7 | CELLULAR RESPIRATION

Figure 7.1 This geothermal energy plant transforms thermal energy from deep in the ground into electrical energy, which can be easily used. (credit: modification of work by the U.S. Department of Defense)

Chapter Outline

Introduction

The electrical energy plant in **Figure 7.1** converts energy from one form to another form that can be more easily used. This type of generating plant starts with underground thermal energy (heat) and transforms it into electrical energy that will be transported to homes and factories. Like a generating plant, plants and animals also must take in energy from the environment and convert it into a form that their cells can use. Energy enters an organism's body in one form and is converted into another form that can fuel the organism's life functions. In the process of photosynthesis, plants and other photosynthetic producers take in energy in the form of light (solar energy) and convert it into chemical energy, glucose, which stores this energy in its chemical bonds. Then, a series of metabolic pathways, collectively called cellular respiration, extract the energy from the carbon–carbon bonds of glucose and convert it into a form that all living things can use—both producers, such as plants, and consumers, such as animals.

Nearly all organisms perform glycolysis, the first part of both aerobic and anaerobic respiration. One of the key enzymes of glycolysis is pyruvate kinase. Without this enzyme, an organism will die because it is unable to convert nutrients into the energy it needs for survival. Scientists have taken advantage of that fact by blocking pyruvate kinase in some deadly parasites, such as the ones that cause African Sleeping Sickness and Chagas disease. Read more about this research **here (http://openstaxcollege.org/l/32africa)** .

7.1 | Energy in Living Systems

In this section, you will explore the following questions:

- What is the importance of electrons for the transfer of energy in living systems?
- How is ATP used by the cell as an energy source?

Connection for AP® Courses

As we learned in previous chapters, living organisms require free energy to power life processes such as growth, reproduction, movement, and active transport. ATP (adenosine triphosphate) functions as the energy currency for cells. It allows the cells to store energy and transfer it within the cells to provide energy for cellular processes such as growth, movement and active transport. The ATP molecule consists of a ribose sugar and an adenine base with three phosphates attached. In the hydrolysis of ATP, free energy is supplied when a phosphate group or two are detached, and either ADP (adenosine diphosphate) or AMP (adenosine monophosphate) is produced. Energy derived from the metabolism of glucose is used to convert ADP to ATP during cellular respiration. As we explore cellular respiration, we'll learn that the two ways ATP is regenerated by the cell are called substrate-level phosphorylation and oxidative phosphorylation.

Information presented and the examples highlighted in the section support concepts and Learning Objectives outlined in Big Idea 2 and Big Idea 4 of the AP® Biology Curriculum Framework, as shown in the table. The Learning Objectives listed in the Curriculum Framework provide a transparent foundation for the AP® Biology course, an inquiry-based laboratory experience, instructional activities, and AP® exam questions. A Learning Objective merges required content with one or more of the seven Science Practices.

Big Idea 2	Biological systems utilize free energy and molecular building blocks to grow, to reproduce, and to maintain dynamic homeostasis.
Enduring Understanding 2.A	Growth, reproduction and maintenance of living systems require free energy and matter.
Essential Knowledge	**2.A.2** Organisms capture and store free energy for use in biological processes.
Science Practice	**1.4** The student can use representations and models to analyze situations or solve problems qualitatively and quantitatively.
Science Practice	**3.1** The student can pose scientific questions.
Learning Objective	**2.4** The student is able to use representations to pose scientific questions about what mechanisms and structural features allow organisms to capture, store, and use free energy.
Essential Knowledge	**2.A.2** Organisms capture and store free energy for use in biological processes.
Science Practice	**6.2** The student can construct explanations of phenomena based on evidence produced through scientific practices.
Learning Objective	**2.5** The student is able to construct explanations of the mechanisms and structural features of cells that allow organisms to capture, store, or use free energy.

The Science Practice Challenge Questions contain additional test questions for this section that will help you prepare for the AP exam. These questions address the following standards:
[APLO 2.5][APLO 2.16]

Energy production within a cell involves many coordinated chemical pathways. Most of these pathways are combinations of oxidation and reduction reactions. Oxidation and reduction occur in tandem. An oxidation reaction strips an electron from an atom in a compound, and the addition of this electron to another compound is a reduction reaction. Because oxidation

and reduction usually occur together, these pairs of reactions are called oxidation reduction reactions, or **redox reactions**.

Electrons and Energy

The removal of an electron from a molecule, oxidizing it, results in a decrease in potential energy in the oxidized compound. The electron (sometimes as part of a hydrogen atom), does not remain unbonded, however, in the cytoplasm of a cell. Rather, the electron is shifted to a second compound, reducing the second compound. The shift of an electron from one compound to another removes some potential energy from the first compound (the oxidized compound) and increases the potential energy of the second compound (the reduced compound). The transfer of electrons between molecules is important because most of the energy stored in atoms and used to fuel cell functions is in the form of high-energy electrons. The transfer of energy in the form of electrons allows the cell to transfer and use energy in an incremental fashion—in small packages rather than in a single, destructive burst. This chapter focuses on the extraction of energy from food; you will see that as you track the path of the transfers, you are tracking the path of electrons moving through metabolic pathways.

Electron Carriers

In living systems, a small class of compounds functions as electron shuttles: They bind and carry high-energy electrons between compounds in pathways. The principal electron carriers we will consider are derived from the B vitamin group and are derivatives of nucleotides. These compounds can be easily reduced (that is, they accept electrons) or oxidized (they lose electrons). Nicotinamide adenine dinucleotide (NAD) (**Figure 7.2**) is derived from vitamin B3, niacin. NAD^+ is the oxidized form of the molecule; NADH is the reduced form of the molecule after it has accepted two electrons and a proton (which together are the equivalent of a hydrogen atom with an extra electron).

NAD^+ can accept electrons from an organic molecule according to the general equation:

$$\underset{\text{Reducing agent}}{RH} + \underset{\text{Oxidizing agent}}{NAD^+} \rightarrow \underset{\text{Reduced}}{NADH} + \underset{\text{Oxidized}}{R}$$

When electrons are added to a compound, they are reduced. A compound that reduces another is called a reducing agent. In the above equation, RH is a reducing agent, and NAD^+ is reduced to NADH. When electrons are removed from compound, it is oxidized. A compound that oxidizes another is called an oxidizing agent. In the above equation, NAD^+ is an oxidizing agent, and RH is oxidized to R.

Similarly, flavin adenine dinucleotide (FAD^+) is derived from vitamin B_2, also called riboflavin. Its reduced form is $FADH_2$. A second variation of NAD, NADP, contains an extra phosphate group. Both NAD^+ and FAD^+ are extensively used in energy extraction from sugars, and NADP plays an important role in anabolic reactions and photosynthesis.

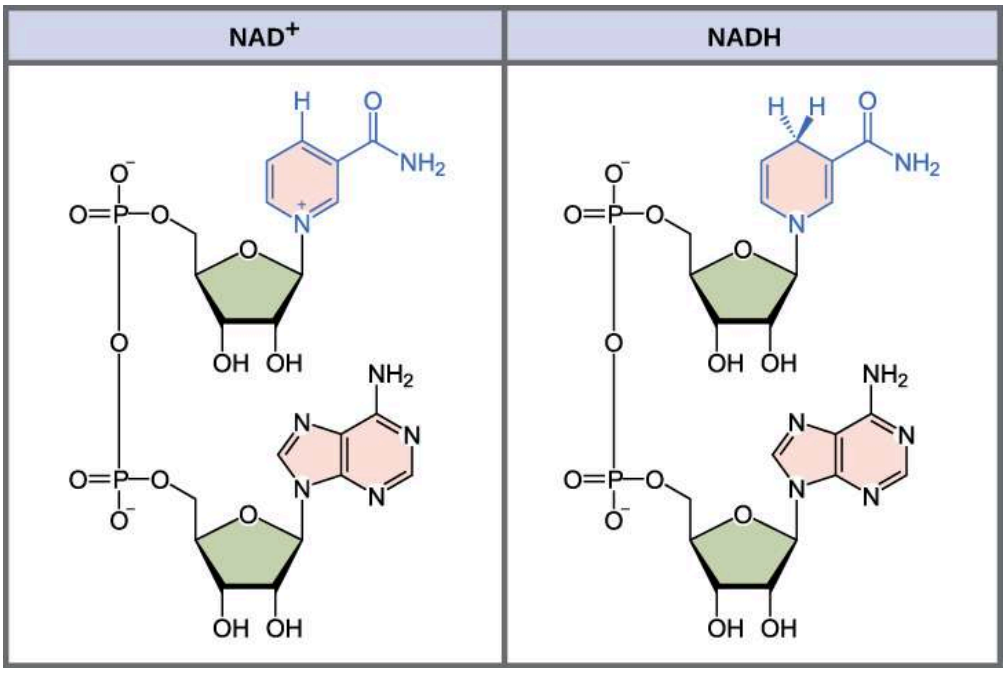


Figure 7.2 The oxidized form of the electron carrier (NAD^+) is shown on the left and the reduced form (NADH) is shown on the right. The nitrogenous base in NADH has one more hydrogen ion and two more electrons than in NAD^+.

ATP in Living Systems

A living cell cannot store significant amounts of free energy. Excess free energy would result in an increase of heat in the cell, which would result in excessive thermal motion that could damage and then destroy the cell. Rather, a cell must be able to handle that energy in a way that enables the cell to store energy safely and release it for use only as needed. Living cells accomplish this by using the compound adenosine triphosphate (ATP). ATP is often called the "energy currency" of the cell, and, like currency, this versatile compound can be used to fill any energy need of the cell. How? It functions similarly to a rechargeable battery.

When ATP is broken down, usually by the removal of its terminal phosphate group, energy is released. The energy is used to do work by the cell, usually by the released phosphate binding to another molecule, activating it. For example, in the mechanical work of muscle contraction, ATP supplies the energy to move the contractile muscle proteins. Recall the active transport work of the sodium-potassium pump in cell membranes. ATP alters the structure of the integral protein that functions as the pump, changing its affinity for sodium and potassium. In this way, the cell performs work, pumping ions against their electrochemical gradients.

ATP Structure and Function

At the heart of ATP is a molecule of adenosine monophosphate (AMP), which is composed of an adenine molecule bonded to a ribose molecule and to a single phosphate group (**Figure 7.3**). The addition of a second phosphate group to this core molecule results in the formation of adenosine diphosphate (ADP); the addition of a third phosphate group forms adenosine triphosphate (ATP).

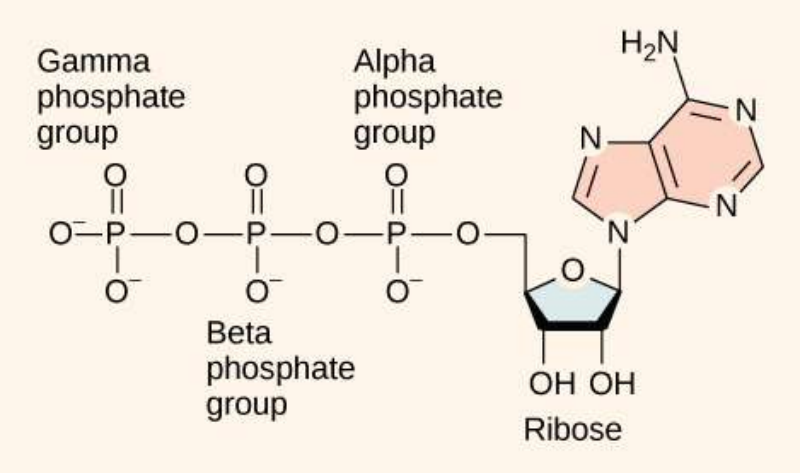


Figure 7.3 ATP (adenosine triphosphate) has three phosphate groups that can be removed by hydrolysis to form ADP (adenosine diphosphate) or AMP (adenosine monophosphate).The negative charges on the phosphate group naturally repel each other, requiring energy to bond them together and releasing energy when these bonds are broken.

The addition of a phosphate group to a molecule requires energy. Phosphate groups are negatively charged and thus repel one another when they are arranged in series, as they are in ADP and ATP. This repulsion makes the ADP and ATP molecules inherently unstable. The release of one or two phosphate groups from ATP, a process called **dephosphorylation**, releases energy.

Energy from ATP

Hydrolysis is the process of breaking complex macromolecules apart. During hydrolysis, water is split, or lysed, and the resulting hydrogen atom (H^+) and a hydroxyl group (OH^-) are added to the larger molecule. The hydrolysis of ATP produces ADP, together with an inorganic phosphate ion (P_i), and the release of free energy. To carry out life processes, ATP is continuously broken down into ADP, and like a rechargeable battery, ADP is continuously regenerated into ATP by the reattachment of a third phosphate group. Water, which was broken down into its hydrogen atom and hydroxyl group during ATP hydrolysis, is regenerated when a third phosphate is added to the ADP molecule, reforming ATP.

Obviously, energy must be infused into the system to regenerate ATP. Where does this energy come from? In nearly every living thing on earth, the energy comes from the metabolism of glucose. In this way, ATP is a direct link between the limited set of exergonic pathways of glucose catabolism and the multitude of endergonic pathways that power living cells.

Phosphorylation

Recall that, in some chemical reactions, enzymes may bind to several substrates that react with each other on the enzyme,

forming an intermediate complex. An intermediate complex is a temporary structure, and it allows one of the substrates (such as ATP) and reactants to more readily react with each other; in reactions involving ATP, ATP is one of the substrates and ADP is a product. During an endergonic chemical reaction, ATP forms an intermediate complex with the substrate and enzyme in the reaction. This intermediate complex allows the ATP to transfer its third phosphate group, with its energy, to the substrate, a process called phosphorylation. **Phosphorylation** refers to the addition of the phosphate (~P). This is illustrated by the following generic reaction:

$$\text{A} + \text{enzyme} + \text{ATP} \rightarrow [\text{A} - \text{enzyme} - \sim \text{P}] \rightarrow \text{B} + \text{enzyme} + \text{ADP} + \text{phosphate ion}$$

When the intermediate complex breaks apart, the energy is used to modify the substrate and convert it into a product of the reaction. The ADP molecule and a free phosphate ion are released into the medium and are available for recycling through cell metabolism.

Substrate Phosphorylation

ATP is generated through two mechanisms during the breakdown of glucose. A few ATP molecules are generated (that is, regenerated from ADP) as a direct result of the chemical reactions that occur in the catabolic pathways. A phosphate group is removed from an intermediate reactant in the pathway, and the free energy of the reaction is used to add the third phosphate to an available ADP molecule, producing ATP (**Figure 7.4**). This very direct method of phosphorylation is called **substrate-level phosphorylation**.

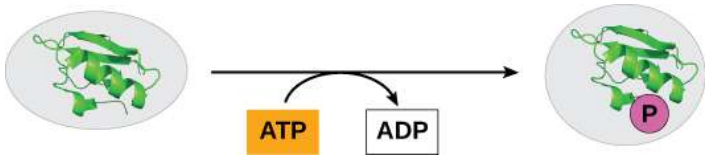


Figure 7.4 In phosphorylation reactions, the gamma phosphate of ATP is attached to a protein.

Oxidative Phosphorylation

Most of the ATP generated during glucose catabolism, however, is derived from a much more complex process, chemiosmosis, which takes place in mitochondria (**Figure 7.5**) within a eukaryotic cell or the plasma membrane of a prokaryotic cell. **Chemiosmosis**, a process of ATP production in cellular metabolism, is used to generate 90 percent of the ATP made during glucose catabolism and is also the method used in the light reactions of photosynthesis to harness the energy of sunlight. The production of ATP using the process of chemiosmosis is called **oxidative phosphorylation** because of the involvement of oxygen in the process.

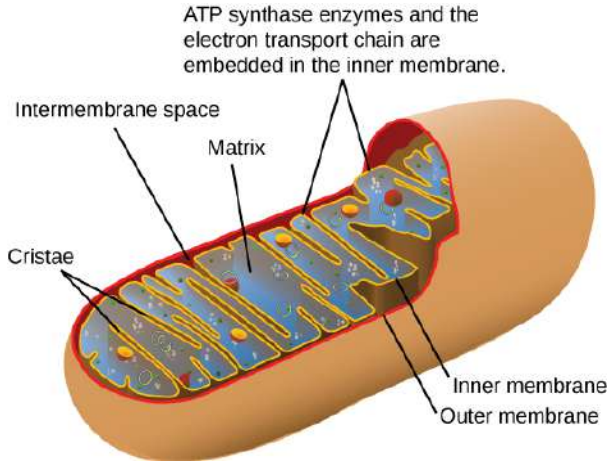


Figure 7.5 In eukaryotes, oxidative phosphorylation takes place in mitochondria. In prokaryotes, this process takes place in the plasma membrane. (Credit: modification of work by Mariana Ruiz Villareal)

science practices CONNECTION for AP® Courses

Think About It

Explain why it is more metabolically efficient for cells to extract energy from ATP rather than from the bonds of carbohydrates directly.

career CONNECTION

Mitochondrial Disease Physician

What happens when the critical reactions of cellular respiration do not proceed correctly? Mitochondrial diseases are genetic disorders of metabolism. Mitochondrial disorders can arise from mutations in nuclear or mitochondrial DNA, and they result in the production of less energy than is normal in body cells. In type 2 diabetes, for instance, the oxidation efficiency of NADH is reduced, impacting oxidative phosphorylation but not the other steps of respiration. Symptoms of mitochondrial diseases can include muscle weakness, lack of coordination, stroke-like episodes, and loss of vision and hearing. Most affected people are diagnosed in childhood, although there are some adult-onset diseases. Identifying and treating mitochondrial disorders is a specialized medical field. The educational preparation for this profession requires a college education, followed by medical school with a specialization in medical genetics. Medical geneticists can be board certified by the American Board of Medical Genetics and go on to become associated with professional organizations devoted to the study of mitochondrial diseases, such as the Mitochondrial Medicine Society and the Society for Inherited Metabolic Disease.

7.2 | Glycolysis

In this section, you will explore the following question:

- What is the overall result, in terms of molecules produced, in the breakdown of glucose by glycolysis?

Connection for AP® Courses

All organisms, from simple bacteria and yeast to complex plants and animals, carry out some form of cellular respiration to capture and supply free energy for cellular processes. Although cellular respiration and photosynthesis evolved as independent processes, today they are interdependent. The products of photosynthesis, carbohydrates and oxygen gas, are used during cellular respiration. Likewise, the byproduct of cellular respiration, CO_2 gas, is used during photosynthesis. Glycolysis is the first pathway used in the breakdown of glucose to extract free energy. Used by nearly all organisms on earth today, glycolysis likely evolved as one of the first metabolic pathways. It is important to note that glycolysis occurs in the cytoplasm of both prokaryotic and eukaryotic cells. (Remember that only eukaryotic cells have mitochondria.)

Like all metabolic pathways, glycolysis occurs in steps or stages. In the first stage, the six-carbon ring of glucose is prepared for cleavage (“splitting”) into two three-carbon molecules by investing two molecules of ATP to energize the separation. (Don’t worry; the cell will get the investment of ATP back. It’s like the stock market: You have to invest money to, hopefully, make money!) As glucose is metabolized further, bonds are rearranged through a series of enzyme-catalyzed steps, and free energy is released to form ATP from ADP and free phosphate molecules. The availability of enzymes can affect the rate of glucose metabolism. Two molecules of pyruvate are ultimately produced. High-energy electrons and hydrogen atoms pass to NAD^+, reducing it to NADH. Although two molecules of ATP were invested to destabilize glucose at the beginning of the process, four molecules of ATP are formed by substrate-level phosphorylation, resulting in a net gain of two ATP and two NADH molecules for the cell.

Information presented and the examples highlighted in the section support concepts and Learning Objectives outlined in

Big Idea 1 and Big Idea 2 of the AP® Biology Curriculum Framework, as shown in the table. The Learning Objectives listed in the Curriculum Framework provide a transparent foundation for the AP® Biology course, an inquiry-based laboratory experience, instructional activities, and AP® exam questions. A Learning Objective merges required content with one or more of the seven Science Practices.

Big Idea 1	The process of evolution drives the diversity and unity of life.
Enduring Understanding 1.B	Organisms are linked by lines of descent from common ancestry.
Essential Knowledge	**1.B.1** Organisms share many conserved core processes and features that evolved and are widely distributed among organisms today.
Science Practice	**7.2** The student can connect concepts in and across domain(s) to generalize or extrapolate in and/or across enduring understandings and/or big ideas.
Learning Objective	**1.15** The student is able to describe specific examples of conserved core biological processes and features shared by all domains or within one domain of life, and how these shared, conserved core processes and features support the concept of common ancestry for all organisms.
Big Idea 2	Biological systems utilize free energy and molecular building blocks to grow, to reproduce, and to maintain dynamic homeostasis.
Enduring Understanding 2.A	Growth, reproduction and maintenance of living systems require free energy and matter.
Essential Knowledge	**2.A.2** Organisms capture and store free energy for use in biological processes.
Science Practice	**1.4** The student can use representations and models to analyze situations or solve problems qualitatively and quantitatively.
Science Practice	**3.1** The student can pose scientific questions.
Learning Objective	**2.4** The student is able to use representations to pose scientific questions about what mechanisms and structural features allow organisms to capture, store, and use free energy.
Essential Knowledge	**2.A.2** Organisms capture and store free energy for use in biological processes.
Science Practice	**6.2** The student can construct explanations of phenomena based on evidence produced through scientific practices.
Learning Objective	**2.5** The student is able to construct explanations of the mechanisms and structural features of cells that allow organisms to capture, store, or use free energy.

You have read that nearly all of the energy used by living cells comes to them in the bonds of the sugar, glucose. **Glycolysis** is the first step in the breakdown of glucose to extract energy for cellular metabolism. Nearly all living organisms carry out glycolysis as part of their metabolism. The process does not use oxygen and is therefore **anaerobic**. Glycolysis takes place in the cytoplasm of both prokaryotic and eukaryotic cells. Glucose enters heterotrophic cells in two ways. One method is through secondary active transport in which the transport takes place against the glucose concentration gradient. The other mechanism uses a group of integral proteins called GLUT proteins, also known as glucose transporter proteins. These transporters assist in the facilitated diffusion of glucose.

Glycolysis begins with the six carbon ring-shaped structure of a single glucose molecule and ends with two molecules of a three-carbon sugar called **pyruvate**. Glycolysis consists of two distinct phases. The first part of the glycolysis pathway traps the glucose molecule in the cell and uses energy to modify it so that the six-carbon sugar molecule can be split evenly into the two three-carbon molecules. The second part of glycolysis extracts energy from the molecules and stores it in the form of ATP and NADH, the reduced form of NAD^+.

First Half of Glycolysis (Energy-Requiring Steps)

Step 1. The first step in glycolysis (**Figure 7.6**) is catalyzed by hexokinase, an enzyme with broad specificity that catalyzes the phosphorylation of six-carbon sugars. Hexokinase phosphorylates glucose using ATP as the source of the phosphate, producing glucose-6-phosphate, a more reactive form of glucose. This reaction prevents the phosphorylated glucose molecule from continuing to interact with the GLUT proteins, and it can no longer leave the cell because the negatively charged phosphate will not allow it to cross the hydrophobic interior of the plasma membrane.

Step 2. In the second step of glycolysis, an isomerase converts glucose-6-phosphate into one of its isomers, fructose-6-phosphate. An **isomerase** is an enzyme that catalyzes the conversion of a molecule into one of its isomers. (This change from phosphoglucose to phosphofructose allows the eventual split of the sugar into two three-carbon molecules.).

Step 3. The third step is the phosphorylation of fructose-6-phosphate, catalyzed by the enzyme phosphofructokinase. A second ATP molecule donates a high-energy phosphate to fructose-6-phosphate, producing fructose-1,6-bisphosphate. In this pathway, phosphofructokinase is a rate-limiting enzyme. It is active when the concentration of ADP is high; it is less active when ADP levels are low and the concentration of ATP is high. Thus, if there is "sufficient" ATP in the system, the pathway slows down. This is a type of end product inhibition, since ATP is the end product of glucose catabolism.

Step 4. The newly added high-energy phosphates further destabilize fructose-1,6-bisphosphate. The fourth step in glycolysis employs an enzyme, aldolase, to cleave fructose-1,6-bisphosphate into two three-carbon isomers: dihydroxyacetone-phosphate and glyceraldehyde-3-phosphate.

Step 5. In the fifth step, an isomerase transforms the dihydroxyacetone-phosphate into its isomer, glyceraldehyde-3-phosphate. Thus, the pathway will continue with two molecules of glyceraldehyde-3-phosphate. At this point in the pathway, there is a net investment of energy from two ATP molecules in the breakdown of one glucose molecule.

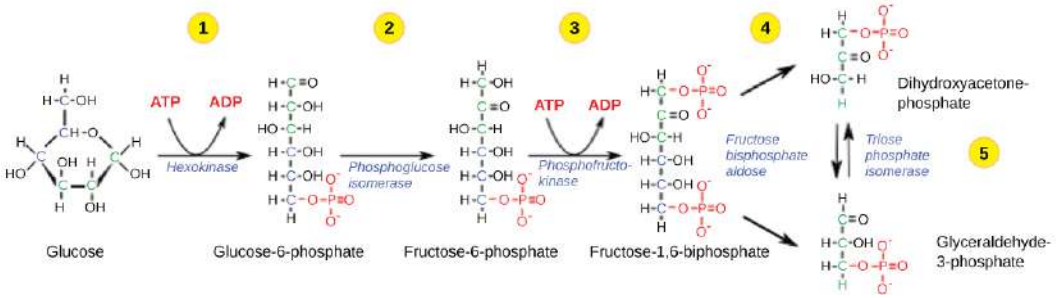


Figure 7.6 The first half of glycolysis uses two ATP molecules in the phosphorylation of glucose, which is then split into two three-carbon molecules.

Second Half of Glycolysis (Energy-Releasing Steps)

So far, glycolysis has cost the cell two ATP molecules and produced two small, three-carbon sugar molecules. Both of these molecules will proceed through the second half of the pathway, and sufficient energy will be extracted to pay back the two ATP molecules used as an initial investment and produce a profit for the cell of two additional ATP molecules and two even higher-energy NADH molecules.

Step 6. The sixth step in glycolysis (**Figure 7.7**) oxidizes the sugar (glyceraldehyde-3-phosphate), extracting high-energy electrons, which are picked up by the electron carrier NAD^+, producing NADH. The sugar is then phosphorylated by the addition of a second phosphate group, producing 1,3-bisphosphoglycerate. Note that the second phosphate group does not require another ATP molecule.

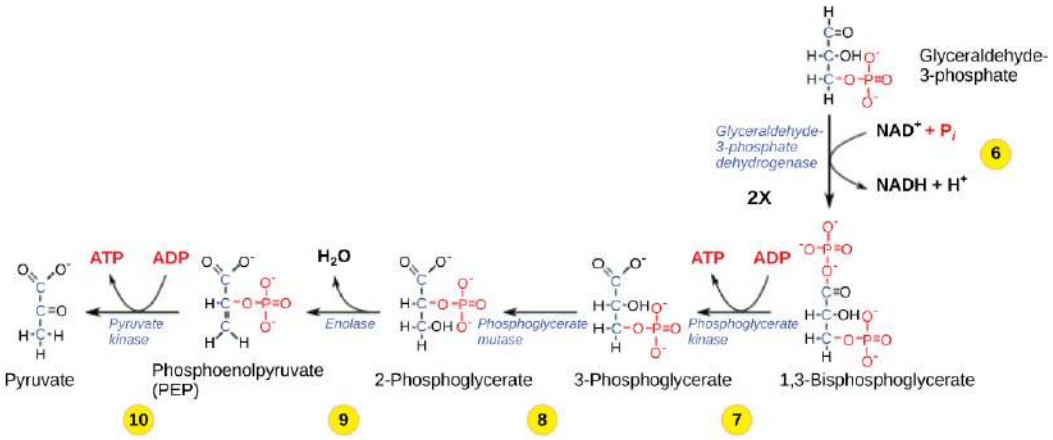


Figure 7.7 The second half of glycolysis involves phosphorylation without ATP investment (step 6) and produces two NADH and four ATP molecules per glucose.

Here again is a potential limiting factor for this pathway. The continuation of the reaction depends upon the availability of the oxidized form of the electron carrier, NAD^+. Thus, NADH must be continuously oxidized back into NAD^+ in order to keep this step going. If NAD^+ is not available, the second half of glycolysis slows down or stops. If oxygen is available in the system, the NADH will be oxidized readily, though indirectly, and the high-energy electrons from the hydrogen released in this process will be used to produce ATP. In an environment without oxygen, an alternate pathway (fermentation) can provide the oxidation of NADH to NAD^+.

Step 7. In the seventh step, catalyzed by phosphoglycerate kinase (an enzyme named for the reverse reaction), 1,3-bisphosphoglycerate donates a high-energy phosphate to ADP, forming one molecule of ATP. (This is an example of substrate-level phosphorylation.) A carbonyl group on the 1,3-bisphosphoglycerate is oxidized to a carboxyl group, and 3-phosphoglycerate is formed.

Step 8. In the eighth step, the remaining phosphate group in 3-phosphoglycerate moves from the third carbon to the second carbon, producing 2-phosphoglycerate (an isomer of 3-phosphoglycerate). The enzyme catalyzing this step is a mutase (isomerase).

Step 9. Enolase catalyzes the ninth step. This enzyme causes 2-phosphoglycerate to lose water from its structure; this is a dehydration reaction, resulting in the formation of a double bond that increases the potential energy in the remaining phosphate bond and produces phosphoenolpyruvate (PEP).

Step 10. The last step in glycolysis is catalyzed by the enzyme pyruvate kinase (the enzyme in this case is named for the reverse reaction of pyruvate's conversion into PEP) and results in the production of a second ATP molecule by substrate-level phosphorylation and the compound pyruvic acid (or its salt form, pyruvate). Many enzymes in enzymatic pathways are named for the reverse reactions, since the enzyme can catalyze both forward and reverse reactions (these may have been described initially by the reverse reaction that takes place in vitro, under non-physiological conditions).

LINK TO LEARNING

Gain a better understanding of the breakdown of glucose by glycolysis by visiting this **site (http://openstaxcollege.org/l/glycolysis)** to see the process in action.

everyday CONNECTION for AP® Courses

Glycolysis occurs in the cytoplasm of nearly every cell. Organisms, from the small, circular colonies of bacteria pictured here to the human holding the petri dish, perform glycolysis using the same ten enzymes. Because of this, it is thought that glycolysis must have evolved in the very earliest forms of life.

Figure 7.8

ATP energy is needed for glycolysis. Explain how this ATP debt is paid off during the reaction. How is this ATP debt paid off during the reaction?

a. by the phosphorylation of fructose-6-phosphate
b. by the oxidation of glyceraldehyde-3-phosphate
c. by the formation of 3-phosphoglycerate
d. by the formation of phosphoenolpyruvate

Outcomes of Glycolysis

Glycolysis starts with glucose and ends with two pyruvate molecules, a total of four ATP molecules and two molecules of NADH. Two ATP molecules were used in the first half of the pathway to prepare the six-carbon ring for cleavage, so the cell has a net gain of two ATP molecules and 2 NADH molecules for its use. If the cell cannot catabolize the pyruvate molecules further, it will harvest only two ATP molecules from one molecule of glucose. Mature mammalian red blood cells are not capable of **aerobic respiration**—the process in which organisms convert energy in the presence of oxygen—and glycolysis is their sole source of ATP. If glycolysis is interrupted, these cells lose their ability to maintain their sodium-potassium pumps, and eventually, they die.

The last step in glycolysis will not occur if pyruvate kinase, the enzyme that catalyzes the formation of pyruvate, is not available in sufficient quantities. In this situation, the entire glycolysis pathway will proceed, but only two ATP molecules will be made in the second half. Thus, pyruvate kinase is a rate-limiting enzyme for glycolysis.

science practices CONNECTION for AP® Courses

Think About It

- Nearly all organisms on Earth carry out some form of glycolysis. How does that fact support or not support the assertion that glycolysis is one of the oldest metabolic pathways? Justify your answer.
- Human red blood cells do not perform aerobic respiration, but they do perform glycolysis. What might happen if glycolysis were blocked in a red blood cell? Could red blood cells tap into other sources of free energy needed for their functions?

7.3 | Oxidation of Pyruvate and the Citric Acid Cycle

In this section, you will explore the following question:

- How is pyruvate, the product of glycolysis, prepared for entry into the citric acid cycle?
- What are the products of the citric acid cycle?

Connection for AP® Courses

In the next stage of cellular respiration—and in the presence of oxygen—pyruvate produced in glycolysis is transformed into an acetyl group attached to a carrier molecule of coenzyme A. The resulting acetyl CoA is usually delivered from the cytoplasm to the mitochondria, a process that uses some ATP. In the mitochondria, acetyl CoA continues on to the citric acid cycle. The citric acid cycle (CAC or TCA- tricarboxylic acid cycle) is also known as the Krebs cycle. During the conversion of pyruvate into the acetyl group, a molecule of CO_2 and two high-energy electrons are removed. (Remember that glycolysis produces two molecules of pyruvate, and each can attach to a molecule of CoA and then enter the citric acid cycle. (A simple rule is to “count the carbons.” Because matter and energy cannot be created or destroyed, we must account for everything.) The electrons are picked up by NAD^+, and NADH carries the electrons to a later pathway (the electron transport chain described below) for ATP production. The glucose molecule that originally entered cellular respiration in glycolysis has been completely oxidized. Chemical potential energy stored within the glucose molecules has been transferred to NADH or has been used to synthesize ATP molecules.

The citric acid cycle occurs in the mitochondrial matrix and involves a series of redox and decarboxylation reactions that again remove high energy electrons and produce CO_2. These electrons are carried by NADH and $FADH_2$ to the electron transport chain located in the cristae of the mitochondrion. (You do not need to memorize the steps in the citric acid cycle, but if provided with a diagram of the cycle, you should be able to interpret the steps.) During the cycle, ATP is synthesized from ADP and inorganic phosphate by substrate-level phosphorylation.

Big Idea 2	Biological systems utilize free energy and molecular building blocks to grow, to reproduce, and to maintain dynamic homeostasis.
Enduring Understanding 2.A	Growth, reproduction and maintenance of living systems require free energy and matter.
Essential Knowledge	**2.A.2** Organisms capture and store free energy for use in biological processes.
Science Practice	**1.4** The student can use representations and models to analyze situations or solve problems qualitatively and quantitatively.
Science Practice	**3.1** The student can pose scientific questions.
Learning Objective	**2.4** The student is able to use representations to pose scientific questions about what mechanisms and structural features allow organisms to capture, store, and use free energy.
Essential Knowledge	**2.A.2** Organisms capture and store free energy for use in biological processes
Science Practice	**6.2** The student can construct explanations of phenomena based on evidence produced through scientific practices.
Learning Objective	**2.5** The student is able to construct explanations of the mechanisms and structural features of cells that allow organisms to capture, store, or use free energy.
Big Idea 4	Biological systems interact, and these systems and their interactions possess complex properties.
Enduring Understanding 4.A	Interactions within biological systems lead to complex properties.
Essential Knowledge	**4.A.2** The structure and function of subcellular components, and their interactions, provide essential cellular processes.
Science Practice	**1.4** The student can use representations and models to analyze situations or solve problems qualitatively and quantitatively.
Learning Objective	**4.6** The student is able to use representations and models to analyze situations qualitatively to describe how interactions of subcellular structures, which possess specialized functions, provide essential functions.

The Science Practice Challenge Questions contain additional test questions for this section that will help you prepare for the AP exam. These questions address the following standards:
[APLO 2.1][APLO 2.5][APLO 2.16][APLO 2.17][APLO 2.18]

If oxygen is available, aerobic respiration will go forward. In eukaryotic cells, the pyruvate molecules produced at the end of glycolysis are transported into mitochondria. There, pyruvate will be transformed into an acetyl group that will be picked up and activated by a carrier compound called coenzyme A (CoA). The resulting compound is called **acetyl CoA**. CoA is made from vitamin B5, pantothenic acid. Acetyl CoA can be used in a variety of ways by the cell, but its major function is to deliver the acetyl group derived from pyruvate to the next stage of the pathway in glucose catabolism.

Breakdown of Pyruvate

In order for pyruvate, the product of glycolysis, to enter the next pathway, it must undergo several changes. The conversion is a three-step process (**Figure 7.9**).

Step 1. A carboxyl group is removed from pyruvate, releasing a molecule of carbon dioxide into the surrounding medium. The result of this step is a two-carbon hydroxyethyl group bound to the enzyme (pyruvate dehydrogenase). This is the first of the six carbons from the original glucose molecule to be removed. This step proceeds twice (remember: there are *two* pyruvate molecules produced at the end of glycolsis) for every molecule of glucose metabolized; thus, two of the six carbons will have been removed at the end of both steps.

Step 2. The hydroxyethyl group is oxidized to an acetyl group, and the electrons are picked up by NAD^+, forming NADH. The high-energy electrons from NADH will be used later to generate ATP.

Step 3. The enzyme-bound acetyl group is transferred to CoA, producing a molecule of acetyl CoA.

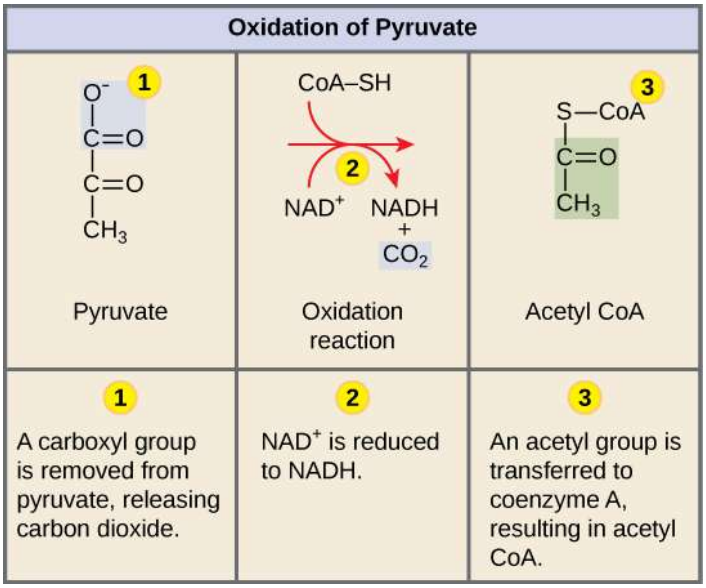


Figure 7.9 Upon entering the mitochondrial matrix, a multi-enzyme complex converts pyruvate into acetyl CoA. In the process, carbon dioxide is released and one molecule of NADH is formed.

Note that during the second stage of glucose metabolism, whenever a carbon atom is removed, it is bound to two oxygen atoms, producing carbon dioxide, one of the major end products of cellular respiration.

Acetyl CoA to CO_2

In the presence of oxygen, acetyl CoA delivers its acetyl group to a four-carbon molecule, oxaloacetate, to form citrate, a six-carbon molecule with three carboxyl groups; this pathway will harvest the remainder of the extractable energy from what began as a glucose molecule. This single pathway is called by different names: the **citric acid cycle** (for the first intermediate formed—citric acid, or citrate—when acetate joins to the oxaloacetate), the **TCA cycle** (since citric acid or citrate and isocitrate are tricarboxylic acids), and the **Krebs cycle**, after Hans Krebs, who first identified the steps in the pathway in the 1930s in pigeon flight muscles.

Citric Acid Cycle

Like the conversion of pyruvate to acetyl CoA, the citric acid cycle takes place in the matrix of mitochondria. Almost all of the enzymes of the citric acid cycle are soluble, with the single exception of the enzyme succinate dehydrogenase, which is embedded in the inner membrane of the mitochondrion. Unlike glycolysis, the citric acid cycle is a closed loop: The last part of the pathway regenerates the compound used in the first step. The eight steps of the cycle are a series of redox, dehydration, hydration, and decarboxylation reactions that produce two carbon dioxide molecules, one GTP/ATP, and reduced forms of NADH and $FADH_2$ (**Figure 7.10**). This is considered an aerobic pathway because the NADH and $FADH_2$ produced must transfer their electrons to the next pathway in the system, which will use oxygen. If this transfer does not occur, the oxidation steps of the citric acid cycle also do not occur. Note that the citric acid cycle produces very little ATP directly and does not directly consume oxygen.

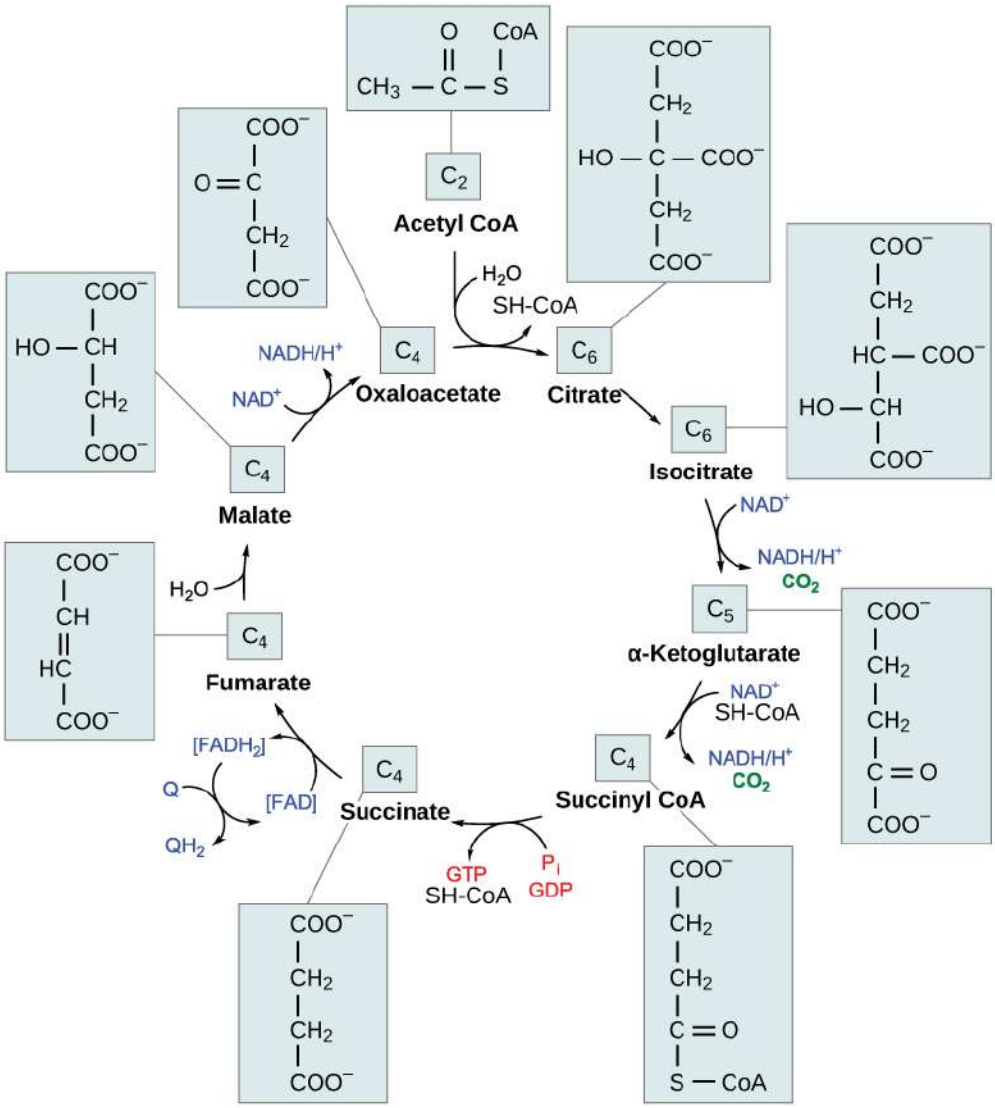


Figure 7.10 In the citric acid cycle, the acetyl group from acetyl CoA is attached to a four-carbon oxaloacetate molecule to form a six-carbon citrate molecule. Through a series of steps, citrate is oxidized, releasing two carbon dioxide molecules for each acetyl group fed into the cycle. In the process, three NAD^+ molecules are reduced to NADH, one FAD molecule is reduced to $FADH_2$, and one ATP or GTP (depending on the cell type) is produced (by substrate-level phosphorylation). Because the final product of the citric acid cycle is also the first reactant, the cycle runs continuously in the presence of sufficient reactants. (credit: modification of work by "Yikrazuul"/Wikimedia Commons)

Steps in the Citric Acid Cycle

Step 1. Prior to the start of the first step, a transitional phase occurs during which pyruvic acid is converted to acetyl CoA. Then, the first step of the cycle begins: This is a condensation step, combining the two-carbon acetyl group with a four-carbon oxaloacetate molecule to form a six-carbon molecule of citrate. CoA is bound to a sulfhydryl group (-SH) and diffuses away to eventually combine with another acetyl group. This step is irreversible because it is highly exergonic. The rate of this reaction is controlled by negative feedback and the amount of ATP available. If ATP levels increase, the rate of this reaction decreases. If ATP is in short supply, the rate increases.

Step 2. In step two, citrate loses one water molecule and gains another as citrate is converted into its isomer, isocitrate.

Step 3. In step three, isocitrate is oxidized, producing a five-carbon molecule, α-ketoglutarate, together with a molecule of CO_2 and two electrons, which reduce NAD^+ to NADH. This step is also regulated by negative feedback from ATP and NADH, and a positive effect of ADP.

Steps 3 and 4. Steps three and four are both oxidation and decarboxylation steps, which release electrons that reduce NAD^+ to NADH and release carboxyl groups that form CO_2 molecules. α-Ketoglutarate is the product of step three, and a succinyl group is the product of step four. CoA binds the succinyl group to form succinyl CoA. The enzyme that catalyzes step four

is regulated by feedback inhibition of ATP, succinyl CoA, and NADH.

Step 5. In step five, a phosphate group is substituted for coenzyme A, and a high-energy bond is formed. This energy is used in substrate-level phosphorylation (during the conversion of the succinyl group to succinate) to form either guanine triphosphate (GTP) or ATP. There are two forms of the enzyme, called isoenzymes, for this step, depending upon the type of animal tissue in which they are found. One form is found in tissues that use large amounts of ATP, such as heart and skeletal muscle. This form produces ATP. The second form of the enzyme is found in tissues that have a high number of anabolic pathways, such as liver tissues. This form produces GTP. GTP is energetically equivalent to ATP; however, its use is more restricted. In particular, protein synthesis primarily uses GTP.

Step 6. Step six is a dehydration process that converts succinate into fumarate. Two hydrogen atoms are transferred to FAD, producing $FADH_2$. The energy contained in the electrons of these atoms is insufficient to reduce NAD^+ but adequate to reduce FAD. Unlike NADH, this carrier remains attached to the enzyme and transfers the electrons to the electron transport chain directly. This process is made possible by the localization of the enzyme catalyzing this step inside the inner membrane of the mitochondrion.

Step 7. Water is added to fumarate during step seven, and malate is produced. The last step in the citric acid cycle regenerates oxaloacetate by oxidizing malate. Another molecule of NADH is produced in the process.

Click through each step of the citric acid cycle **here (http://openstaxcollege.org/l/krebs_cycle)** .

Why is the mitochondria considered the powerhouse of the cell?

a. Glycolysis takes place in mitochondria which extract energy by glucose breakdown for cellular metabolism.

b. Most of the ATP is produced in mitochondria by oxidative phosphorylation.

c. All the pathways involved in ATP production take place in the mitochondria.

d. The outer membrane of mitochondria is loaded with proteins involved in electron transfer and ATP synthesis.

Products of the Citric Acid Cycle

Two carbon atoms come into the citric acid cycle from each acetyl group, representing four out of the six carbons of one glucose molecule. Two carbon dioxide molecules are released on each turn of the cycle; however, these do not necessarily contain the most recently added carbon atoms. The two acetyl carbon atoms will eventually be released on later turns of the cycle; thus, all six carbon atoms from the original glucose molecule are eventually incorporated into carbon dioxide. Each turn of the cycle forms three NADH molecules and one $FADH_2$ molecule. These carriers will connect with the last portion of aerobic respiration to produce ATP molecules. One GTP or ATP is also made in each cycle. Several of the intermediate compounds in the citric acid cycle can be used in synthesizing non-essential amino acids; therefore, the cycle is amphibolic (both catabolic and anabolic).

Think About It

Explain how citrate from the citric acid cycle might affect glycolysis. What other factors might affect the efficiency of the citric acid cycle and its products?

7.4 | Oxidative Phosphorylation

In this section, you will explore the following questions:

- How do electrons move through the electron transport chain and what happens to their energy levels?
- How is a proton (H^+) gradient established and maintained by the electron transport chain and how many ATP molecules are produced by chemiosmosis?

Connection for AP® Courses

The electron transport chain (ETC) is the stage of aerobic respiration that uses free oxygen as the final electron acceptor of the electrons removed during glucose metabolism in glycolysis and the citric acid cycle. The ETC is located in membrane of the mitochondrial cristae, an area with many folds that increase the surface area available for chemical reactions. Electrons carried by NADH and $FADH_2$ are delivered to electron acceptor proteins embedded in the membrane as they move toward the final electron acceptor, O_2, forming water. The electrons pass through a series of redox reactions, using free energy at three points to transport hydrogen ions across the membrane. This process contributes to the formation of the H^+ gradient used in chemiosmosis. As the protons are driven down their concentration gradient through ATP synthase, ATP is generated from ADP and inorganic phosphate. Under aerobic conditions, the stages of cellular respiration can generate 36-38 ATP.

Information presented and the examples highlighted in the section support concepts outlined in Big Idea 2 of the AP® Biology Curriculum Framework, as shown in the table. As shown in the table, concepts covered in this section also align to the Learning Objectives listed in the Curriculum Framework that provide a transparent foundation for the AP® Biology course, an inquiry-based laboratory experience, instructional activities, and AP® exam questions. A Learning Objective merges required content with one or more of the seven Science Practices.

Big Idea 2	Biological systems utilize free energy and molecular building blocks to grow, to reproduce, and to maintain dynamic homeostasis.
Enduring Understanding 2.A	Growth, reproduction and maintenance of living systems require free energy and matter.
Essential Knowledge	**2.A.1** All living systems require constant input of free energy.
Science Practice	**1.4** The student can use representations and models to analyze situations or solve problems qualitatively and quantitatively.
Science Practice	**3.1** The student can pose scientific questions.
Learning Objective	**2.4** The student is able to use representations to pose scientific questions about what mechanisms and structural features allow organisms to capture, store, and use free energy.
Essential Knowledge	**2.A.1** All living systems require constant input of free energy.
Science Practice	**6.2** The student can construct explanations of phenomena based on evidence produced through scientific practices.
Learning Objective	**2.5** The student is able to construct explanations of the mechanisms and structural features of cells that allow organisms to capture, store, or use free energy.

The Science Practice Challenge Questions contain additional test questions for this section that will help you prepare for the AP exam. These questions address the following standards:
[APLO 2.5][APLO 2.15][APLO 2.18][APLO 2.22]

You have just read about two pathways Introduce glucose catabolism—glycolysis and the citric acid cycle—that generate ATP. Most of the ATP generated during the aerobic catabolism of glucose, however, is not generated directly from these

pathways. Rather, it is derived from a process that begins with moving electrons through a series of electron transporters that undergo redox reactions. This causes hydrogen ions to accumulate within the matrix space. Therefore, a concentration gradient forms in which hydrogen ions diffuse out of the matrix space by passing through ATP synthase. The current of hydrogen ions powers the catalytic action of ATP synthase, which phosphorylates ADP, producing ATP.

Electron Transport Chain

The electron transport chain (**Figure 7.11**) is the last component of aerobic respiration and is the only part of glucose metabolism that uses atmospheric oxygen. Oxygen continuously diffuses into plants; in animals, it enters the body through the respiratory system. Electron transport is a series of redox reactions that resemble a relay race or bucket brigade in that electrons are passed rapidly from one component to the next, to the endpoint of the chain where the electrons reduce molecular oxygen, producing water. There are four complexes composed of proteins, labeled I through IV in **Figure 7.11**, and the aggregation of these four complexes, together with associated mobile, accessory electron carriers, is called the electron transport chain. The electron transport chain is present in multiple copies in the inner mitochondrial membrane of eukaryotes and the plasma membrane of prokaryotes.

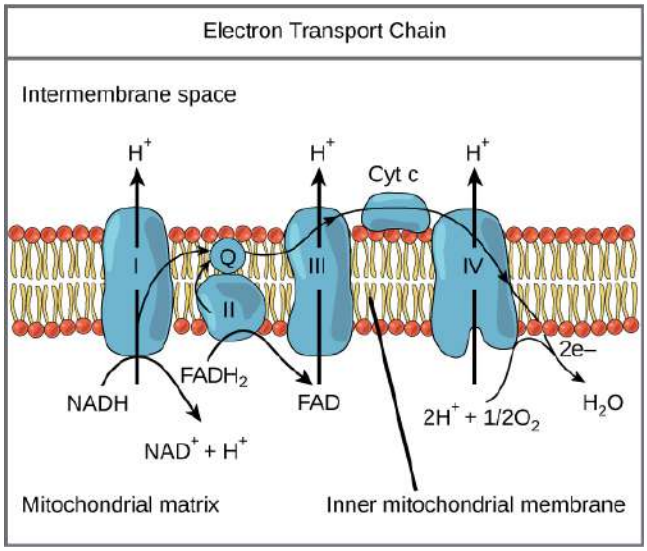


Figure 7.11 The electron transport chain is a series of electron transporters embedded in the inner mitochondrial membrane that shuttles electrons from NADH and $FADH_2$ to molecular oxygen. In the process, protons are pumped from the mitochondrial matrix to the intermembrane space, and oxygen is reduced to form water.

Complex I

To start, two electrons are carried to the first complex aboard NADH. This complex, labeled I, is composed of flavin mononucleotide (FMN) and an iron-sulfur (Fe-S)-containing protein. FMN, which is derived from vitamin B_2, also called riboflavin, is one of several prosthetic groups or co-factors in the electron transport chain. A **prosthetic group** is a non-protein molecule required for the activity of a protein. Prosthetic groups are organic or inorganic, non-peptide molecules bound to a protein that facilitate its function; prosthetic groups include co-enzymes, which are the prosthetic groups of enzymes. The enzyme in complex I is NADH dehydrogenase and is a very large protein, containing 45 amino acid chains. Complex I can pump four hydrogen ions across the membrane from the matrix into the intermembrane space, and it is in this way that the hydrogen ion gradient is established and maintained between the two compartments separated by the inner mitochondrial membrane.

Q and Complex II

Complex II directly receives $FADH_2$, which does not pass through complex I. The compound connecting the first and second complexes to the third is **ubiquinone** (Q). The Q molecule is lipid soluble and freely moves through the hydrophobic core of the membrane. Once it is reduced, (QH_2), ubiquinone delivers its electrons to the next complex in the electron transport chain. Q receives the electrons derived from NADH from complex I, and the electrons derived from $FADH_2$ from complex II. This enzyme and $FADH_2$ form a small complex that delivers electrons directly to the electron transport chain, bypassing the first complex. Since these electrons bypass and thus do not energize the proton pump in the first complex, fewer ATP molecules are made from the $FADH_2$ electrons. The number of ATP molecules ultimately obtained is directly proportional to the number of protons pumped across the inner mitochondrial membrane.

Complex III

The third complex is composed of cytochrome b, another Fe-S protein, Rieske center (2Fe-2S center), and cytochrome c proteins; this complex is also called cytochrome oxidoreductase. Cytochrome proteins have a prosthetic group of heme. The heme molecule is similar to the heme in hemoglobin, but it carries electrons, not oxygen. As a result, the iron ion at its core is reduced and oxidized as it passes the electrons, fluctuating between different oxidation states: Fe^{++} (reduced) and Fe^{+++} (oxidized). The heme molecules in the cytochromes have slightly different characteristics due to the effects of the different proteins binding them, giving slightly different characteristics to each complex. Complex III pumps protons through the membrane and passes its electrons to cytochrome c for transport to the fourth complex of proteins and enzymes (cytochrome c is the acceptor of electrons from Q; however, whereas Q carries pairs of electrons, cytochrome c can accept only one at a time).

Complex IV

The fourth complex is composed of cytochrome proteins c, a, and a_3. This complex contains two heme groups (one in each of the two cytochromes, a, and a_3) and three copper ions (a pair of Cu_A and one Cu_B in cytochrome a_3). The cytochromes hold an oxygen molecule very tightly between the iron and copper ions until the oxygen is completely reduced. The reduced oxygen then picks up two hydrogen ions from the surrounding medium to make water (H_2O). The removal of the hydrogen ions from the system contributes to the ion gradient used in the process of chemiosmosis.

Chemiosmosis

In chemiosmosis, the free energy from the series of redox reactions just described is used to pump hydrogen ions (protons) across the membrane. The uneven distribution of H^+ ions across the membrane establishes both concentration and electrical gradients (thus, an electrochemical gradient), owing to the hydrogen ions' positive charge and their aggregation on one side of the membrane.

If the membrane were open to diffusion by the hydrogen ions, the ions would tend to diffuse back across into the matrix, driven by their electrochemical gradient. Recall that many ions cannot diffuse through the nonpolar regions of phospholipid membranes without the aid of ion channels. Similarly, hydrogen ions in the matrix space can only pass through the inner mitochondrial membrane through an integral membrane protein called ATP synthase (**Figure 7.12**). This complex protein acts as a tiny generator, turned by the force of the hydrogen ions diffusing through it, down their electrochemical gradient. The turning of parts of this molecular machine facilitates the addition of a phosphate to ADP, forming ATP, using the potential energy of the hydrogen ion gradient.

visual CONNECTION

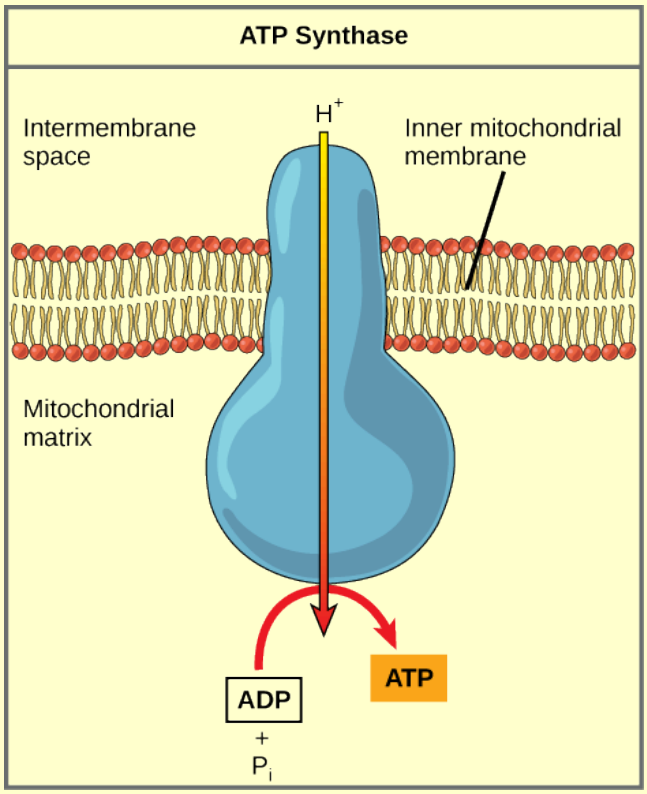


Figure 7.12 ATP synthase is a complex, molecular machine that uses a proton (H^+) gradient to form ATP from ADP and inorganic phosphate (Pi). (Credit: modification of work by Klaus Hoffmeier)

Dinitrophenol (DNP) is an uncoupler that makes the inner mitochondrial membrane leak protons (H^+). It was used until 1938 as a weight-loss drug. Why do you think this might be an effective weight-loss drug?

a. DNP dissipates the proton gradient in the matrix, preventing the production of ATP. The body then increases its metabolic rate, leading to weight loss.

b. DNP decreases the proton gradient in the inner mitochondrial space, leading to rapid consumption of acetyl-CoA, which causes weight loss.

c. DNP blocks the movement of protons through the ATP synthase, halting ATP production. The stored energy dissipates as heat, causing weight loss.

d. DNP uncouples the production of ATP by increasing the proton gradient in the matrix. The stored energy dissipates as heat, causing weight loss.

Chemiosmosis (**Figure 7.13**) is used to generate 90 percent of the ATP made during aerobic glucose catabolism; it is also the method used in the light reactions of photosynthesis to harness the energy of sunlight in the process of photophosphorylation. Recall that the production of ATP using the process of chemiosmosis in mitochondria is called oxidative phosphorylation. The overall result of these reactions is the production of ATP from the energy of the electrons removed from hydrogen atoms. These atoms were originally part of a glucose molecule. At the end of the pathway, the electrons are used to reduce an oxygen molecule to oxygen ions. The extra electrons on the oxygen attract hydrogen ions (protons) from the surrounding medium, and water is formed.

visual CONNECTION

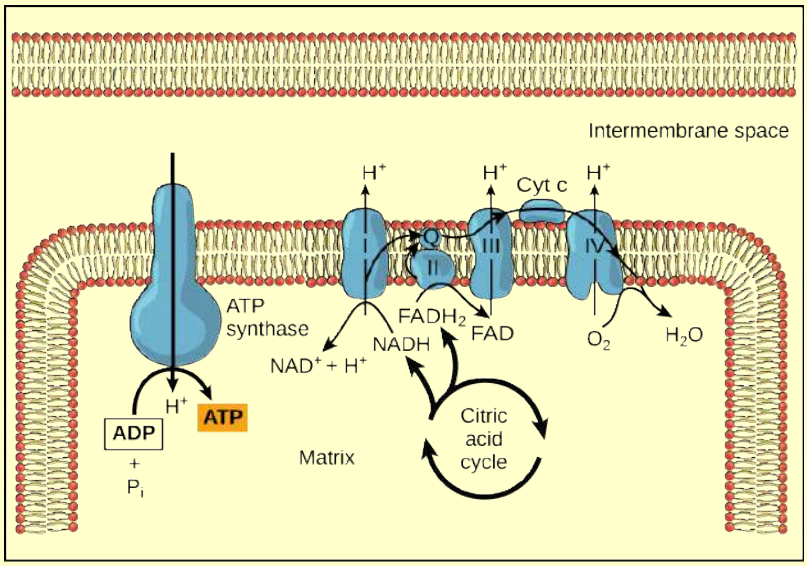


Figure 7.13 In oxidative phosphorylation, the pH gradient formed by the electron transport chain is used by ATP synthase to form ATP.

Cyanide inhibits cytochrome c oxidase, a component of the electron transport chain. If cyanide poisoning occurs, would you expect the pH of the intermembrane space to increase or decrease? What effect would cyanide have on ATP synthesis?

a. The proton concentration of the intermembrane space would decrease, stopping the production of ATP.
b. The proton concentration of the intermembrane space would increase, leading to ATP formation.
c. The hydrogen ion concentration of the intermembrane space would decrease, causing a high production of ATP.
d. The proton concentration of the intermembrane space would increase, causing production of ATP in large amounts.

ATP Yield

The number of ATP molecules generated from the catabolism of glucose varies. For example, the number of hydrogen ions that the electron transport chain complexes can pump through the membrane varies between species. Another source of variance stems from the shuttle of electrons across the membranes of the mitochondria. (The NADH generated from glycolysis cannot easily enter mitochondria.) Thus, electrons are picked up on the inside of mitochondria by either NAD^+ or FAD^+. As you have learned earlier, these FAD^+ molecules can transport fewer ions; consequently, fewer ATP molecules are generated when FAD^+ acts as a carrier. NAD^+ is used as the electron transporter in the liver and FAD^+ acts in the brain.

Another factor that affects the yield of ATP molecules generated from glucose is the fact that intermediate compounds in these pathways are used for other purposes. Glucose catabolism connects with the pathways that build or break down all other biochemical compounds in cells, and the result is somewhat messier than the ideal situations described thus far. For example, sugars other than glucose are fed into the glycolytic pathway for energy extraction. Moreover, the five-carbon sugars that form nucleic acids are made from intermediates in glycolysis. Certain nonessential amino acids can be made from intermediates of both glycolysis and the citric acid cycle. Lipids, such as cholesterol and triglycerides, are also made from intermediates in these pathways, and both amino acids and triglycerides are broken down for energy through these pathways. Overall, in living systems, these pathways of glucose catabolism extract about 34 percent of the energy contained in glucose.

science practices CONNECTION for AP® Courses

Activity

Use construction paper and other art materials to create your own diagram of the electron transport chain (ETC). Be sure to include all parts of the electron transport chain, as well as the electrons themselves, NAD+ and NADH, and oxygen. On your diagram, label all parts of the ETC that transfers the free energy from electrons to another form. Then, use your model to make predictions about each of the following. Then, share your answers with the class.

a. What would happen to free energy release if a cytochrome failed to undergo one of the redox reactions involved in the electron transport chain?

b. What ultimately happens to the free energy in the electrons that travel down the ETC?

c. Did you remember to have a pair of electrons travel down the ETC? What would happen if only one electron reached oxygen?

Think About It

- Dinitrophenol (DNP) is an uncoupler that makes the inner mitochondrial membrane leaky to protons. It was used until 1938 as a weight loss drug. What effect would DNP have on the change in pH across the inner mitochondrial membrane and the overall process of cellular respiration? Why do you think DNP might be an effective weight-loss drug? Why is DNP no longer used?
- Cyanide inhibits cytochrome c oxidase, a component of the electron transport chain. If cyanide poisoning occurs, would you expect the pH of the intermembrane space to increase or decrease? Explain the effect of cyanide on ATP synthesis.

7.5 | Metabolism without Oxygen

In this section, you will explore the following question:

- What is the fundamental difference between anaerobic cellular respiration and the different types of fermentation?

Connection for AP® Courses

As was previously stated, under aerobic conditions cellular respiration can yield 36-38 ATP molecules. If oxygen is not present, ATP is only produced by substrate-level phosphorylation. Without oxygen, organisms must use another electron acceptor. Most organisms will use some form of fermentation to accomplish the regeneration of NAD^+ to ensure the continuation of glycolysis. In alcohol fermentation, pyruvate from glycolysis is converted to ethyl alcohol; during lactic acid fermentation, pyruvate is reduced to form lactate as an end-product. Without fermentation and anaerobic respiration, we wouldn't have yogurt or soy sauce. Nor would our muscle cells cramp from the buildup of lactate when we exercise vigorously and oxygen is scarce.

Information presented and the examples highlighted in the section support concepts and Learning Objectives outlined in Big Idea 2 of the AP® Biology Curriculum Framework, as shown in the table. The Learning Objectives listed in the Curriculum Framework provide a transparent foundation for the AP® Biology course, an inquiry-based laboratory experience, instructional activities, and AP® exam questions. A Learning Objective merges required content with one or more of the seven Science Practices.

Big Idea 2	Biological systems utilize free energy and molecular building blocks to grow, to reproduce, and to maintain dynamic homeostasis.

Enduring Understanding 2.A	Growth, reproduction and maintenance of living systems require free energy and matter.
Essential Knowledge	**2.A.2** Organisms capture and store free energy for use in biological processes.
Science Practice	**1.4** The student can use representations and models to analyze situations or solve problems qualitatively and quantitatively.
Science Practice	**3.1** The student can pose scientific questions.
Learning Objective	**2.4** The student is able to use representations to pose scientific questions about what mechanisms and structural features allow organisms to capture, store, and use free energy.
Essential Knowledge	**2.A.2** Organisms capture and store free energy for use in biological processes.
Science Practice	**6.2** The student can construct explanations of phenomena based on evidence produced through scientific practices.
Learning Objective	**2.5** The student is able to construct explanations of the mechanisms and structural features of cells that allow organisms to capture, store, or use free energy.

The Science Practice Challenge Questions contain additional test questions for this section that will help you prepare for the AP exam. These questions address the following standards:
[APLO 2.21][APLO 2.24][APLO 4.14][APLO 4.26]

In aerobic respiration, the final electron acceptor is an oxygen molecule, O_2. If aerobic respiration occurs, then ATP will be produced using the energy of high-energy electrons carried by NADH or $FADH_2$ to the electron transport chain. If aerobic respiration does not occur, NADH must be reoxidized to NAD^+ for reuse as an electron carrier for the glycolytic pathway to continue. How is this done? Some living systems use an organic molecule as the final electron acceptor. Processes that use an organic molecule to regenerate NAD^+ from NADH are collectively referred to as **fermentation**. In contrast, some living systems use an inorganic molecule as a final electron acceptor. Both methods are called **anaerobic cellular respiration** in which organisms convert energy for their use in the absence of oxygen.

Anaerobic Cellular Respiration

Certain prokaryotes, including some species of bacteria and Archaea, use anaerobic respiration. For example, the group of Archaea called methanogens reduces carbon dioxide to methane to oxidize NADH. These microorganisms are found in soil and in the digestive tracts of ruminants, such as cows and sheep. Similarly, sulfate-reducing bacteria and Archaea, most of which are anaerobic (**Figure 7.14**), reduce sulfate to hydrogen sulfide to regenerate NAD^+ from NADH.

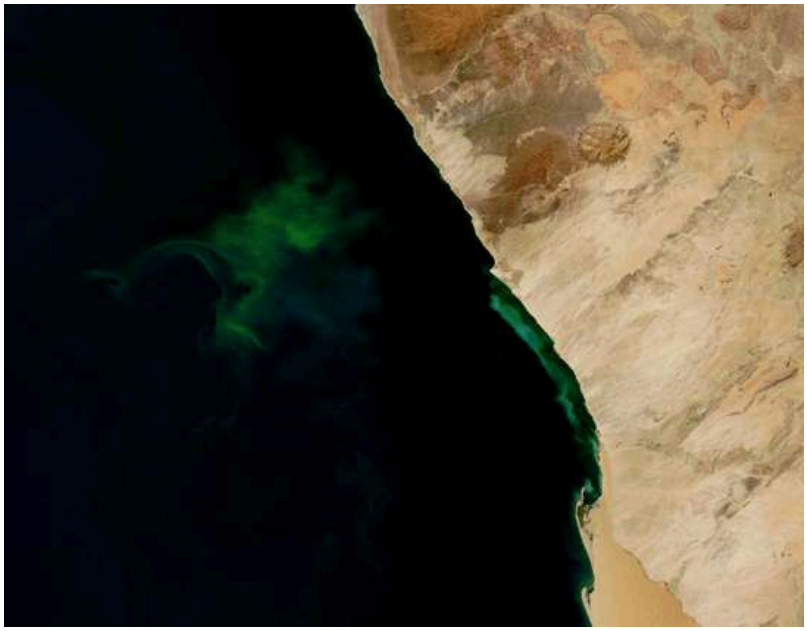


Figure 7.14 The green color seen in these coastal waters is from an eruption of hydrogen sulfide-producing bacteria. These anaerobic, sulfate-reducing bacteria release hydrogen sulfide gas as they decompose algae in the water. (credit: modification of work by NASA/Jeff Schmaltz, MODIS Land Rapid Response Team at NASA GSFC, Visible Earth Catalog of NASA images)

LINK TO LEARNING

Visit this **site (http://openstaxcollege.org/l/fermentation)** to see anaerobic cellular respiration in action.

How does the formation of NAD^+ differ between aerobic and anaerobic respiration?

a. NAD^+ is formed in aerobic respiration by a fermentation process and formed in anaerobic respiration by oxidation of $NADH$.

b. NAD^+ is formed by a fermentation process in anaerobic conditions by the conversion of pyruvate into lactate and by simple oxidation of $NADH$ in aerobic respiration.

c. Under aerobic conditions, the electron acceptor is a molecule other than oxygen for NAD^+ production, whereas under anaerobic conditions the electron acceptor is oxygen.

d. NAD^+ is formed by a fermentation process in anaerobic conditions whereas in aerobic respiration it is formed by the breakdown of pyruvate into lactic acid or alcohol.

Lactic Acid Fermentation

The fermentation method used by animals and certain bacteria, like those in yogurt, is lactic acid fermentation (**Figure 7.15**). This type of fermentation is used routinely in mammalian red blood cells and in skeletal muscle that has an insufficient oxygen supply to allow aerobic respiration to continue (that is, in muscles used to the point of fatigue). In muscles, lactic acid accumulation must be removed by the blood circulation and the lactate brought to the liver for further metabolism. The chemical reactions of lactic acid fermentation are the following:

$$\text{Pyruvic acid} + \text{NADH} \leftrightarrow \text{lactic acid} + \text{NAD}^+$$

The enzyme used in this reaction is lactate dehydrogenase (LDH). The reaction can proceed in either direction, but the reaction from left to right is inhibited by acidic conditions. Such lactic acid accumulation was once believed to cause muscle stiffness, fatigue, and soreness, although more recent research disputes this hypothesis. Once the lactic acid has been removed from the muscle and circulated to the liver, it can be reconverted into pyruvic acid and further catabolized for energy.

visual CONNECTION

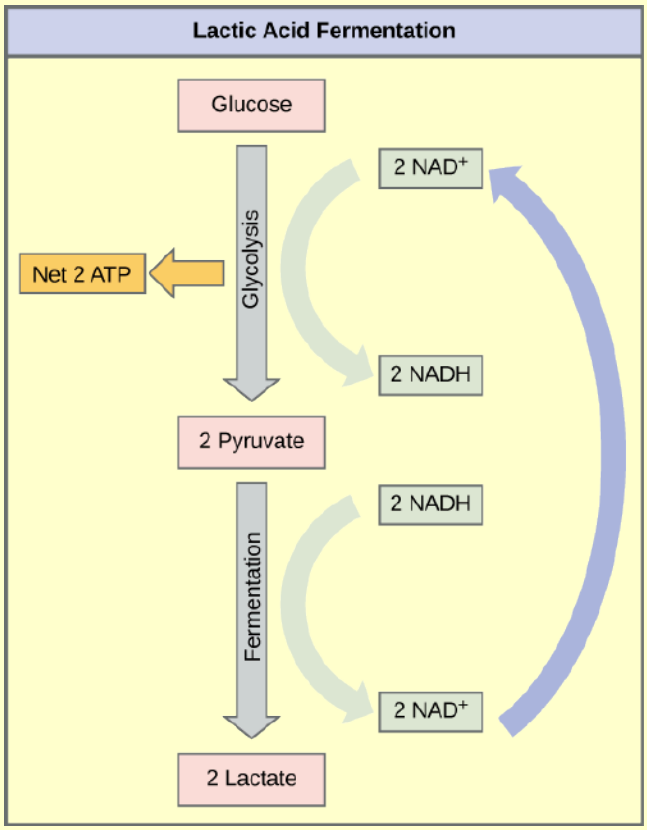


Figure 7.15 Lactic acid fermentation is common in muscle cells that have run out of oxygen.

Tremetol, a metabolic poison found in the white snake root plant, prevents the metabolism of lactate. When cows eat this plant, it is concentrated in the milk they produce. Humans who consume the milk become ill. Symptoms of this disease, which include vomiting, abdominal pain, and tremors, become worse after exercise. Why do you think this is the case?

Tremetol, a metabolic poison found in the white snake root plant, prevents the metabolism of lactate. When cows eat this plant, it is concentrated in the milk they produce. Humans who consume the milk become ill. Symptoms of this disease, which include vomiting, abdominal pain, and tremors, become worse after exercise. Why do you think this is the case?

a. Tremetol inhibits enzymes that convert lactate into less harmful compounds. Exercise worsens this by producing more lactate.

b. Tremetol increases the production of lactate dehydrogenase, causing lactic acid to accumulate in the body.

c. Tremetol inhibits the production of NAD^+ after exercise. The lack of oxygen causes lactic acid to accumulate in the body.

d. Tremetol binds to lactic acid, inhibiting its breakdown into other compounds and causing it to accumulate after exercising.

Alcohol Fermentation

Another familiar fermentation process is alcohol fermentation (**Figure 7.16**) that produces ethanol, an alcohol. The first chemical reaction of alcohol fermentation is the following (CO_2 does not participate in the second reaction):

$$\text{pyruvic acid} + H^+ \rightarrow CO_2 + \text{acetaldehyde} + \text{NADH} + H^+ \rightarrow \text{ethanol} + NAD^+$$

The first reaction is catalyzed by pyruvate decarboxylase, a cytoplasmic enzyme, with a coenzyme of thiamine pyrophosphate (TPP, derived from vitamin B_1 and also called thiamine). A carboxyl group is removed from pyruvic acid, releasing carbon dioxide as a gas. The loss of carbon dioxide reduces the size of the molecule by one carbon, making acetaldehyde. The second reaction is catalyzed by alcohol dehydrogenase to oxidize NADH to NAD^+ and reduce acetaldehyde to ethanol. The fermentation of pyruvic acid by yeast produces the ethanol. Ethanol tolerance of yeast is variable, ranging from about 5 percent to 21 percent, depending on the yeast strain and environmental conditions.

Figure 7.16 Fermentation of grape juice produces CO_2 as a byproduct. Fermentation tanks have valves so that the pressure inside the tanks created by the carbon dioxide produced can be released.

Other Types of Fermentation

Other fermentation methods occur in bacteria. Many prokaryotes are facultatively anaerobic. This means that they can switch between aerobic respiration and fermentation, depending on the availability of oxygen. Certain prokaryotes, like *Clostridia*, are obligate anaerobes. Obligate anaerobes live and grow in the absence of molecular oxygen. Oxygen is a poison to these microorganisms and kills them on exposure. It should be noted that all forms of fermentation, except lactic acid fermentation, produce gas. The production of particular types of gas is used as an indicator of the fermentation of specific carbohydrates, which plays a role in the laboratory identification of the bacteria. Various methods of fermentation are used by assorted organisms to ensure an adequate supply of NAD^+ for the sixth step in glycolysis. Without these pathways, that step would not occur and no ATP would be harvested from the breakdown of glucose.

science practices CONNECTION for AP® Courses

Lab Investigation

Lab Investigation: Respiration of Sugars by Yeast. You are given the opportunity to design and conduct experiments to investigate whether yeasts are able to metabolize a variety of sugars, using gas pressure sensors or other means to measure CO_2 production.

Think About It

Tremetol, a metabolic poison found in the white snake plant root, prevents the metabolism of lactate. When female cows eat this plant, tremetol becomes concentrated in their milk. Humans who consume the milk become ill. Explain why the symptoms of this disease, which include vomiting, abdominal pain, and tremors, becomes worse after exercise.

7.6 | Connections of Carbohydrate, Protein, and Lipid Metabolic Pathways

In this section, you will explore the following question:

- How do carbohydrate metabolic pathways, glycolysis, and the citric acid cycle interrelate with protein and lipid metabolism pathways?

Connection for AP® Courses

The breakdown and synthesis of carbohydrates, proteins, lipids, and nucleic acids connect with the metabolic pathways of glycolysis and the citric acid cycle but enter the pathways at different points. Thus, these macromolecules can be used as sources of free energy.

Information presented and the examples highlighted in the section support concepts and Learning Objectives outlined in Big Idea 2 of the AP® Biology Curriculum Framework, as shown in the table. The Learning Objectives listed in the Curriculum Framework provide a transparent foundation for the AP® Biology course, an inquiry-based laboratory experience, instructional activities, and AP® exam questions. A Learning Objective merges required content with one or more of the seven Science Practices.

Essential Knowledge	**2.A.2** Organisms capture and store free energy for use in biological processes.
Science Practice	**6.2** The student can construct explanations of phenomena based on evidence produced through scientific practices.
Learning Objective	**2.5** The student is able to construct explanations of the mechanisms and structural features of cells that allow organisms to capture, store, or use free energy.
Essential Knowledge	**2.A.1** All living systems require constant input of free energy.
Science Practice	**6.1** The student can justify claims with evidence.
Learning Objective	**2.2** The student is able to justify a scientific claim that free energy is required for living systems to maintain organization, to grow or to reproduce, but that multiple strategies exist in different living systems.

The Science Practice Challenge Questions contain additional test questions for this section that will help you prepare for the AP exam. These questions address the following standards:
[APLO 2.5][APLO 2.15][APLO 3.20][APLO 1.5][APLO 1.26][APLO 4.18]

You have learned about the catabolism of glucose, which provides energy to living cells. But living things consume more than glucose for food. How does a turkey sandwich end up as ATP in your cells? This happens because all of the catabolic pathways for carbohydrates, proteins, and lipids eventually connect into glycolysis and the citric acid cycle pathways (see **Figure 7.18**). Metabolic pathways should be thought of as porous—that is, substances enter from other pathways, and intermediates leave for other pathways. These pathways are not closed systems. Many of the substrates, intermediates, and products in a particular pathway are reactants in other pathways.

Connections of Other Sugars to Glucose Metabolism

Glycogen, a polymer of glucose, is an energy storage molecule in animals. When there is adequate ATP present, excess glucose is shunted into glycogen for storage. Glycogen is made and stored in both liver and muscle. The glycogen will be hydrolyzed into glucose 1-phosphate monomers (G-1-P) if blood sugar levels drop. The presence of glycogen as a source of glucose allows ATP to be produced for a longer period of time during exercise. Glycogen is broken down into G-1-P and converted into G-6-P in both muscle and liver cells, and this product enters the glycolytic pathway.

Sucrose is a disaccharide with a molecule of glucose and a molecule of fructose bonded together with a glycosidic linkage. Fructose is one of the three dietary monosaccharides, along with glucose and galactose (which is part of the milk sugar, the disaccharide lactose), which are absorbed directly into the bloodstream during digestion. The catabolism of both fructose and galactose produces the same number of ATP molecules as glucose.

Connections of Proteins to Glucose Metabolism

Proteins are hydrolyzed by a variety of enzymes in cells. Most of the time, the amino acids are recycled into the synthesis of new proteins. If there are excess amino acids, however, or if the body is in a state of starvation, some amino acids will be shunted into the pathways of glucose catabolism (**Figure 7.17**). Each amino acid must have its amino group removed prior to entry into these pathways. The amino group is converted into ammonia. In mammals, the liver synthesizes urea from two ammonia molecules and a carbon dioxide molecule. Thus, urea is the principal waste product in mammals, produced from the nitrogen originating in amino acids, and it leaves the body in urine.

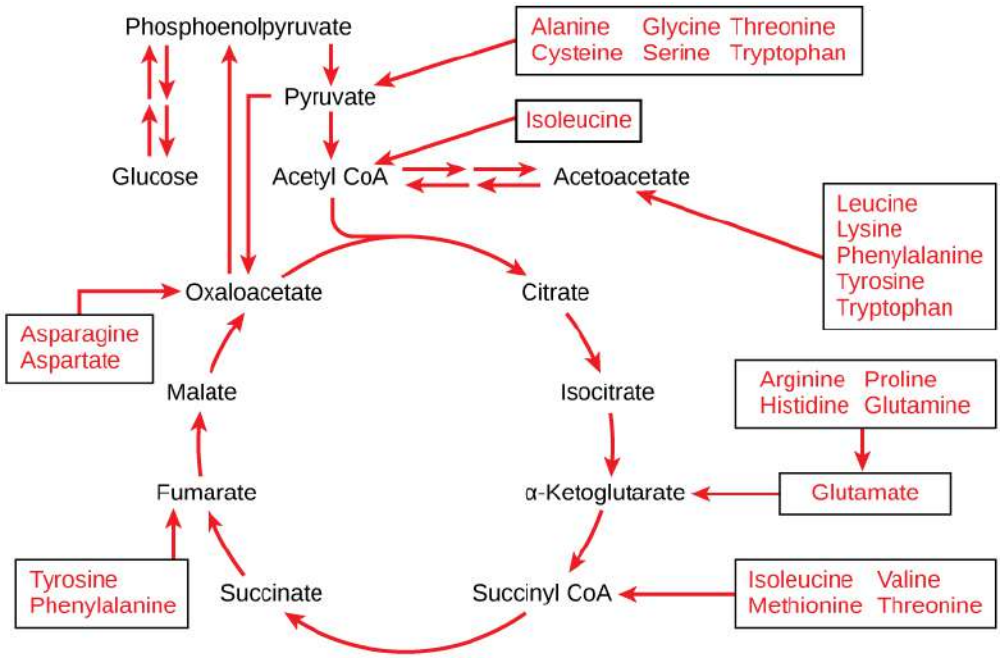


Figure 7.17 The carbon skeletons of certain amino acids (indicated in boxes) derived from proteins can feed into the citric acid cycle. (credit: modification of work by Mikael Häggström)

Connections of Lipid and Glucose Metabolisms

The lipids that are connected to the glucose pathways are cholesterol and triglycerides. Cholesterol is a lipid that contributes to cell membrane flexibility and is a precursor of steroid hormones. The synthesis of cholesterol starts with acetyl groups and proceeds in only one direction. The process cannot be reversed.

Triglycerides are a form of long-term energy storage in animals. Triglycerides are made of glycerol and three fatty acids. Animals can make most of the fatty acids they need. Triglycerides can be both made and broken down through parts of the glucose catabolism pathways. Glycerol can be phosphorylated to glycerol-3-phosphate, which continues through glycolysis. Fatty acids are catabolized in a process called beta-oxidation that takes place in the matrix of the mitochondria and converts their fatty acid chains into two carbon units of acetyl groups. The acetyl groups are picked up by CoA to form acetyl CoA that proceeds into the citric acid cycle.

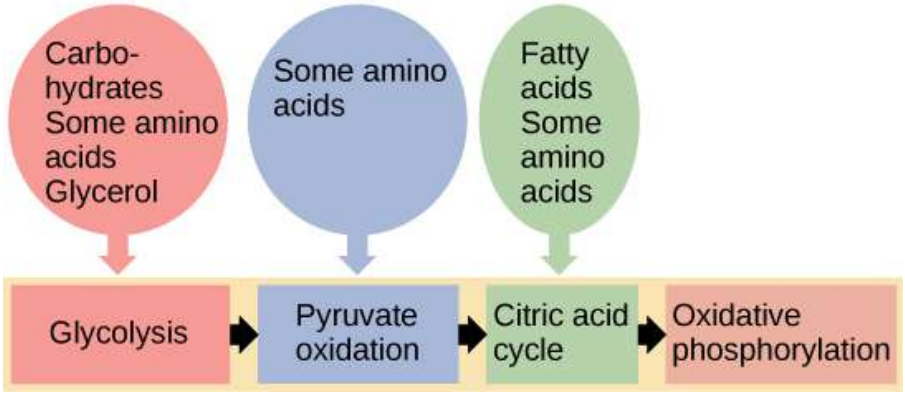


Figure 7.18 Glycogen from the liver and muscles, hydrolyzed into glucose-1-phosphate, together with fats and proteins, can feed into the catabolic pathways for carbohydrates.

evolution CONNECTION

Pathways of Photosynthesis and Cellular Metabolism

The processes of photosynthesis and cellular metabolism consist of several very complex pathways. It is generally thought that the first cells arose in an aqueous environment—a "soup" of nutrients—probably on the surface of some porous clays. If these cells reproduced successfully and their numbers climbed steadily, it follows that the cells would begin to deplete the nutrients from the medium in which they lived as they shifted the nutrients into the components of their own bodies. This hypothetical situation would have resulted in natural selection favoring those organisms that could exist by using the nutrients that remained in their environment and by manipulating these nutrients into materials upon which they could survive. Selection would favor those organisms that could extract maximal value from the nutrients to which they had access.

An early form of photosynthesis developed that harnessed the sun's energy using water as a source of hydrogen atoms, but this pathway did not produce free oxygen (anoxygenic photosynthesis). (Early photosynthesis did not produce free oxygen because it did not use water as the source of hydrogen ions; instead, it used materials like hydrogen sulfide and consequently produced sulfur). It is thought that glycolysis developed at this time and could take advantage of the simple sugars being produced, but these reactions were unable to fully extract the energy stored in the carbohydrates. The development of glycolysis probably predated the evolution of photosynthesis, as it was well suited to extract energy from materials spontaneously accumulating in the "primeval soup." A later form of photosynthesis used water as a source of electrons and hydrogen, and generated free oxygen. Over time, the atmosphere became oxygenated, but not before the oxygen released oxidized metals in the ocean and created a "rust" layer in the sediment, permitting the dating of the rise of the first oxygenic photosynthesizers. Living things adapted to exploit this new atmosphere that allowed aerobic respiration as we know it to evolve. When the full process of oxygenic photosynthesis developed and the atmosphere became oxygenated, cells were finally able to use the oxygen expelled by photosynthesis to extract considerably more energy from the sugar molecules using the citric acid cycle and oxidative phosphorylation.

According to the Evolution Connection passage, in what order did the metabolic pathways evolve?

a. 1. anoxygenic photosynthesis
   2. glycolysis
   3. oxygenic photosynthesis
   4. citric acid cycle and oxidative phosphorylation

b. 1. glycolysis
   2. citric acid cycle and oxidative phosphorylation
   3. anoxygenic photosynthesis
   4. oxygenic photosynthesis

c. 1. anoxygenic photosynthesis
   2. oxygenic photosynthesis
   3. glycolysis
   4. citric acid cycle and oxidative phosphorylation

d. 1. glycolysis
   2. anoxygenic photosynthesis
   3. oxygenic photosynthesis
   4. citric acid cycle and oxidative phosphorylation

science practices CONNECTION for AP® Courses

Think About It

Explain how free energy can be obtained from the metabolism of carbohydrates, proteins, lipids, and even nucleic acids. Which of these molecules provides the largest amount of free energy? Justify your answer.

7.7 | Regulation of Cellular Respiration

In this section, you will explore the following question:

- What mechanisms control cellular respiration?

Connection for AP® Courses

Cellular respiration is controlled by a variety of means. For example, the entry of glucose into a cell is controlled by the transport proteins that aid glucose passage through the cell membrane. However, most of the control of the respiration processes is accomplished through negative feedback inhibition of specific enzymes that respond to the intracellular concentrations of ATP, ADP, NAD^+, and FAD, etc.

Information presented and the examples highlighted in the section support concepts and learning objectives outlined in Big Idea 2 of the AP® Biology Curriculum Framework, as shown in the table. The Learning Objectives listed in the Curriculum Framework provide a transparent foundation for the AP® Biology course, an inquiry-based laboratory experience, instructional activities, and AP® exam questions. A Learning Objective merges required content with one or more of the seven Science Practices.

Big Idea 2	Biological systems utilize free energy and molecular building blocks to grow, to reproduce, and to maintain dynamic homeostasis.
Enduring Understanding 2.C	Organisms use feedback mechanisms to regulate growth and reproduction, and to maintain dynamic homeostasis.
Essential Knowledge	**2.C.1** Organisms use feedback mechanisms to maintain their internal environments and respond to external environmental changes.
Science Practice	**7.2** The student can connect concepts in and across domain(s) to generalize or extrapolate in and/or across enduring understandings and/or big ideas.
Learning Objective	**2.16** The student is able to connect how organisms use negative feedback to maintain their internal environments.
Essential Knowledge	**2.C.1** Organisms use feedback mechanisms to maintain their internal environments and respond to external environmental changes.
Science Practice	**5.3** The student can evaluate the evidence provided by data sets in relation to a particular scientific question.
Learning Objective	**2.17** The student is able to evaluate data that show the effect(s) of changes in concentration of key molecules on negative feedback mechanisms.

Cellular respiration must be regulated in order to provide balanced amounts of energy in the form of ATP. The cell also must generate a number of intermediate compounds that are used in the anabolism and catabolism of macromolecules. Without controls, metabolic reactions would quickly come to a stand-still as the forward and backward reactions reached a state of

equilibrium. Resources would be used inappropriately. A cell does not need the maximum amount of ATP that it can make all the time: At times, the cell needs to shunt some of the intermediates to pathways for amino acid, protein, glycogen, lipid, and nucleic acid production. In short, the cell needs to control its metabolism.

Regulatory Mechanisms

A variety of mechanisms is used to control cellular respiration. Some type of control exists at each stage of glucose metabolism. Access of glucose to the cell can be regulated using the **GLUT proteins** that transport glucose (**Figure 7.19**). Different forms of the GLUT protein control passage of glucose into the cells of specific tissues.

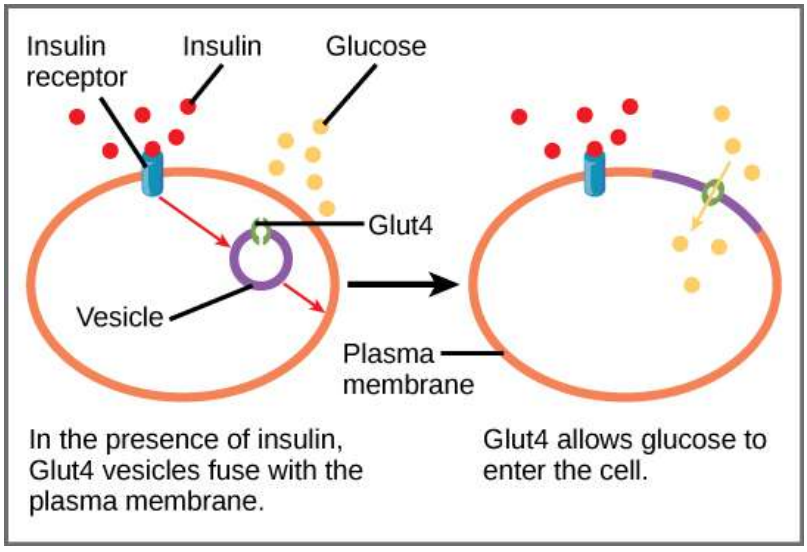


Figure 7.19 GLUT4 is a glucose transporter that is stored in vesicles. A cascade of events that occurs upon insulin binding to a receptor in the plasma membrane causes GLUT4-containing vesicles to fuse with the plasma membrane so that glucose may be transported into the cell.

Some reactions are controlled by having two different enzymes—one each for the two directions of a reversible reaction. Reactions that are catalyzed by only one enzyme can go to equilibrium, stalling the reaction. In contrast, if two different enzymes (each specific for a given direction) are necessary for a reversible reaction, the opportunity to control the rate of the reaction increases, and equilibrium is not reached.

A number of enzymes involved in each of the pathways—in particular, the enzyme catalyzing the first committed reaction of the pathway—are controlled by attachment of a molecule to an allosteric site on the protein. The molecules most commonly used in this capacity are the nucleotides ATP, ADP, AMP, NAD^+, and NADH. These regulators, allosteric effectors, may increase or decrease enzyme activity, depending on the prevailing conditions. The allosteric effector alters the steric structure of the enzyme, usually affecting the configuration of the active site. This alteration of the protein's (the enzyme's) structure either increases or decreases its affinity for its substrate, with the effect of increasing or decreasing the rate of the reaction. The attachment signals to the enzyme. This binding can increase or decrease the enzyme's activity, providing feedback. This feedback type of control is effective as long as the chemical affecting it is attached to the enzyme. Once the overall concentration of the chemical decreases, it will diffuse away from the protein, and the control is relaxed.

Control of Catabolic Pathways

Enzymes, proteins, electron carriers, and pumps that play roles in glycolysis, the citric acid cycle, and the electron transport chain tend to catalyze non-reversible reactions. In other words, if the initial reaction takes place, the pathway is committed to proceeding with the remaining reactions. Whether a particular enzyme activity is released depends upon the energy needs of the cell (as reflected by the levels of ATP, ADP, and AMP).

Glycolysis

The control of glycolysis begins with the first enzyme in the pathway, hexokinase (**Figure 7.20**). This enzyme catalyzes the phosphorylation of glucose, which helps to prepare the compound for cleavage in a later step. The presence of the negatively charged phosphate in the molecule also prevents the sugar from leaving the cell. When hexokinase is inhibited, glucose diffuses out of the cell and does not become a substrate for the respiration pathways in that tissue. The product of the hexokinase reaction is glucose-6-phosphate, which accumulates when a later enzyme, phosphofructokinase, is inhibited.

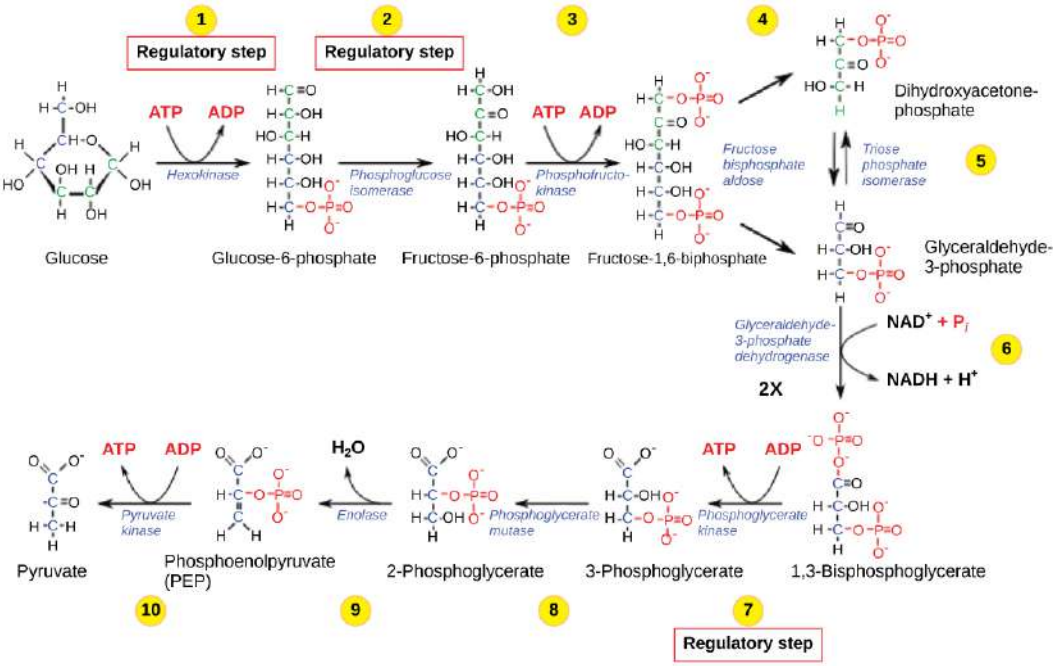


Figure 7.20 The glycolysis pathway is primarily regulated at the three key enzymatic steps (1, 2, and 7) as indicated. Note that the first two steps that are regulated occur early in the pathway and involve hydrolysis of ATP.

Phosphofructokinase is the main enzyme controlled in glycolysis. High levels of ATP, citrate, or a lower, more acidic pH decrease the enzyme's activity. An increase in citrate concentration can occur because of a blockage in the citric acid cycle. Fermentation, with its production of organic acids like lactic acid, frequently accounts for the increased acidity in a cell; however, the products of fermentation do not typically accumulate in cells.

The last step in glycolysis is catalyzed by pyruvate kinase. The pyruvate produced can proceed to be catabolized or converted into the amino acid alanine. If no more energy is needed and alanine is in adequate supply, the enzyme is inhibited. The enzyme's activity is increased when fructose-1,6-bisphosphate levels increase. (Recall that fructose-1,6-bisphosphate is an intermediate in the first half of glycolysis.) The regulation of pyruvate kinase involves phosphorylation by a kinase (pyruvate kinase kinase), resulting in a less-active enzyme. Dephosphorylation by a phosphatase reactivates it. Pyruvate kinase is also regulated by ATP (a negative allosteric effect).

If more energy is needed, more pyruvate will be converted into acetyl CoA through the action of pyruvate dehydrogenase. If either acetyl groups or NADH accumulate, there is less need for the reaction and the rate decreases. Pyruvate dehydrogenase is also regulated by phosphorylation: A kinase phosphorylates it to form an inactive enzyme, and a phosphatase reactivates it. The kinase and the phosphatase are also regulated.

Citric Acid Cycle

The citric acid cycle is controlled through the enzymes that catalyze the reactions that make the first two molecules of NADH (**Figure 7.10**). These enzymes are isocitrate dehydrogenase and α-ketoglutarate dehydrogenase. When adequate ATP and NADH levels are available, the rates of these reactions decrease. When more ATP is needed, as reflected in rising ADP levels, the rate increases. α-ketoglutarate dehydrogenase will also be affected by the levels of succinyl CoA—a subsequent intermediate in the cycle—causing a decrease in activity. A decrease in the rate of operation of the pathway at this point is not necessarily negative, as the increased levels of the α-ketoglutarate not used by the citric acid cycle can be used by the cell for amino acid (glutamate) synthesis.

Electron Transport Chain

Specific enzymes of the electron transport chain are unaffected by feedback inhibition, but the rate of electron transport through the pathway is affected by the levels of ADP and ATP. Greater ATP consumption by a cell is indicated by a buildup of ADP. As ATP usage decreases, the concentration of ADP decreases, and now, ATP begins to build up in the cell. This change in the relative concentration of ADP to ATP triggers the cell to slow down the electron transport chain.

Visit this **site (http://openstaxcollege.org/l/electron_transp)** to see an animation of the electron transport chain and ATP synthesis.

Which statement best describes the formation and importance of the hydrogen ion gradient during the electron transport chain?

a. A hydrogen ion gradient across the membrane establishes a concentration gradient and not an electrical gradient, thus assisting during the electron transport chain.

b. A hydrogen ion gradient is established by pumping two hydrogen ions across the membrane from the matrix in the intermembrane space. Its uneven distribution across the membrane establishes both concentration and electrical gradients.

c. A hydrogen ion gradient is established by pumping four hydrogen ions across the membrane from the matrix into the intermembrane space and its uneven distribution across the membrane establishes concentration and electrical gradients.

d. Hydrogen ions are present in the intermembrane space from the beginning and results in the formation of gradients necessary for the function of ATP synthase.

For a summary of feedback controls in cellular respiration, see **Table 7.1**.

Summary of Feedback Controls in Cellular Respiration

Pathway	Enzyme affected	Elevated levels of effector	Effect on pathway activity
glycolysis	hexokinase	glucose-6-phosphate	decrease
	phosphofructokinase	low-energy charge (ATP, AMP), fructose-6-phosphate via fructose-2,6-bisphosphate	increase
		high-energy charge (ATP, AMP), citrate, acidic pH	decrease
	pyruvate kinase	fructose-1,6-bisphosphate	increase
		high-energy charge (ATP, AMP), alanine	decrease
pyruvate to acetyl CoA conversion	pyruvate dehydrogenase	ADP, pyruvate	increase
		acetyl CoA, ATP, NADH	decrease
citric acid cycle	isocitrate dehydrogenase	ADP	increase
		ATP, NADH	decrease

Table 7.1

Summary of Feedback Controls in Cellular Respiration

Pathway	Enzyme affected	Elevated levels of effector	Effect on pathway activity
	α-ketoglutarate dehydrogenase	Calcium ions, ADP	increase
		ATP, NADH, succinyl CoA	decrease
electron transport chain		ADP	increase
		ATP	decrease

Table 7.1

Think About It

Phosphofructokinase is a key enzyme in glycolysis. High levels of ATP or citrate or low pH can decrease the enzyme's activity. Explain why this is beneficial to the cell.

KEY TERMS

acetyl CoA combination of an acetyl group derived from pyruvic acid and coenzyme A, which is made from pantothenic acid (a B-group vitamin)

aerobic respiration process in which organisms convert energy in the presence of oxygen

anaerobic process that does not use oxygen

anaerobic cellular respiration process in which organisms convert energy for their use in the absence of oxygen

ATP synthase (also, F1F0 ATP synthase) membrane-embedded protein complex that adds a phosphate to ADP with energy from protons diffusing through it

chemiosmosis process in which there is a production of adenosine triphosphate (ATP) in cellular metabolism by the involvement of a proton gradient across a membrane

citric acid cycle (also, Krebs cycle) series of enzyme-catalyzed chemical reactions of central importance in all living cells

dephosphorylation removal of a phosphate group from a molecule

fermentation process of regenerating NAD^+ with either an inorganic or organic compound serving as the final electron acceptor; occurs in the absence of oxygen

GLUT protein integral membrane protein that transports glucose

glycolysis process of breaking glucose into two three-carbon molecules with the production of ATP and NADH

isomerase enzyme that converts a molecule into its isomer

Krebs cycle (also, citric acid cycle) alternate name for the citric acid cycle, named after Hans Krebs who first identified the steps in the pathway in the 1930s in pigeon flight muscles; see citric acid cycle

oxidative phosphorylation production of ATP using the process of chemiosmosis and oxygen

phosphorylation addition of a high-energy phosphate to a compound, usually a metabolic intermediate, a protein, or ADP

prosthetic group (also, prosthetic cofactor) molecule bound to a protein that facilitates the function of the protein

pyruvate three-carbon sugar that can be decarboxylated and oxidized to make acetyl CoA, which enters the citric acid cycle under aerobic conditions; the end product of glycolysis

redox reaction chemical reaction that consists of the coupling of an oxidation reaction and a reduction reaction

substrate-level phosphorylation production of ATP from ADP using the excess energy from a chemical reaction and a phosphate group from a reactant

TCA cycle (also, citric acid cycle) alternate name for the citric acid cycle, named after the group name for citric acid, tricarboxylic acid (TCA); see citric acid cycle

ubiquinone soluble electron transporter in the electron transport chain that connects the first or second complex to the third

CHAPTER SUMMARY

7.1 Energy in Living Systems

ATP functions as the energy currency for cells. It allows the cell to store energy briefly and transport it within the cell to support endergonic chemical reactions. The structure of ATP is that of an RNA nucleotide with three phosphates attached. As ATP is used for energy, a phosphate group or two are detached, and either ADP or AMP is produced. Energy derived

from glucose catabolism is used to convert ADP into ATP. When ATP is used in a reaction, the third phosphate is temporarily attached to a substrate in a process called phosphorylation. The two processes of ATP regeneration that are used in conjunction with glucose catabolism are substrate-level phosphorylation and oxidative phosphorylation through the process of chemiosmosis.

7.2 Glycolysis

Glycolysis is the first pathway used in the breakdown of glucose to extract energy. It was probably one of the earliest metabolic pathways to evolve and is used by nearly all of the organisms on earth. Glycolysis consists of two parts: The first part prepares the six-carbon ring of glucose for cleavage into two three-carbon sugars. ATP is invested in the process during this half to energize the separation. The second half of glycolysis extracts ATP and high-energy electrons from hydrogen atoms and attaches them to NAD^+. Two ATP molecules are invested in the first half and four ATP molecules are formed by substrate phosphorylation during the second half. This produces a net gain of two ATP and two NADH molecules for the cell.

7.3 Oxidation of Pyruvate and the Citric Acid Cycle

In the presence of oxygen, pyruvate is transformed into an acetyl group attached to a carrier molecule of coenzyme A. The resulting acetyl CoA can enter several pathways, but most often, the acetyl group is delivered to the citric acid cycle for further catabolism. During the conversion of pyruvate into the acetyl group, a molecule of carbon dioxide and two high-energy electrons are removed. The carbon dioxide accounts for two (conversion of two pyruvate molecules) of the six carbons of the original glucose molecule. The electrons are picked up by NAD^+, and the NADH carries the electrons to a later pathway for ATP production. At this point, the glucose molecule that originally entered cellular respiration has been completely oxidized. Chemical potential energy stored within the glucose molecule has been transferred to electron carriers or has been used to synthesize a few ATPs.

The citric acid cycle is a series of redox and decarboxylation reactions that remove high-energy electrons and carbon dioxide. The electrons temporarily stored in molecules of NADH and $FADH_2$ are used to generate ATP in a subsequent pathway. One molecule of either GTP or ATP is produced by substrate-level phosphorylation on each turn of the cycle. There is no comparison of the cyclic pathway with a linear one.

7.4 Oxidative Phosphorylation

The electron transport chain is the portion of aerobic respiration that uses free oxygen as the final electron acceptor of the electrons removed from the intermediate compounds in glucose catabolism. The electron transport chain is composed of four large, multiprotein complexes embedded in the inner mitochondrial membrane and two small diffusible electron carriers shuttling electrons between them. The electrons are passed through a series of redox reactions, with a small amount of free energy used at three points to transport hydrogen ions across a membrane. This process contributes to the gradient used in chemiosmosis. The electrons passing through the electron transport chain gradually lose energy, High-energy electrons donated to the chain by either NADH or $FADH_2$ complete the chain, as low-energy electrons reduce oxygen molecules and form water. The level of free energy of the electrons drops from about 60 kcal/mol in NADH or 45 kcal/mol in $FADH_2$ to about 0 kcal/mol in water. The end products of the electron transport chain are water and ATP. A number of intermediate compounds of the citric acid cycle can be diverted into the anabolism of other biochemical molecules, such as nonessential amino acids, sugars, and lipids. These same molecules can serve as energy sources for the glucose pathways.

7.5 Metabolism without Oxygen

If NADH cannot be oxidized through aerobic respiration, another electron acceptor is used. Most organisms will use some form of fermentation to accomplish the regeneration of NAD^+, ensuring the continuation of glycolysis. The regeneration of NAD^+ in fermentation is not accompanied by ATP production; therefore, the potential of NADH to produce ATP using an electron transport chain is not utilized.

7.6 Connections of Carbohydrate, Protein, and Lipid Metabolic Pathways

The breakdown and synthesis of carbohydrates, proteins, and lipids connect with the pathways of glucose catabolism. The simple sugars are galactose, fructose, glycogen, and pentose. These are catabolized during glycolysis. The amino acids from proteins connect with glucose catabolism through pyruvate, acetyl CoA, and components of the citric acid cycle. Cholesterol synthesis starts with acetyl groups, and the components of triglycerides come from glycerol-3-phosphate from glycolysis and acetyl groups produced in the mitochondria from pyruvate.

7.7 Regulation of Cellular Respiration

Cellular respiration is controlled by a variety of means. The entry of glucose into a cell is controlled by the transport proteins that aid glucose passage through the cell membrane. Most of the control of the respiration processes is accomplished through the control of specific enzymes in the pathways. This is a type of negative feedback, turning the enzymes off. The enzymes respond most often to the levels of the available nucleosides ATP, ADP, AMP, NAD^+, and FAD. Other intermediates of the pathway also affect certain enzymes in the systems.

REVIEW QUESTIONS

1. What is the most important energy currency used by cells?

a. ATP

b. ADP

c. AMP

d. adenosine

2. What happens when a chemical is reduced during a reaction?

a. The compound is reduced to a simpler form.

b. An electron is added to the chemical.

c. A hydrogen atom is removed from the substrate.

d. acts as a catabolic reaction

3. Which of the following molecules are oxidizing agents?

a. FAD^+ and NAD^+

b. $FADH_2$ and NADH

c. FAD and $FADH_2$

d. NAD^+ and NADH

4. Which of the following reactions releases energy?

a. $\text{AMP} + \text{phosphate} \rightarrow \text{ADP} + H_2O$

b. $\text{ADP} + \text{phosphate} \rightarrow \text{ATP} + H_2O$

c. $\text{ATP} + H_2O \rightarrow \text{ADP} + \text{Phosphate}$

d. $\text{AMP} + H_2O \rightarrow \text{ATP} + \text{Phosphate}$

5. During the second half of glycolysis, what occurs?

a. ATP is used up.

b. Fructose is split in two.

c. ATP is produced.

d. Glucose becomes fructose.

6. GLUTs are integral membrane proteins that assist in the facilitated diffusion of glucose into and out of cells. What reaction in glycolysis prevents glucose from being transported back out of the cell?

a. Hexokinase dephosphorylates glucose using ATP, creating a glucose molecules that can't cross the hydrophilic portion of the plasma membrane.

b. Hexokinase phosphorylates glucose using ADP, creating a glucose molecules that can't cross the hydrophobic interior of the plasma membrane.

c. Hexokinase dephosphorylates glucose using ADP, creating a glucose molecule that can't cross the hydrophilic portion of the plasma membrane.

d. Hexokinase phosphorylates glucose using ATP, creating a glucose molecule that can't cross the hydrophobic interior of the plasma membrane.

7. How many ATP molecules are used and produced per molecule of glucose during glycolysis?

a. The first half of glycolysis uses 2 ATPs, and the second half of glycolysis produces 4 ATPs.

b. The first half of glycolysis produces 2 ATPs, and the second half of glycolysis uses 4 ATPs.

c. The first half of glycolysis uses 4 ATPs, and the second half of glycolysis produces 2 ATPs.

d. The first half of glycolysis produces 4 ATPS, and the second half of glycolysis uses 2 ATPs.

8. What is removed from pyruvate during its conversion into an acetyl group?

a. oxygen

b. ATP

c. B vitamin

d. carbon dioxide

9. What do the electrons added to NAD^+ do in aerobic respiration?

a. They become part of a fermentation pathway.

b. They go to another pathway for ATP production.

c. They energize the acetyl group in the citric acid cycle.

d. They are converted to NADP.

10. GTP, which can be converted to ATP, is produced during which reaction of the citric acid cycle?

a. isocitrate into α-ketoglutarate
b. succinyl-CoA into succinate
c. fumarate into malate
d. malate into oxaloacetate

11. How many NADH molecules are produced on each turn of the citric acid cycle?

a. one
b. two
c. three
d. four

12. What compound receives electrons from NADH?

a. FMN
b. ubiquinone
c. cytochrome c1
d. oxygen

13. Chemiosmosis involves the movement of what? Where does it occur?

a. electrons across the cell membrane
b. hydrogen atoms across a mitochondrial membrane
c. hydrogen ions across a mitochondrial membrane
d. glucose through the cell membrane

14. What is the function of an electron in the electron transport chain?

a. to dephosphorylate ATP, producing ADP
b. to power active transport pumps
c. to reduce heme in complex III
d. to oxidize oxygen

15. What would be the outcome if hydrogen ions were able to diffuse through the mitochondrial membrane into the mitochondria without the need for integral membrane proteins?

a. ATP would not be produced.
b. Pyruvate would not be produced.
c. Citric acid would not be produced.
d. Carbon dioxide would not be produced.

16. Which of the following fermentation methods can occur in animal skeletal muscles?

a. lactic acid fermentation
b. alcohol fermentation
c. mixed acid fermentation
d. propionic fermentation

17. Which molecules are produced in glycolysis and used in fermentation?

a. acetyl-CoA and NADH
b. lactate, ATP, and CO_2
c. glucose, ATP , and NAD^+
d. pyruvate and NADH

18. What are the products of alcohol fermentation?

a. methane and NADH
b. lactic acid and FAD^+
c. ethanol and NAD^+
d. pyruvic acid and NADH

19. In the first step of glycolysis, what is glucose transformed into?

a. glucose-6-phosphate
b. fructose-1,6-bisphosphate
c. dihydroxyacetone phosphate
d. phosphoenolpyruvate

20. What is beta-oxidation?

a. the main process used to break down glucose
b. the main process used to assemble glucose
c. the main process used to break down fatty acids
d. the main process used to remove amino groups from amino acids

21. Which of the following statements about catabolic pathways is false?

a. Carbohydrates can feed into oxidative phosphorylation.
b. Glycerol can be broken down into glucose and feed into glycolysis.
c. Amino acids can feed into pyruvate oxidation.
d. Fatty acids can feed into the citric acid cycle.

22. What impact, if any, do high levels of ADP have on glycolysis?

a. They increase the activity of enzymes involved with glycolysis.
b. The high levels decrease the activity of enzymes involved with glycolysis.
c. They have no effect on the activity of any enzymes involved with glycolysis.
d. The high levels slow down all pathways involved with glycolysis.

23. The control of which enzyme exerts the greatest control of glycolysis?

a. hexokinase
b. phosphofructokinase
c. glucose-6-phosphatase
d. aldolase

24. Which of the following does not occur as ATP concentration increases relative to ADP?

a. decreased activity of phosphofructokinase
b. increased activity of pyruvate kinase
c. decreased activity of isocitrate dehydrogenase
d. slowdown of the electron transport chain

CRITICAL THINKING QUESTIONS

25. Why is it beneficial for cells to use ATP rather than directly using the energy stored in the bonds of carbohydrates to power cellular reactions? What are the greatest drawbacks to harnessing energy from the bonds of several different compounds?

a. ATP is readily available in the form of a single unit that provides a consistent, appropriate amount of energy. The cell would need to tailor each reaction to each energy source if it harvested energy from different compounds.
b. ATP energy cannot activate the ROS dependent stress response whereas food molecules are responsible for activating ROS.
c. ATP is low in energy, but food molecules possess higher levels of energy that cells can use.
d. ATP is readily available to cells, unlike compounds that have to first be phosphorylated in order to release their energy.

26. What role does NAD^+ play in redox reactions?

a. NAD^+, an oxidizing agent, can accept electrons and protons from organic molecules and get reduced to $NADH$.
b. NAD^+, a reducing agent, can donate its electrons and protons to organic molecules.
c. NAD^+, an oxidizing agent, can accept electrons from organic molecules and get reduced to $NADH_2$.
d. NAD^+, a reducing agent, can donate its electrons and protons to inorganic molecules.

27. Which statement best explains how electrons are transferred and the role of each species. Remember that R represents a hydrocarbon molecule and RH represents the same molecule with a particular hydrogen identified.

$$RH + NAD^+ \rightarrow NADH + R$$

a. RH acts as a reducing agent and donates its electrons to the oxidizing agent NAD^+, forming $NADH$ and R.
b. NAD^+, the oxidizing agent, donates its electrons to the reducing agent RH, forming R and $NADH$.
c. RH acts as an oxidizing agent and donates electrons to the reducing agent NAD^+, producing $NADH$ and R.
d. NAD^+, the reducing agent, accepts electrons from the oxidizing agent RH, producing $NADH$ and R.

28. Nearly all organisms on earth carry out some form of glycolysis. How does this fact support or not support the assertion that glycolysis is one of the oldest metabolic pathways?

a. To be present in so many different organisms, glycolysis was probably present in a common ancestor rather than evolving many separate times.
b. Glycolysis is present in nearly all organisms because it is an advanced and recently evolved pathway that has been widely used as it is so beneficial.
c. Glycolysis is absent in a few higher organisms. This contradicts the fact that it is one of the oldest metabolic pathways.
d. Glycolysis is present in some organisms and absent in others. The mentioned fact may or may not support this assertion.

29. Red blood cells (RBCs) do not perform aerobic respiration, but they do perform glycolysis. Why do all cells need an energy source and what would happen if glycolysis were blocked in a red blood cell?

a. Cells require energy to perform certain basic functions. Blocking glycolysis in RBCs causes imbalance in the membrane potential, leading to cell death.

b. Cells need energy to perform cell division. Blocking glycolysis in RBCs interrupts the process of mitosis leading to nondisjunction.

c. Cells maintain the influx and efflux of organic substances using energy. Blocking glycolysis stops the binding of CO_2 to the RBCs, causing cell death.

d. Cells require energy to recognize attacking pathogens. Blocked glycolysis inhibits the process of recognition, causing invasion of the RBCs by a pathogen.

30. What is the primary difference between a circular pathway and a linear pathway?

a. The reactant and the product are the same in a circular pathway but different in a linear pathway.

b. The circular pathway components get exhausted whereas those of the linear pathway do not and are continually regenerated.

c. Circular pathways are not suited for amphibolic pathways whereas linear pathways are.

d. Circular pathways contain a single chemical reaction that is repeated while linear pathways have multiple events.

31. Cellular respiration breaks down glucose and releases carbon dioxide and water. Which steps in the oxidation of pyruvate produces carbon dioxide?

a. Removal of a carboxyl group from pyruvate releases carbon dioxide. The pyruvate dehydrogenase complex comes into play.

b. Removal of an acetyl group from pyruvate releases carbon dioxide. The pyruvate decarboxylase complex comes into play.

c. Removal of a carbonyl group from pyruvate releases carbon dioxide. The pyruvate dehydrogenase complex comes into play.

d. Removal of an acetyl group from pyruvate releases carbon dioxide. The pyruvate dehydrogenase complex comes into play.

32. What three steps are included in the breakdown of pyruvate?

a. Pyruvate dehydrogenase removes a carboxyl group from pyruvate producing carbon dioxide. Dihydrolipoyl transacetylase oxidizes a hydroxyethyl group to an acetyl group, producing NADH. Lastly, an enzyme-bound acetyl group is transferred to CoA, producing a molecule of acetyl-CoA.

b. Pyruvate dehydrogenase oxidizes hydroxyethyl group to an acetyl group, producing NADH. It further removes a carboxyl group from pyruvate producing carbon dioxide. Lastly, dihydrolipoyl transacetylase transfers enzyme-bound acetyl group to CoA forming an acetyl-CoA molecule.

c. Pyruvate dehydrogenase transfers enzyme-bound acetyl group to CoA forming an acetyl CoA molecule. It then oxidizes a hydroxyethyl group to an acetyl group, producing NADH. Dihydrolipoyl transacetylase removes a carboxyl group from pyruvate producing carbon dioxide.

d. Pyruvate dehydrogenase removes carboxyl group from pyruvate producing carbon dioxide. Dihydrolipoyl dehydrogenase transfers enzyme-bound acetyl groups to CoA forming an acetyl-CoA molecule. Lastly, a hydroxyethyl group is oxidized to an acetyl group, producing NADH.

33. How do the roles of ubiquinone and cytochrome c differ from the other components of the electron transport chain?

a. CoQ and cytochrome c are mobile electron carriers while NADH dehydrogenase and succinate dehydrogenase are bound to the inner mitochondrial membrane.

b. CoQ and cytochrome covalently bind electrons while NADH dehydrogenase and succinate dehydrogenase are bound to the inner mitochondrial membrane.

c. CoQ and cytochrome c are bound to the inner mitochondrial membrane while NADH dehydrogenase and succinate dehydrogenase are mobile electron carriers.

d. CoQ and cytochrome c covalently bind electrons while NADH dehydrogenase and succinate dehydrogenase are mobile electron carriers.

34. What accounts for the different number of ATP molecules that are formed through cellular respiration?

a. Transport of NADH from cytosol to mitochondria is an active process that decreases the number of ATP produced.

b. The ATPs produced are utilized in the anaplerotic reactions that are used for the replenishment of the intermediates.

c. Most of the ATP's produced are rapidly used for the phosphorylation of certain compounds found in plants.

d. A large number of ATP molecules are used in the detoxification of xenobiotic compounds produced during cellular respiration.

35. Which of the following best describes complex IV in the electron transport chain?

a. Complex IV consists of an oxygen molecule held between the cytochrome and copper ions. The electrons flowing finally reach the oxygen, producing water.

b. Complex IV contains a molecule of flavin mononucleotide and iron-sulfur clusters. The electrons from NADH are transported here to coenzyme Q.

c. Complex IV contains cytochrome b, c, and Fe-S. Here, the proton motive Q cycle takes place.

d. Complex IV contains a membrane-bound enzyme that accepts electrons from $FADH_2$ to make FAD. This electron is then transferred to ubiquinone.

36. What is the primary difference between fermentation and anaerobic respiration?

a. Fermentation uses only glycolysis and its final electron acceptor is an organic molecule, whereas anaerobic respiration uses glycolysis, TCA and the ETC but finally give electrons to an inorganic molecule.

b. Fermentation uses glycolysis, TCA and ETC but finally gives electrons to an inorganic molecule, whereas anaerobic respiration uses only glycolysis and its final electron acceptor is an organic molecule.

c. Fermentation uses glycolysis and its final electron acceptor is an inorganic molecule, whereas anaerobic respiration uses glycolysis, TCA and ETC but finally give electrons to an organic molecule.

d. Fermentation uses glycolysis, TCA and ETC but finally gives electrons to an organic molecule, whereas anaerobic respiration uses only glycolysis and its final electron acceptor is an inorganic molecule.

37. What type of cellular respiration is represented in the following equation, and why?

$$CO_2 + H_2 + NADH \rightarrow CH_4 + H_2O + NAD^+$$

a. Anaerobic respiration, because the final electron acceptor is inorganic.

b. Aerobic respiration, because oxygen is the final electron acceptor.

c. Anaerobic respiration, because NADH donates its electrons to a methane molecule.

d. Aerobic respiration, because water is being produced as a product.

38. Would you describe metabolic pathways as inherently wasteful or inherently economical, and why?

a. Metabolic pathways are economical due to feedback inhibition. Also, intermediates from one pathway can be utilized by other pathways.

b. Metabolic pathways are wasteful as they perform uncoordinated catabolic and anabolic reactions that wastes some of the energy that is stored.

c. Metabolic pathways are economical due to the presence of anaplerotic reactions that replenish the intermediates.

d. Metabolic pathways are wasteful as most of the energy produced is utilized in maintaining the reduced environment of the cytosol.

39. What lipids are connected to glucose catabolism pathways and how are they connected?

a. Cholesterol and triglycerides can be converted to glycerol-3-phosphate that continues through glycolysis.

b. Glucagon and glycogen can be converted to 3-phosphoglyceraldehyde that is an intermediate of glycolysis.

c. Chylomicrons and fatty acids get converted to 1,3-bisphosphoglycerate that continues in glycolysis, forming pyruvate.

d. Sphingolipids and triglycerides form glucagon that can be fed into glycolysis.

40. How does citrate from the citric acid cycle affect glycolysis?

a. Citrate and ATP are negative regulators of phosphofructokinase-1.

b. Citrate and ATP are negative regulators of hexokinase.

c. Citrate and ATP are positive regulators of phosphofructokinase-1.

d. Citrate and ATP are positive regulators of hexokinase.

41. Why might negative feedback mechanisms be more common than positive feedback mechanisms in living cells?

a. Negative feedback mechanisms maintain homeostasis whereas positive feedback drives the system away from equilibrium.

b. Positive feedback mechanisms maintain a balanced amount of substances whereas negative feedback restricts them.

c. Negative feedback turns the system off, making it deficient of certain substances. Positive feedback balances out these deficits.

d. Positive feedback brings substance amounts back to equilibrium while negative feedback produces excess amounts of the substance.

TEST PREP FOR AP® COURSES

42.

Organism	Temperature (°C)	Average respiration (mL O2/g/min)
Mouse	10	0.0518
Mouse	25	0.0321
Cricket	10	0.0013
Cricket	25	0.0038

The table shows the amount of oxygen consumed (third column) by different animals (first column) at different temperatures. This type of apparatus measures the change in volume of air to detect the removal of oxygen. However, organisms produce carbon dioxide as they take in oxygen. To provide accurate measurements, what would you need to add to the setup?

a. a substance that removes carbon dioxide gas

b. a plant that will add oxygen to allow an animal to breathe

c. a glucose reserve

d. a substance that adds carbon dioxide gas

43.

Organism	Temperature (°C)	Average respiration (mL O2/g/min)
Mouse	10	0.0518
Mouse	25	0.0321
Cricket	10	0.0013
Cricket	25	0.0038

According to the data, the crickets at 25°C have greater oxygen consumption per gram of tissue than do the crickets at 10°C. This trend in oxygen consumption is the opposite of that in mice. The difference in trends in oxygen consumption among crickets and mice is due to what?

a. their difference in size

b. their mode of nutrition

c. their difference in metabolic heat production

d. their mode of ATP production

44. Where in a cell does glycolysis take place in both prokaryotes and eukaryotes?

a. the cytosol

b. the mitochondria

c. the plasma membrane

d. the nucleus

45. A new species of obligate anaerobe, a bacterium, has been found that lives in hot, acidic conditions. While other pathways may also be present, which metabolic pathway is the most likely to be present in this species?

a. aerobic respiration

b. the citric acid cycle

c. oxidative phosphorylation

d. glycolysis

46. What evidence provides the strongest support that glycolysis is an older and more conserved pathway than the citric acid cycle?

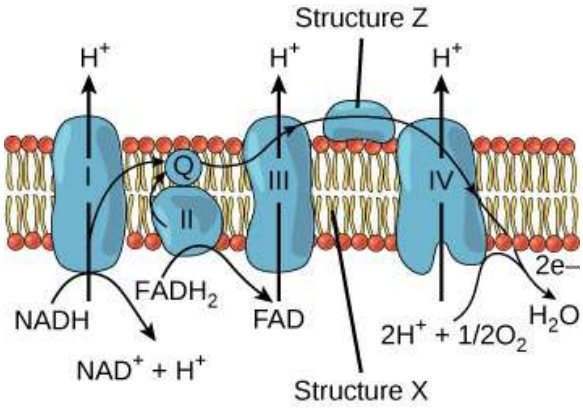
a. Glycolysis is the primitive pathway as it is found in all three domains. It also occurs in anaerobic conditions and in the cytosol.

b. This pathway occurs in the cytosol, is found in all animals and plants, and does not require oxygen.

c. Glycolysis takes place in anaerobic conditions, can metabolize cholesterol and fatty acids, and occurs even in methanogens.

d. This pathway only occurs in the mitochondria. It is highly flexible because it is found in almost all organisms.

47.



What is Structure X in the graphic?

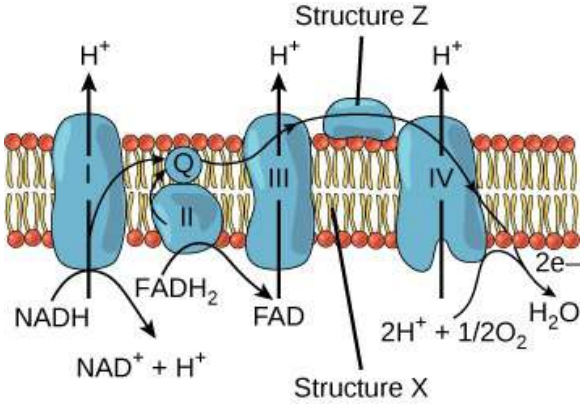
a. the inner mitochondrial membrane

b. the mitochondrial matrix

c. a eukaryotic plasma membrane

d. the cytosol

48.



What would be the most direct result of blocking structure Z in the graphic?

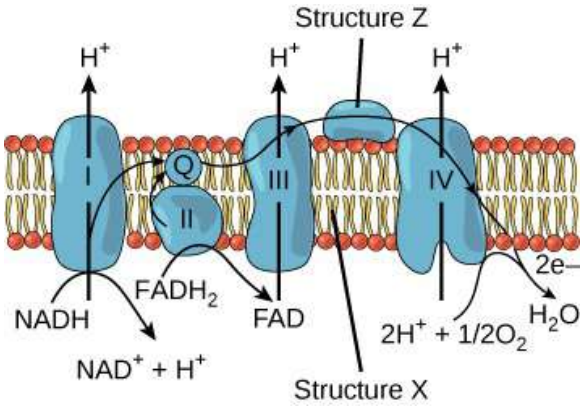
a. Cytochrome c would not pass electrons from complex III to complex IV.

b. Ubiquinone would not pass electrons from complex III to complex IV.

c. $NADH$ would not be converted to NAD_+ and the electron transport chain would stop.

d. No protons would be pumped across the membrane.

49.



Where do the electrons moving along the membrane in the figure come from, and where do the electrons end up?

a. The electrons are released by $NADH$ and $FADH_2$ and finally accepted by oxygen to form water.

b. The electrons are given off by water and finally accepted by NAD^+ and FAD^+ to produce the energy currencies $NADH$ and $FADH_2$.

c. The electrons are emitted by ubiquinone that are, in turn, transferred from complex I to complex II. Water finally accepts the electrons.

d. The electrons are given out by $NADH$ and $FADH_2$ and are, in turn, finally accepted by H_2O.

50. Glucose catabolism pathways are sequential and lead to the production of ATP. What is the correct order of the pathways for the breakdown of a molecule of glucose as shown in the formula?

$$C_6H_{12}O_6 + O_2 \rightarrow CO_2 + H_2O + \text{energy}$$

a. oxidative phosphorylation → citric acid cycle → oxidation of pyruvate → glycolysis

b. the oxidation of pyruvate → citric acid cycle → glycolysis → oxidative phosphorylation

c. glycolysis → oxidation of pyruvate → citric acid cycle → oxidative phosphorylation

d. citric acid cycle → glycolysis → oxidative phosphorylation → oxidation of pyruvate

51. Which of the following statements most directly supports the claim that different species of organisms use different metabolic strategies to meet their energy requirements for growth, reproduction, and homeostasis?

a. During cold periods, pond-dwelling animals can increase the number of unsaturated fatty acids in their cell membranes while some plants make antifreeze proteins to prevent ice crystal formation in their tissues.

b. Bacteria lack introns while many eukaryotic genes contain many of these intervening sequences.

c. Carnivores have more teeth that are specialized for ripping food while herbivores have more teeth specialized for grinding food.

d. Plants generally use starch molecules for storage while animals use glycogen and fats for storage.

52. Which of the following best describes how the citric acid cycle relates to glycolysis, oxidative phosphorylation, and chemiosmosis?

a. Glycolysis produces pyruvate, which is converted to acetyl-CoA and enters the citric acid cycle. This cycle produces $NADH$ and $FADH_2$, which donate electrons to the electron transport chain to pump protons and produce ATP through chemiosmosis. Production of ATP using an electron transport chain and chemiosmosis is called oxidative phosphorylation.

b. The citric acid produces pyruvate, which converts to glucose to enter glycolysis. This pathway produces $NADH$ and $FADH_2$, which enter oxidative phosphorylation to produce ATP through chemiosmosis.

c. Citric acid produces $NADH$ and $FADH_2$, which undergo oxidative phosphorylation. This produces ATP by pumping protons through chemiosmosis. The ATP produced is utilized in large amount in the process of glycolysis.

d. Glycolysis produces pyruvate, which directly enters the citric acid cycle. This cycle produces the energy currency that undergoes the electron transport chain to produce water and ATP.

SCIENCE PRACTICE CHALLENGE QUESTIONS

53. Combustion of carbohydrates, like in a fireplace, is a reduction-oxidation reaction in which the carbon atom is oxidized and the oxygen atom is reduced, producing water and carbon dioxide. Oxidative phosphorylation and glycolysis are also reduction-oxidation reactions that produce the same products. Explain the differences and similarities among these abiotic and biotic processes in terms of the changes in entropy and heat that contribute to the free energy extracted from chemical bonds, the spontaneity of each, and the role of catalysis.

54. A. **[Extension]** Living systems require free energy to carry out cellular functions, and employ various strategies to capture, use, and store free energy. **Explain** the advantage that the higher energy efficiency per kg of the Krebs cycle provides to *you* compared to a metabolism based on glycolysis alone. Your explanation should make use of all the following facts:

- ΔG for glycolysis is -135kJ per mole of glucose
- ΔG for aerobic respiration is -2880kJ per mole glucose
- the basal metabolic rate of mammals is often represented as -300kJ/day • $m^{0.75}$
- the molar mass of glucose is 180 g/mole

B. **Explain** the bioenergetic difference between aerobic and anaerobic respiration in terms of the difference between free-energy production and power. Your explanation should make use of all the following facts:

- power is the rate of free-energy production
- cancer cells derive most of their free energy from glycolysis
- enzymes of the citric acid (Kreb's) cycle form coordinate complexes on the cytoskeleton within the mitochondria

C. The life cycle of the human parasite *Trypanosoma brucei* is divided between the body of the tsetse fly and the human blood stream. The parasite causes "sleeping sickness" in Sub-Saharan Africa. Within the human bloodstream, the parasite depends on glycolysis, with enzymes compartmentalized in a membrane-bound organelle called the glycosome. In the insect host, the parasite utilizes glycolysis as well as substrate-level and oxidative phosphorylation. **Explain** the advantage of a life cycle in the human host that employs anaerobic respiration with a rate of free-energy production that is enhanced by compartmentalization in the glycosome and a life cycle in the insect host that is aerobic.

D. **Predict** the advantages of a biological system that uses both glycolysis and oxidative phosphorylation. Your

prediction should make use of all the following facts:

- signaling can be used to detect low-oxygen environments and to regulate response
- some cells, such as muscle and blood cells, must function in both low- and high-oxygen environments
- glycolysis is reversible
- the citric acid cycle is not reversible
- thermoregulation is needed for homeostasis

55. Dinitrophenol (DNP) was used in the manufacture of munitions in World War I. In the 1930s, it was used as a weight loss drug. Use in the U.S. cannot be regulated by the FDA because DNP is considered a dietary supplement. Attempts to ban the drug in the U.K. following the death of four users in 2015 failed in Parliament. DNP is a small molecule that is soluble in the mitochondrial inner membrane. The hydroxyl group reversibly dissociates a proton.

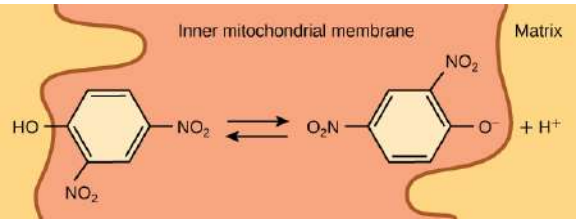


Figure 7.21

A. **Predict** the effect of DNP on the electrochemical gradient across the inner mitochondrial membrane.

B. **Explain** how DNP can be used to reduce weight.

C. The effects of DNP can be reversed by administering glucose. However, treatment with a combination of glucose and 2-deoxyglucose, which is an inhibitor of glycolysis, does not reverse the effects of DNP. **Explain**, in terms of the products of glycolysis, why this reversal of the effects of DNP was unexpected. (Hint: It might be useful to review the reactants and products of glycolysis.)

D. Obesity correlates with an epidemic of other health issues, such as elevated blood pressure, heart disease, and diabetes II. A slow-release form of DNP (CRMP) is patented. With slow-release technology, a drug can be delivered in small doses over time from a pill whose matrix limits solubility. A simple but nonscientific question that can be raised is: Will a slow-release drug retard progress toward behavioral changes that can reduce the magnitude of this epidemic? Scientific questions can be pursued by testing the outcomes predicted by possible answers. **Refine this question** for discussion in small groups. Be prepared to **justify** the merits of your question.

56. As shown in **Figure 7.11**, cyanide inhibits the electron transport chain by competing with O_2 molecules for the cytochrome c oxidase heme group. Carbon monoxide (CO) has a similar effect. Both cyanide and carbon monoxide cause poisoning in victims of smoke inhalation.

A. **Predict** the effects of these poisons on the following properties of mitochondria just after exposure: the pH of the intermembrane space, the concentration of NADH, and the rate of production of ATP in the matrix. **Justify** your predictions.

B. Rotenone is a poison that blocks the transfer of electrons from Complex I of the electron transport chain to ubiquinone. Methylene blue is a molecule with many uses involving its reduction-oxidation properties. Recent studies show the effectiveness of methylene blue in increasing the body's metabolic rate and as a treatment for Alzheimer's patients. The oxidized form of methylene blue is reduced by NADH, and its reduced form is oxidized by O_2. **Explain** the use of methylene blue as an antidote for rotenone poisoning.

57. *E. coli* are enteric (gut-dwelling) facultative anaerobic bacteria. (Facultative anaerobes can grow either with or without free oxygen. Obligatory anaerobes grow only in the absence of free oxygen.) Researchers planned to grow cultures of *E. coli* under a range of conditions to model the transition from strictly anaerobic to aerobic respiration.

The oxygen content of atmospheres at constant total pressure will be controlled by volumes of nitrogen and oxygen gases. Ratios of volume, $r = V_{O_2}/V_{N_2}$ between 0 and 0.25 of shaken growth flasks can be measured in terms of optical density, which is the percent of transmission of light through a sample of the growing *E. coli* culture. A rule of thumb is that the range of strict anaerobes is when $r < 0.01$, and the boundary for aerobic respiration is when $r = 0.05$. A large number of flasks that can be constantly shaken at fixed temperature, and from which samples can be taken without atmospheric contamination, are available for this study.

These results of the experiment will be used to infer growth rates of *E. coli* along the entire 7.5 m length of the average human intestine (small intestine and large intestine), where the oxygen content varies from atmospheric to anaerobic conditions. The retention time of food in the small intestine, whose average length is 2.5 m, is approximately four hours. The retention time of food over the entire length of the intestine is between 24 and 72 hours.

A. **Describe and apply a mathematical model** that can be used to represent the variation of oxygen environments of a bacterium that is being transported with the food along the length of the intestine.

B. **Design** the experimental sampling times in terms of growth intervals of interest in this study: i) the time when the bacteria is passing the small-large intestine boundary; ii) the time when the bacteria reaches the end of the large intestine; and iii) the time when the bacterium reaches facultative anaerobic conditions, $r < 0.05$.

C. Sketch a graph that **predicts** the distribution of aerobic, facultative anaerobic and obligatory anaerobic bacteria along the length of the entire intestine based on these parameters. Keep in mind that anaerobes have a lower

respiration rate.

58. White snakeroot is a plant that contains chemicals that deactivate the enzyme lactate dehydrogenase. Humans who consume milk from cows or goats that eat white snakeroot can become ill. Symptoms of milk poisoning include vomiting, abdominal pain, and tremors, which become worse after exercise. Beyond childhood, most people do not express the enzyme lactase that catalyzes the breakdown of lactose into glucose and galactose. Consumption of milk can produce symptoms similar to those of milk poisoning. After a period of consumption of dairy foods, though, prebiotic adaptation (changes in the microbes in the intestine) imparts lactose tolerance. Since dairy foods are a valuable source of calcium, proteins, and vitamin D, considerable research has been conducted to characterize adaptation.

Explain the similarities and differences between the effect of milk poisoning by white snakeroot and lactose intolerance, and the possibility of prebiotic adaptation for each.