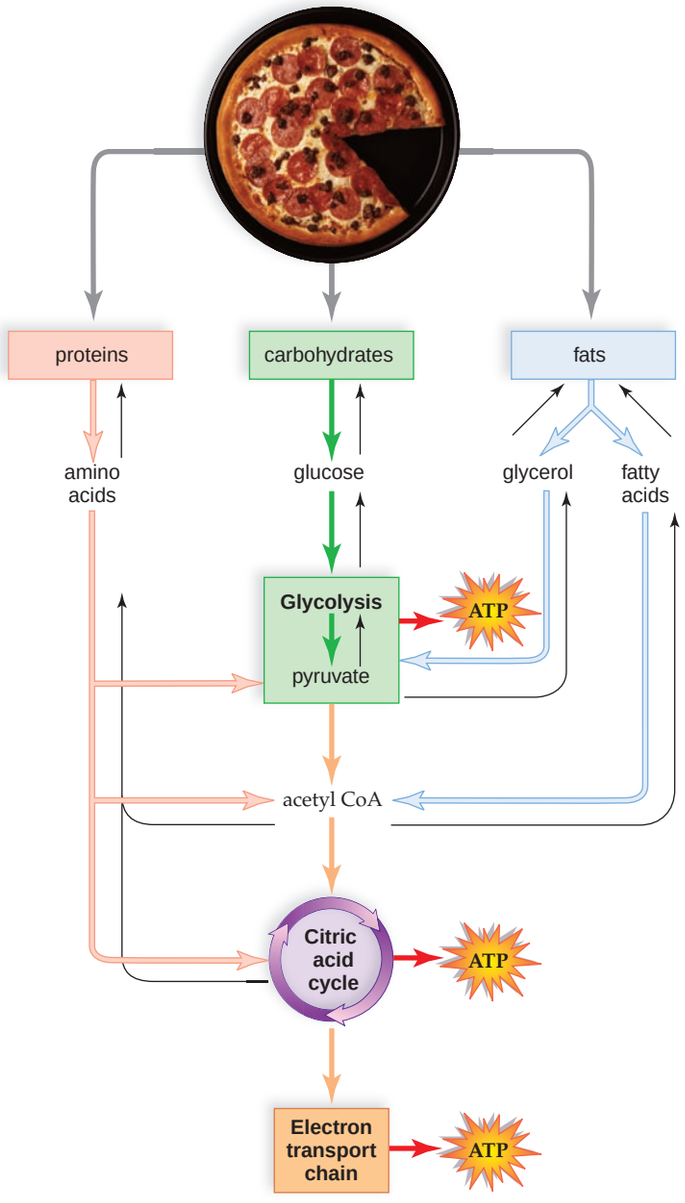


Figure 8.10 The metabolic pool concept. Carbohydrates, fats, and proteins can be used as energy sources, and their monomers (carbohydrates and proteins) or subunits (fats) enter degradative pathways at specific points. Catabolism produces molecules that can also be used for anabolism of other compounds.

Some substrates of the citric acid cycle can be converted to amino acids through transamination—the transfer of an amino group to an organic acid, forming a different amino acid. Plants are able to synthesize all of the amino acids they need. Animals, however, lack some of the enzymes necessary for synthesis of all amino acids. Adult humans, for example, can synthesize 11 of the common amino acids, but they cannot synthesize the other 9. The amino acids that cannot be synthesized must be supplied

by the diet; they are called the essential amino acids. (The amino acids that can be synthesized are called nonessential.) It is quite possible for animals to suffer from protein deficiency if their diets do not contain adequate quantities of all the essential amino acids.

The Energy Organelles Revisited

The equation for photosynthesis in a chloroplast is opposite to that of cellular respiration in a mitochondrion (Fig. 8.11):

$$\text{energy} + 6\,CO_2 + 6\,H_2O \underset{\text{cellular respiration}}{\overset{\text{photosynthesis}}{\rightleftharpoons}} C_6H_{12}O_6 + 6\,O_2$$

While you were studying photosynthesis and cellular respiration, you may have noticed a remarkable similarity in the structural organization of chloroplasts and mitochondria. Through evolution, all organisms are related, and the similar organization of these organelles suggests that they may be related also. The two organelles carry out related but opposite processes:

1. *Use of membrane.* In a chloroplast, an inner membrane forms the thylakoids of the grana. In a mitochondrion, an inner membrane forms the convoluted cristae.
2. *Electron transport chain (ETC).* An ETC is located on the thylakoid membrane of chloroplasts and the cristae of mitochondria. In chloroplasts, the electrons passed down the ETC have been energized by the Sun; in mitochondria, energized electrons have been removed from glucose and glucose products. In both, the ETC establishes an electrochemical gradient of H^+ with subsequent ATP production by chemiosmosis.
3. *Enzymes.* In a chloroplast, the stroma contains the enzymes of the Calvin cycle and in mitochondria, the matrix contains the enzymes of the citric acid cycle. In the Calvin cycle, NADPH and ATP are used to reduce carbon dioxide to a carbohydrate. In the citric acid cycle, the oxidation of glucose products produces NADH and ATP.

Flow of Energy

The ultimate source of energy for producing a carbohydrate in chloroplasts is the Sun; the ultimate goal of cellular respiration in a mitochondrion is the conversion of carbohydrate energy into that of ATP molecules. Therefore, energy flows from the Sun, through chloroplasts to carbohydrates, and then through mitochondria to ATP molecules.

This flow of energy maintains biological organization at all levels from molecules, organisms, and ultimately the biosphere. In keeping with the energy laws, some energy is lost with each chemical transformation, and eventually, the solar energy captured by plants is lost in the form of heat. Therefore, living things depend on a continual input of solar energy.

Although energy flows through organisms, chemicals cycle within natural systems. Aerobic organisms utilize the carbohydrate and oxygen produced by chloroplasts to generate energy within the mitochondria to sustain life. Likewise, the carbon dioxide produced by mitochondria returns to chloroplasts to be used in the manufacture of carbohydrates, producing oxygen as a by-product. Therefore, chloroplasts and mitochondria are instrumental in not only allowing a flow of energy through living things, but also permitting a cycling of chemicals.

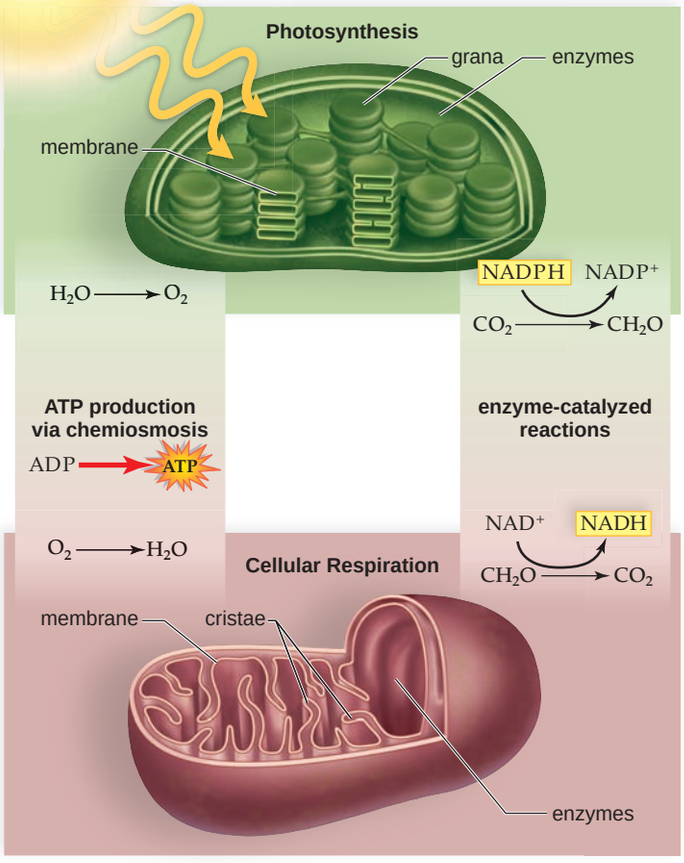


Figure 8.11 Photosynthesis versus cellular respiration.
In photosynthesis (top), water is oxidized and oxygen is released; in cellular respiration (bottom), oxygen is reduced to water. Both processes have an electron transport chain located within membranes (the grana of chloroplasts and the cristae of mitochondria), where ATP is produced by chemiosmosis. Both have enzyme-catalyzed reactions within the semifluid interior. In photosynthesis, CO_2 is reduced to a carbohydrate; in cellular respiration, a carbohydrate is oxidized to CO_2.

Check Your Progress 8.5

1. Evaluate how catabolism and anabolism are balanced within a cell.
2. Compare the structure and function of chloroplasts and mitochondria.

Connecting the Concepts with the Big Ideas

Energy and Homeostasis

- While the first steps of cellular respiration require no oxygen, aerobic conditions are essential for the function of the electron transport chain. In the absence of O_2, fermentations occur to eke out small amounts of ATP but create toxic byproducts like alcohol or lactic acid. (2A2b2)
- The slow, step-by-step enzymatic processes of glycolysis and Krebs cycle metabolize carbohydrates to water and CO_2, allowing slow release of free energy and partial capture in the creation of ATP by the electron transport chain; the remaining energy is lost as heat. (2A2f1-5, 2A2g1-4)
- NAD and FAD constantly ferry electrons and H^+ ions to the electron transport chain where they power ATP production by chemiosmosis. (2A2f4, 2A2g2-4)
- The final electron acceptor in respiration is oxygen. (2A2c*IE*)

Interactions and Systems

- The double-membraned structure of the mitochondrion provides increased surface area and enables compartmentalization of Krebs cycle enzyme and ETC functions. (4A2d1-3)
- In cellular respiration, carbohydrates or other classes of organic molecules are oxidized while oxygen is reduced, producing water; the "waste products" of respiration are the raw materials of photosynthesis. Energy flows but molecules recycle. (4A6a)

*Find the unabridged version of all EK citations at www.glencoe.com/maderAP11.

Media Study Tools

www.glencoe.com/maderAP11

Enhance your study of this chapter with study tools and practice tests. Also ask your instructor about the resources available through ConnectPlus, including the media-rich eBook, interactive learning tools, and animations.

3D Animation
Cellular Respiration

For an interactive exploration of the processes of cellular respiration, take a moment to watch McGraw-Hill's new 3D animation on cellular respiration.

Summarize

8.1 Cellular Respiration

Cellular respiration, during which glucose is completely broken down to CO_2 and H_2O, consists of four phases: glycolysis, the prep reaction, the citric acid cycle, and the passage of electrons along the electron transport chain. Oxidation of substrates involves the removal of hydrogen atoms ($H^+ + e^-$), usually by redox coenzymes. NAD^+ becomes NADH, and FAD becomes $FADH_2$.

8.2 Outside the Mitochondria: Glycolysis

Glycolysis, the breakdown of glucose to two molecules of pyruvate, is a series of enzymatic reactions that occurs in the cytoplasm and is anaerobic. Breakdown releases enough energy to immediately give a net gain of two ATP by substrate-level ATP synthesis and the production of 2 NADH.

8.3 Outside the Mitochondria: Fermentation

Fermentation involves glycolysis followed by the reduction of pyruvate by NADH either to lactate (animals) or to alcohol (yeast) and carbon dioxide (CO_2). The reduction process "frees" NAD^+ so that it can accept more hydrogen atoms from glycolysis.

Although fermentation results in only two ATP molecules, it still serves a purpose. Many of the products of fermentation are used in the baking and brewing industries. In vertebrates, it provides a quick burst of ATP energy for short-term, strenuous muscular activity. The accumulation of lactate puts the individual in oxygen debt because oxygen is needed when lactate is completely metabolized to CO_2 and H_2O.

8.4 Inside the Mitochondria

When oxygen is available, pyruvate from glycolysis enters the mitochondrion, where the prep reaction takes place. During this reaction, oxidation occurs as CO_2 is removed from pyruvate. NAD^+ is reduced, and CoA receives the C_2 acetyl group that remains. Because the reaction must take place twice per glucose molecule, two NADH result.

The acetyl group enters the citric acid cycle, a cyclical series of reactions located in the mitochondrial matrix. Complete oxidation follows, as two CO_2 molecules, three NADH molecules, and one $FADH_2$ molecule are formed. The cycle also produces one ATP molecule. The entire cycle must turn twice per glucose molecule.

The final stage of glucose breakdown involves the electron transport chain located in the cristae of the mitochondria. The electrons received from NADH and $FADH_2$ are passed down a chain of carriers until they are finally received by oxygen, which combines with H^+ to produce water. As the electrons pass down the chain, energy is captured and stored for ATP production.

The cristae of mitochondria contain complexes of the electron transport chain that not only pass electrons from one to the other

but also pump H^+ into the intermembrane space, setting up an electrochemical gradient. When H^+ flows down this gradient through an ATP synthase complex, energy is captured and used to form ATP molecules from ADP and Ⓟ. This is ATP synthesis by chemiosmosis.

Of the 36 or 38 ATP formed by complete glucose breakdown, four are the result of substrate-level ATP synthesis and the rest are produced as a result of the electron transport chain. For most NADH molecules that donate electrons to the electron transport chain, three ATP molecules are produced. However, in some cells, each NADH formed in the cytoplasm results in only two ATP molecules because a shuttle, rather than NADH, takes electrons through the mitochondrial membrane. $FADH_2$ results in the formation of only two ATP because its electrons enter the electron transport chain at a lower energy level.

8.5 Metabolic Pool

Carbohydrate, protein, and fat can be metabolized by entering the degradative pathways at different locations. These pathways also provide metabolites needed for the anabolism of various important substances. Therefore, catabolism and anabolism both use the same pools of metabolites.

Similar to the metabolic pool concept, photosynthesis and cellular respiration can be compared. For example, both utilize an ETC and chemiosmosis. As a result of the ETC in chloroplasts, water is split, while in mitochondria, water is formed. The enzymatic reactions in chloroplasts reduce CO_2 to a carbohydrate, while the enzymatic reactions in mitochondria oxidize carbohydrate with the release of CO_2.

Key Terms

aerobic 137
anabolism 147
anaerobic 137
catabolism 147
cellular respiration 136
chemiosmosis 145
citric acid cycle 137, 143
cytochrome 144
deamination 147
electron transport chain (ETC) 137, 144
FAD 136
fermentation 137, 140
glycolysis 137, 138
metabolic pool 147
mitochondrion 142
NAD^+ 136
preparatory (prep) reaction 137, 142
substrate-level ATP synthesis 138

Assess

Reviewing This Chapter

1. What is the overall chemical equation for the complete breakdown of glucose to CO_2 and H_2O? Explain how this is an oxidation-reduction reaction. 136
2. What are NAD^+ and FAD? What are their functions? 136–37
3. Briefly describe the four phases of cellular respiration. 137
4. What are the main events of glycolysis? How is ATP formed? 138–39
5. What is fermentation, and how does it differ from glycolysis? Mention the benefit of pyruvate reduction during fermentation. What types of organisms carry out lactic acid fermentation, and what types carry out alcoholic fermentation? 140–41
6. Give the substrates and products of the prep reaction. Where does it take place? 142–43
7. What are the main events of the citric acid cycle? 143
8. What is the electron transport chain, and what are its functions? 144–46
9. Describe the organization of protein complexes within the cristae. Explain how the complexes are involved in ATP production. 145
10. Calculate the theoretical energy yield of glycolysis and complete glucose breakdown. Compare the yields from substrate-level ATP synthesis and from the electron transport chain. 146
11. Give examples to support the concept of the metabolic pool. 147
12. Compare the structure and function of chloroplasts and mitochondria. Explain the flow of energy concept. 148

Testing Yourself

Choose the best answer for each question.
For questions 1–8, identify the pathway involved by matching each description to the terms in the key.

KEY:
a. glycolysis
b. citric acid cycle
c. electron transport chain

1. carbon dioxide (CO_2) given off
2. water (H_2O) formed
3. G3P
4. NADH becomes NAD^+
5. pump H^+
6. cytochrome carriers
7. pyruvate
8. FAD becomes $FADH_2$
9. The prep reaction
   a. connects glycolysis to the citric acid cycle.
   b. gives off CO_2.
   c. uses NAD^+.
   d. results in an acetyl group.
   e. All of these are correct.
10. The greatest contributor of electrons to the electron transport chain is
    a. oxygen.
    b. glycolysis.
    c. the citric acid cycle.
    d. the prep reaction.
    e. fermentation.
11. Substrate-level ATP synthesis takes place in
    a. glycolysis and the citric acid cycle.
    b. the electron transport chain and the prep reaction.
    c. glycolysis and the electron transport chain.
    d. the citric acid cycle and the prep reaction.
    e. Both b and d are correct.
12. Which of these is not true of fermentation?
    a. net gain of only two ATP
    b. occurs in cytoplasm
    c. NADH donates electrons to electron transport chain
    d. begins with glucose
    e. carried on by yeast

13. Fatty acids are broken down to
    a. pyruvate molecules, which take electrons to the electron transport chain.
    b. acetyl groups, which enter the citric acid cycle.
    c. amino acids, which excrete ammonia.
    d. glycerol, which is found in fats.
    e. All of these are correct.
14. How many ATP molecules are usually produced per NADH?
    a. 1
    b. 3
    c. 36
    d. 10
15. How many NADH molecules are produced during the complete breakdown of one molecule of glucose?
    a. 5
    b. 30
    c. 10
    d. 6
16. What is the name of the process that adds the third phosphate to an ADP molecule using the flow of hydrogen ions?
    a. substrate-level ATP synthesis
    b. fermentation
    c. reduction
    d. chemiosmosis
17. The metabolic process that produces the most ATP molecules is
    a. glycolysis.
    b. citric acid cycle.
    c. electron transport chain.
    d. fermentation.
18. Which of these is not true of the citric acid cycle? The citric acid cycle
    a. includes the prep reaction.
    b. produces ATP by substrate-level ATP synthesis.
    c. occurs in the mitochondria.
    d. is a metabolic pathway, as is glycolysis.
19. Which of these is not true of the electron transport chain? The electron transport chain
    a. is located on the cristae.
    b. produces more NADH than any metabolic pathway.
    c. contains cytochrome molecules.
    d. ends when oxygen accepts electrons.
20. The oxygen required by cellular respiration is reduced and becomes part of which molecule?
    a. ATP
    b. H_2O
    c. pyruvate
    d. CO_2

Engage

Thinking Scientifically

1. You are able to extract mitochondria from the cell and remove the outer membrane. You want to show that the mitochondria can still produce ATP if placed in the right solution. The solution should be isotonic, but at what pH? Why?
2. You are working with acetyl CoA molecules that contain only radioactive carbon. They are incubated with all the components of the citric acid cycle long enough for one turn of the cycle. Examine Figure 8.7 and explain why the carbon dioxide given off is radioactive.

Bioethical Issue

Alternative Medicine

Feeling tired and run-down? Want to jump-start your mitochondria? If you seem to have no specific ailment, you might be tempted to turn to what is now called alternative medicine. Alternative medicine includes such nonconventional therapies as herbal supplements, acupuncture, chiropractic therapy, homeopathy, osteopathy, and therapeutic touch (e.g., laying on of hands).

Advocates of alternative medicine have made some headway in having alternative medicine practices accepted by almost anyone. For example, Congress has established the National Center for Complementary and Alternative Medicine. It has also passed the Dietary Supplement Health and Education Act, which allows vitamins, minerals, and herbs to be marketed without first being approved by the Food and Drug Administration (FDA).

But is this a mistake? Many physicians believe controlled studies are needed to test the efficacy of alternative medications and practices. Do you agree? Should every food supplement or approach to health be subject to scientific testing, or are there other ways to evaluate successful treatment? Explain your reasoning.