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Some familiar fermentation products.

21

Carbohydrate Metabolism

Learning Goals

1. Discuss the importance of ATP in cellular energy transfer processes.
2. Describe the three stages of catabolism of dietary proteins, carbohydrates, and lipids.
3. Discuss glycolysis in terms of its two major segments.
4. Looking at an equation representing any of the chemical reactions that occur in glycolysis, describe the kind of reaction that is occurring and the significance of that reaction to the pathway.
5. Describe the mechanism of regulation of the rate of glycolysis. Discuss particular examples of that regulation.
6. Discuss the practical and metabolic roles of fermentation reactions.
7. List several products of the pentose phosphate pathway that are required for biosynthesis.
8. Compare glycolysis and gluconeogenesis.
9. Summarize the regulation of blood glucose levels by glycogenesis and glycogenolysis.

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CHEMISTRY CONNECTION

The Man Who Got Tipsy from Eating Pasta

Imagine becoming drunk after eating a plate of spaghetti or a bag of potato chips. That is exactly what happened to Charles Swaart while he was stationed in Tokyo after World War II. Suddenly, he would be completely drunk—without having swallowed a drop of alcohol.

During the next two decades, Swaart continued to have unexplainable bouts of drunkenness and horrible hangovers. The problem was so serious that his liver was being destroyed. But in 1964, Swaart heard of a man in Japan who suffered from the same mysterious—and embarrassing—symptoms. After twenty-five years, physicians diagnosed the problem. There was a mutant strain of the yeast *Candida albicans* living in the gastrointestinal tract of the Japanese man. These yeast cells were using carbohydrates from the man's diet to make ethanol. The metabolic pathways used by these yeast cells were glycolysis and alcohol fermentation, two of the pathways that we will study in this chapter.

Swaart took advantage of the therapy used in Japan. He had to try several antibiotics over the years. But finally, in 1975, all of the mutant yeast cells in his intestine were killed, and his life returned to normal.

Why was it so difficult for physicians to solve this medical mystery? Nonfermenting *Candida albicans* is a regular inhabitant of the human gut. It took some very clever scientific detective work to find this mutant ethanol-producing strain. The scientists even have a hypothesis about where the mutant yeast came from. They think that the radiation released in one of the atomic bomb blasts at Nagasaki or Hiroshima may have caused the mutation.

In this chapter we begin our study of the chemical reactions used by all organisms to provide energy for cellular work. In Chapter 24 we will look at the kinds of DNA damage (mutations) that can produce changes in the structure or function of an organism.

Introduction

Just as we need energy to run, jump, and think, the cell needs a ready supply of cellular energy for the many functions that support these activities. Cells need energy for *active transport*, to move molecules between the environment and the cell. Energy is also needed for *biosynthesis* of small metabolic molecules and production of macromolecules from these intermediates. Finally, energy is required for *mechanical work*, including muscle contraction and motility of sperm cells. Table 21.1 lists some examples of each of these energy-requiring processes.

We need a supply of energy-rich food molecules that can be degraded, or *oxidized*, to provide this needed cellular energy. Our diet includes three major sources of energy: carbohydrates, fats, and proteins. Each of these types of large biological molecules must be broken down into its basic subunits—simple sugars, fatty acids and glycerol, and amino acids—before they can be taken into the cell and used to produce cellular energy. Of these classes of food molecules, carbohydrates are the most readily used. The pathway for the first stages of carbohydrate breakdown is called *glycolysis*. We find the same pathway in organisms as different as the simple bacterium and humans.

Recall that the potential energy of a compound is the bond energy of that compound.

In this chapter we are going to examine the steps of this ancient energy-harvesting pathway. We will see that it is responsible for the capture of some of the bond energy of carbohydrates and the storage of that energy in the molecular form of *adenosine triphosphate (ATP)*. Glycolysis actually releases and stores very little (2.2%) of the potential energy of glucose, but the pathway also serves as a source of biosynthetic building blocks. It also modifies the carbohydrates in such a way that other pathways are able to release as much as 40% of the potential energy.

Table 21.1 The Types of Cellular Work That Require Energy

Biosynthesis: Synthesis of Metabolic Intermediates and Macromolecules
Synthesis of glucose from CO_2 and H_2O in the process of photosynthesis in plants
Synthesis of amino acids
Synthesis of nucleotides
Synthesis of lipids
Protein synthesis from amino acids
Synthesis of nucleic acids
Synthesis of organelles and membranes
Active Transport: Movement of Ions and Molecules
Transport of H^+ to maintain constant pH
Transport of food molecules into the cell
Transport of K^+ and Na^+ into and out of nerve cells for transmission of nerve impulses
Secretion of HCl from parietal cells into the stomach
Transport of waste from the blood into the urine in the kidneys
Transport of amino acids and most hexose sugars into the blood from the intestine
Accumulation of calcium ions in the mitochondria
Motility
Contraction and flexion of muscle cells
Separation of chromosomes during cell division
Ability of sperm to swim via flagella
Movement of foreign substances out of the respiratory tract by cilia on the epithelial lining of the trachea
Translocation of eggs into the fallopian tubes by cilia in the female reproductive tract

21.1 ATP: The Cellular Energy Currency

Learning Goal 1

The degradation of fuel molecules, called **catabolism,** provides the energy for cellular energy-requiring functions, including **anabolism,** or biosynthesis. Actually, the energy of a food source can be released in one of two ways: as heat or, more important to the cell, as chemical bond energy. We can envision two alternative modes of aerobic degradation of the simple sugar glucose. We can, metaphorically, simply set the glucose afire. This would result in its complete oxidation to CO_2 and H_2O and would release 686 kcal/mol of glucose. Yet in terms of a cell, what would be accomplished? Nothing. All of the potential energy of the bonds of glucose is lost as heat and light.

The cell uses a different strategy. With a series of enzymes, biochemical pathways in the cell carry out a step-by-step oxidation of glucose. Small amounts of energy are released at several points in the pathway and that energy is harvested and saved in the bonds of a molecule that has been called the *universal energy currency.* This molecule is **adenosine triphosphate (ATP).**

ATP serves as a "go-between" molecule that couples the *exergonic* (energy releasing) reactions of catabolism and the endergonic (energy requiring) reactions of anabolism. To understand how this molecule harvests the energy and releases it for energy-requiring reactions, we must take a look at the structure of this amazing molecule (Figure 21.1). ATP is a **nucleotide,** which means that it is a molecule composed of a nitrogenous base; a five-carbon sugar; and one, two, or three phosphoryl groups.

Nitrogenous bases are heterocyclic amines. Their structure and functions are discussed in Section 16.2. The five-carbon sugars are discussed in Section 17.4. More information on the structure of nucleotides is found in Section 24.1.

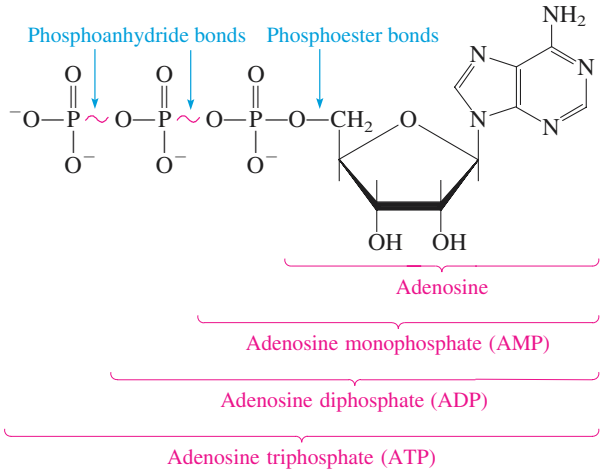


Figure 21.1
The structure of the universal energy currency, ATP.

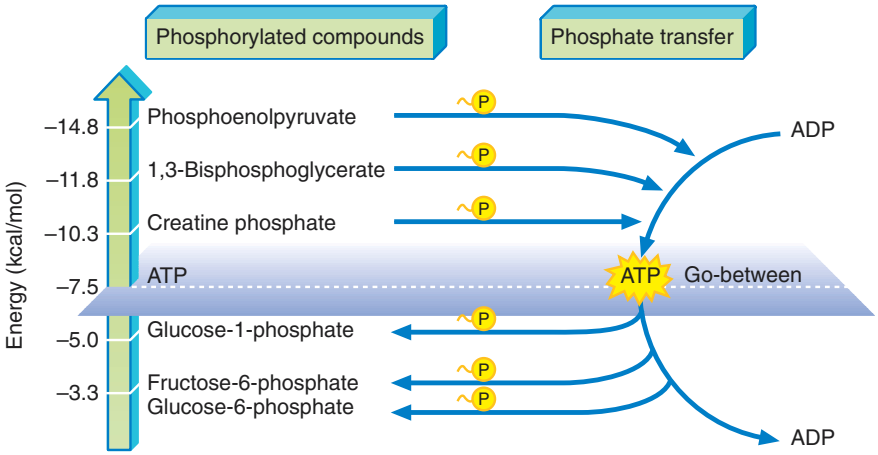


Figure 21.2
An energy comparison of several phosphorylated compounds that are important in cellular metabolic processes.

Nature's high energy bonds, including phosphoanhydride and phosphoester bonds, are discussed in Section 15.4.

In ATP, a phosphoester bond joins the first phosphoryl group to the five-carbon sugar ribose. The next two phosphoryl groups are joined to one another by phosphoanhydride bonds (Figure 21.1). Recall that the phosphoanhydride bond is a *high-energy bond.* When it is broken or hydrolyzed, a large amount of energy is released. When the phosphoanhydride bond of ATP is broken, the energy that is released can be used for cellular work. These high-energy bonds are indicated as squiggles (~) in Figure 21.1.

The structure of ATP is only a part of the reason that the molecule is a good go-between in energy transformations in the cell. ATP must have a higher energy content than the compounds to which it will donate energy, but it must also contain less energy than the compounds that are involved in forming it. In this way, all the reactions are favored because both the reactions that produce ATP and the hydrolysis of ATP to provide energy for cellular work are exergonic. Figure 21.2 shows the relative energies of some phosphorylated compounds, including ATP, that are involved in energy metabolism.

See Sections 15.4 and 24.1 for further information on the structure of ATP and hydrolysis of the phosphoanhydride bonds.

Hydrolysis of ATP yields adenosine diphosphate (ADP), an inorganic phosphate group (P_i), and energy (Figure 21.3). The energy released by this hydrolysis of ATP is then used to drive biological processes, for instance, the phosphorylation of glucose or fructose.

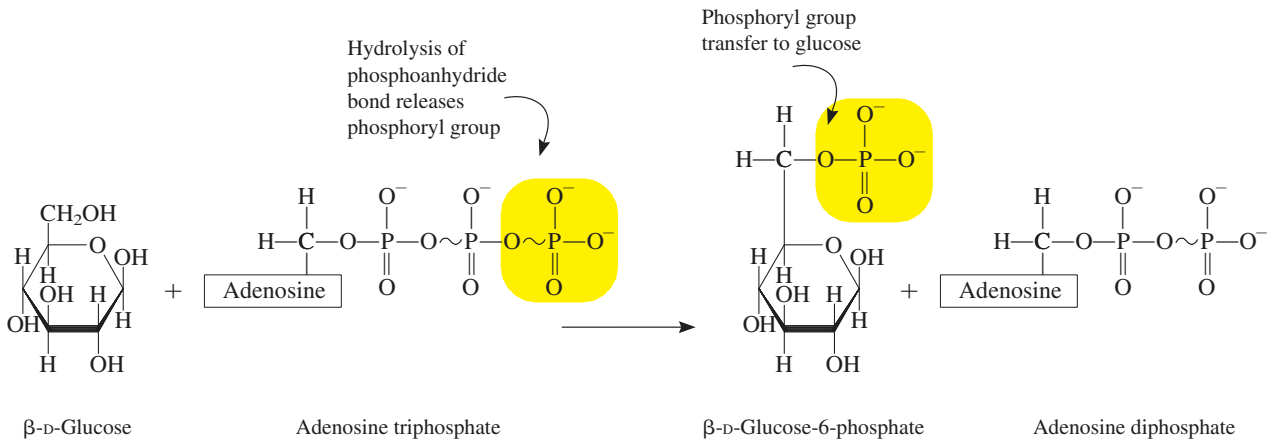


Figure 21.3
The hydrolysis of the phosphoanhydride bond of ATP releases inorganic phosphate and energy. In this coupled reaction catalyzed by an enzyme, the phosphoryl group and some of the released energy are transferred to β-D-glucose.

An example of the way in which the energy of ATP is used can be seen in the first step of glycolysis, the anaerobic degradation of glucose to produce chemical energy. The first step involves the transfer of a phosphoryl group, $—PO_3^{2-}$, from ATP to the C-6 hydroxyl group of glucose (Figure 21.3). This reaction is catalyzed by the enzyme hexokinase.

This reaction can be dissected to reveal the role of ATP as a source of energy. Although this is a coupled reaction, we can think of it as a two-step process. The first step is the hydrolysis of ATP to ADP and phosphate, abbreviated P_i. This is an exergonic reaction that *releases* about 7 kcal/mol of energy:

$$\text{ATP} + H_2O \longrightarrow \text{ADP} + P_i + 7\ \text{kcal/mol}$$

The second step, the synthesis of glucose-6-phosphate from glucose and phosphate, is an endergonic reaction that *requires* 3.0 kcal/mol:

$$3.0\ \text{kcal/mol} + \text{glucose} + P_i \longrightarrow \text{glucose-6-phosphate} + H_2O$$

These two chemical reactions can then be added to give the equation showing the way in which ATP hydrolysis is *coupled* to the phosphorylation of glucose:

$$\begin{array}{r} \text{ATP} + H_2O \longrightarrow \text{ADP} + P_i + 7\ \text{kcal/mol} \\ 3.0\ \text{kcal/mol} + \text{glucose} + P_i \longrightarrow \text{glucose-6-phosphate} + H_2O \\ \hline \text{Net: ATP} + \text{glucose} \longrightarrow \text{glucose-6-phosphate} + \text{ADP} + 4\ \text{kcal/mol} \end{array}$$

Because the hydrolysis of ATP releases more energy than is required to synthesize glucose-6-phosphate from glucose and phosphate, there is an overall energy release in this process and the reaction proceeds spontaneously to the right. The product, glucose-6-phosphate, has more energy than the reactant, glucose, because it now carries some of the energy from the original phosphoanhydride bond of ATP.

The primary function of all catabolic pathways is to harvest the chemical energy of fuel molecules and to store that energy by the production of ATP. This continuous production of ATP is what provides the stored potential energy that is used to power most cellular functions.

Question 21.1 Why is ATP called the universal energy currency?

Question 21.2 List five biological activities that require ATP.

21.2 Overview of Catabolic Processes

Learning Goal 2

Although carbohydrates, fats, and proteins can all be degraded to release energy, carbohydrates are the most readily used energy source. We will begin by examining the oxidation of the hexose glucose. In Chapters 22 and 23 we will see how the pathways of glucose oxidation are also used for the degradation of fats and proteins.

Any catabolic process must begin with a supply of nutrients. When we eat a meal, we are eating quantities of carbohydrates, fats, and proteins. From this point the catabolic processes can be broken down into a series of stages. The three stages of catabolism are summarized in Figure 21.4.

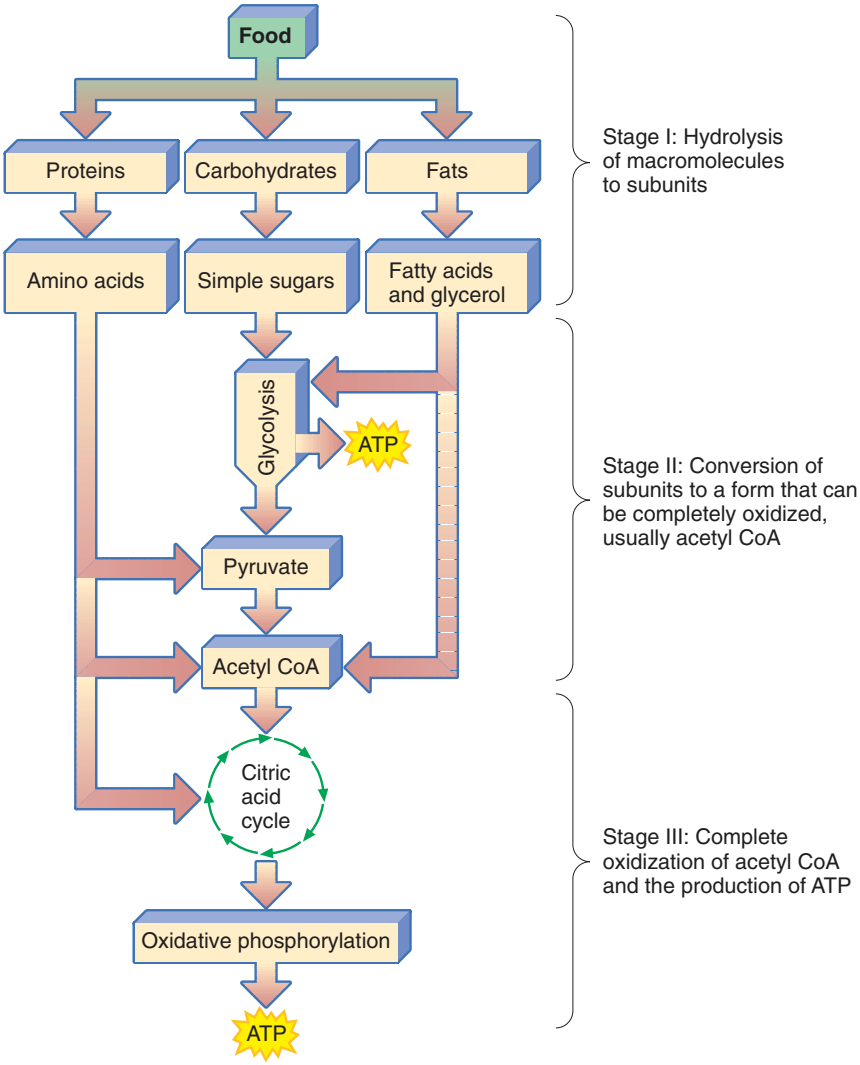


Figure 21.4
The three stages of the conversion of food into cellular energy in the form of ATP.

Stage I: Hydrolysis of Dietary Macromolecules into Small Subunits

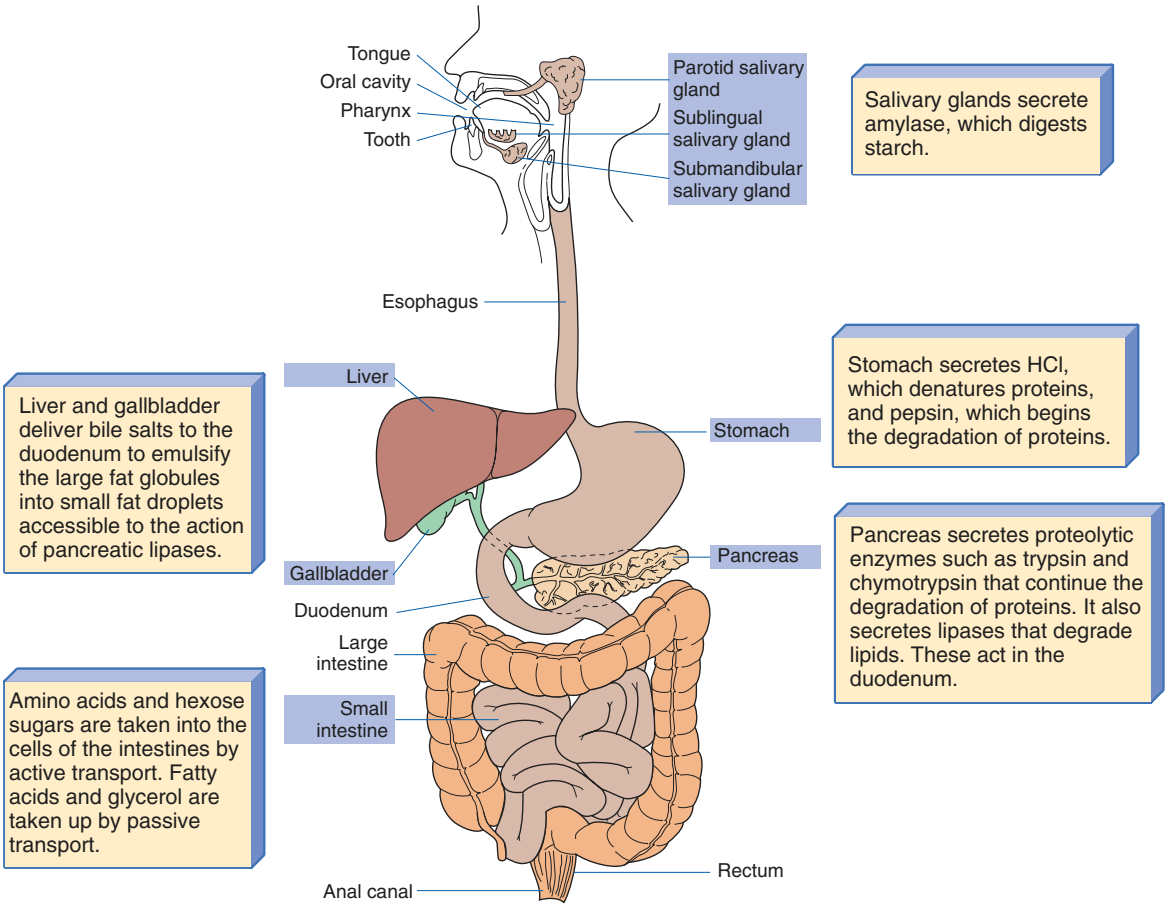
The purpose of the first stage of catabolism is to degrade large food molecules into their component subunits. These subunits—simple sugars, amino acids, fatty acids, and glycerol—are then taken into the cells of the body for use as an energy source. The process of digestion is summarized in Figure 21.5.

Polysaccharides are hydrolyzed to monosaccharides. This process begins in the mouth, where the enzyme amylase begins the hydrolysis of starch. Digestion continues in the small intestine, where pancreatic amylase further hydrolyzes the starch into maltose (a disaccharide of glucose). Maltase catalyzes the hydrolysis of maltose, producing two glucose molecules. Similarly, sucrose is hydrolyzed to glucose and fructose by the enzyme sucrase, and lactose (milk sugar) is degraded into the monosaccharides glucose and galactose by the enzyme lactase in the small intestine. The monosaccharides are taken up by the epithelial cells of the intestine in an energy-requiring process called *active transport*.

The digestion of proteins begins in the stomach, where the low pH denatures the proteins so that they are more easily hydrolyzed by the enzyme pepsin. They are further degraded in the small intestine by trypsin, chymotrypsin, elastase, and other proteases. The products of protein digestion—amino acids and short oligopeptides—are taken up by the cells lining the intestine. This uptake also involves an active transport mechanism.

In the laboratory, a strong acid or base and high temperatures are required for hydrolysis of amide bonds (Section 16.3). However, this reaction proceeds quickly under physiological conditions when catalyzed by enzymes (Section 20.11).

Figure 21.5
An overview of the digestive processes that hydrolyze carbohydrates, proteins, and fats.



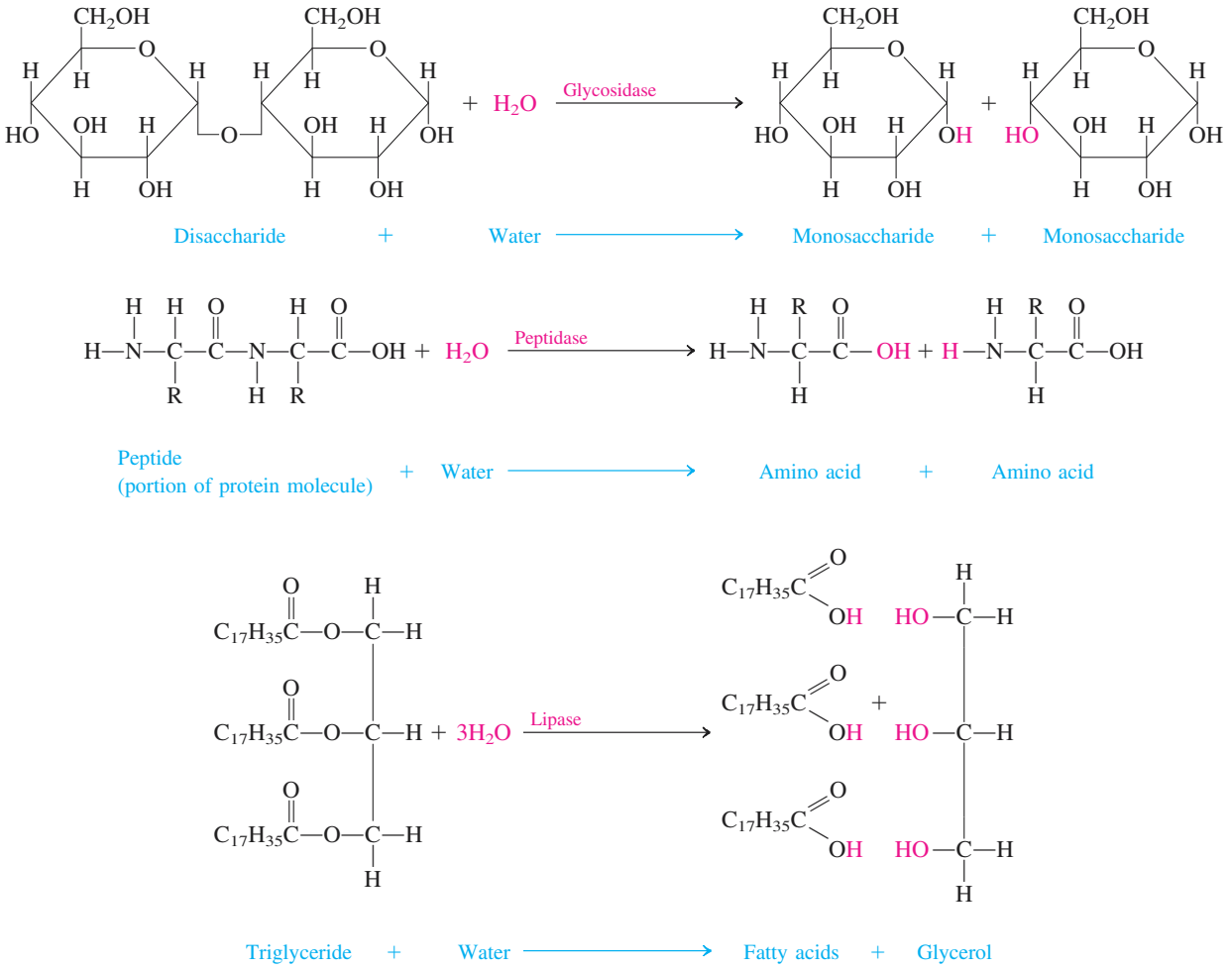


Figure 21.6
A summary of the hydrolysis reactions of carbohydrates, proteins, and fats.

The digestion and transport of fats are considered in greater detail in Chapter 23.

Active and passive transport are discussed in Section 18.6.

Digestion of fats does not begin until the food reaches the small intestine, even though there are lipases in both the saliva and stomach fluid. Fats arrive in the duodenum, the first portion of the small intestine, in the form of large fat globules. Bile salts produced by the liver break these up into an emulsion of tiny fat droplets. Because the small droplets have a greater surface area, the lipids are now more accessible to the action of pancreatic lipase. This enzyme hydrolyzes the fats into fatty acids and glycerol, which are taken up by intestinal cells by a transport process that does not require energy. This process is called *passive transport*. A summary of these hydrolysis reactions is shown in Figure 21.6.

Stage II: Conversion of Monomers into a Form That Can Be Completely Oxidized

The citric acid cycle is considered in detail in Section 22.4.

The monosaccharides, amino acids, fatty acids, and glycerol must now be assimilated into the pathways of energy metabolism. The two major pathways are glycolysis and the citric acid cycle (see Figure 21.4). Sugars usually enter the glycolysis pathway in the form of glucose or fructose. They are eventually converted to acetyl CoA, which is a form that can be completely oxidized in the citric acid cycle. Amino groups are removed from amino acids, and the remaining carbon skeletons enter

the catabolic processes at many steps of the citric acid cycle. Fatty acids are converted to acetyl CoA and enter the citric acid cycle in that form. Glycerol, produced by the hydrolysis of fats, is converted to glyceraldehyde-3-phosphate, one of the intermediates of glycolysis, and enters energy metabolism at that level.

Stage III: The Complete Oxidation of Nutrients and the Production of ATP

Acetyl CoA carries two-carbon remnants of the nutrients, acetyl groups, to the citric acid cycle. Acetyl CoA enters the cycle, and electrons and hydrogen atoms are harvested during the complete oxidation of the acetyl group to CO_2. Coenzyme A is released (recycled) to carry additional acetyl groups to the pathway. The electrons and hydrogen atoms that are harvested are used in the process of oxidative phosphorylation to produce ATP.

Oxidative phosphorylation is described in Section 22.6.

Question 21.3

Briefly describe the three stages of catabolism.

Question 21.4

Discuss the digestion of dietary carbohydrates, lipids, and proteins.

21.3 Glycolysis

An Overview

Glycolysis, also known as the Embden-Meyerhof Pathway, is a pathway for carbohydrate catabolism that begins with the substrate D-glucose. The very fact that all organisms can use glucose as an energy source for glycolysis suggests that glycolysis was the first successful energy-harvesting pathway that evolved on the earth. The pathway evolved at a time when the earth's atmosphere was *anaerobic;* no free oxygen was available. As a result, glycolysis requires no oxygen; it is an anaerobic process. Further, it must have evolved in very simple, single-celled organisms, much like bacteria. These organisms did not have complex organelles in the cytoplasm to carry out specific cellular functions. Thus glycolysis was a process carried out by enzymes that were free in the cytoplasm. To this day, glycolysis remains an anaerobic process carried out by cytoplasmic enzymes, even in cells as complex as our own.

The ten steps of glycolysis are outlined in Figure 21.7. The first substrate in the pathway is the hexose sugar glucose. Ten enzymes are needed to carry out the reactions of the pathway. The first reactions of glycolysis involve an energy investment. ATP molecules are hydrolyzed, energy is released, and phosphoryl groups are added to the hexose sugars. In the remaining steps of glycolysis, energy is harvested to produce a net gain of ATP.

The three major products of glycolysis are seen in Figure 21.7. These are chemical energy in the form of ATP, chemical energy in the form of NADH, and two three-carbon pyruvate molecules. Each of these products is considered below:

- **Chemical energy as ATP.** Four ATP molecules are formed by the process of **substrate-level phosphorylation.** This means that a high-energy phosphoryl group from one of the substrates in glycolysis is transferred to ADP to form ATP. The two substrates involved in these transfer reactions are 1,3-bisphosphoglycerate and phosphoenolpyruvate (see Figure 21.7, steps 7 and 10). Although four ATP molecules are produced during glycolysis, the *net* gain is only two ATP molecules because two ATP molecules are used early in glycolysis (Figure 21.7, steps 1 and 3). The two ATP molecules produced

A MEDICAL PERSPECTIVE

Genetic Disorders of Glycolysis

Imagine always having difficulty with physical exercise. Imagine the coach telling you to get tough and run that lap again, since you were last! Imagine being accused of being lazy because you didn't carry your share of the camping gear. Imagine all that and not knowing why it is that you can't keep up with your friends or the others in your physical education class. This has been the fate of thousands of people who suffer from a metabolic myopathy—a muscle (*myo-*) disorder (*-pathy*) caused by an inability to extract the energy from the food that you eat.

The onset of fatigue during exercise is called *exercise intolerance*. It is one of the major symptoms of a metabolic myopathy. But simple fatigue is just the mildest of the symptoms. Overexertion may cause episodes of muscle breakdown (rhabdomyolysis) in which the muscle cells, unable to provide enough ATP energy for themselves, begin to die. The muscle breakdown causes greatly elevated blood levels of creatine kinase. Creatine kinase is an abundant enzyme in muscle that is critical in energy metabolism (see A Human Perspective: Exercise and Energy Metabolism, in Chapter 22). When muscle cells die, this enzyme is released into the bloodstream. Another symptom is myoglobinuria (myoglobin in the urine). Recall that myoglobin is the oxygen storage protein in muscle. When muscles die, myoglobin ends up in the urine, turning it the color of cola soft drinks. Myoglobinuria may even cause kidney damage. Accompanying these clinical symptoms, many people describe intense muscle pain. They describe it as a cramp, but it is not a cramp, since the muscle is not able to contract because of the lack of energy. Rather, the pain is caused by cell death and tissue damage that result from an inability to produce enough ATP.

There are three glycolytic enzyme deficiencies that lead to metabolic myopathy. The first is phosphofructokinase deficiency or Tarui's disease. Although this is not a sex-linked disorder, the great majority of sufferers are males (nine males to one female). The disorder is most frequently found in U.S. Ashkenazi Jews and Italian families. Onset of symptoms typically occurs between the ages of twenty and forty, although some severe cases have been reported in infants and young children. Patients experiencing the late-onset form of Tarui's disease typically experienced exercise intolerance when they were younger. Vigorous exercise results in myoglobinuria and severe muscle pain. Meals high in carbohydrates worsen the exercise intolerance. Early-onset disease is often associated with respiratory failure, cardiomyopathy (heart muscle disease), seizures, and cortical blindness.

Phosphoglycerate kinase deficiency is a sex-linked genetic disorder (located on the X chromosome). As a result, far more males than females suffer from this disease. There are many clinical features associated with this deficiency, although only rarely are they all found in the same patient. These symptoms range from mental retardation and seizures to a slowly progressive myopathy.

Phosphoglycerate mutase deficiency has been mapped on chromosome 7. The disorder is found predominantly in U.S. African American, Italian, and Japanese families. The clinical features include exercise intolerance, muscle pain, and myoglobinuria following more intense exercise.

Since each of these disorders is caused by the lack of an enzyme, scientists are trying to design a way to replace the lost activity. Oral medication will not work because enzymes are proteins. They would simply be digested, like any other dietary protein. Enzyme replacement therapy is one approach that is being studied. This would involve periodic injections of the enzyme into the bloodstream, a treatment just like the injection of insulin by diabetics. Enzyme replacement therapy would require a large supply of the enzyme. Following the model of insulin, the gene for the enzyme could be cloned into bacteria. The bacteria would then produce the protein, which would be purified for use by humans.

Another strategy is to introduce the gene for the missing enzyme into the patient's cells. This is called gene therapy. This method would also require that the gene for the enzyme be cloned. The DNA would then have to be introduced into the body using a safe procedure that would promote entry into target cells. There are still many obstacles to overcome before this type of treatment will be a reality for sufferers of metabolic myopathy.

A number of physicians are using a commonsense approach to the management of these disorders. Logic tells us that if a person cannot harvest energy from carbohydrates in the diet, perhaps a diet high in protein and lipids might be beneficial. As with any condition of this sort, it is important to consult a physician who understands the metabolic disorder and who will design and supervise a customized diet.

The structure of NAD^+ and the way it functions as a hydride anion carrier are shown in Figure 20.8 and described in Section 20.7.

represent only 2.2% of the potential energy of the glucose molecule. Thus glycolysis is not a very efficient energy-harvesting process.

- **Chemical energy in the form of reduced NAD^+, NADH. Nicotinamide adenine dinucleotide (NAD^+)** is a coenzyme derived from the vitamin niacin. The reduced form of NAD^+, NADH, carries hydride anions, hydrogen atoms with two electrons ($H:^-$), removed during the oxidation of one of the substrates, glyceraldehyde-3-phosphate (see Figure 21.7, step 6). Under aerobic conditions the electrons and hydrogen atom are transported

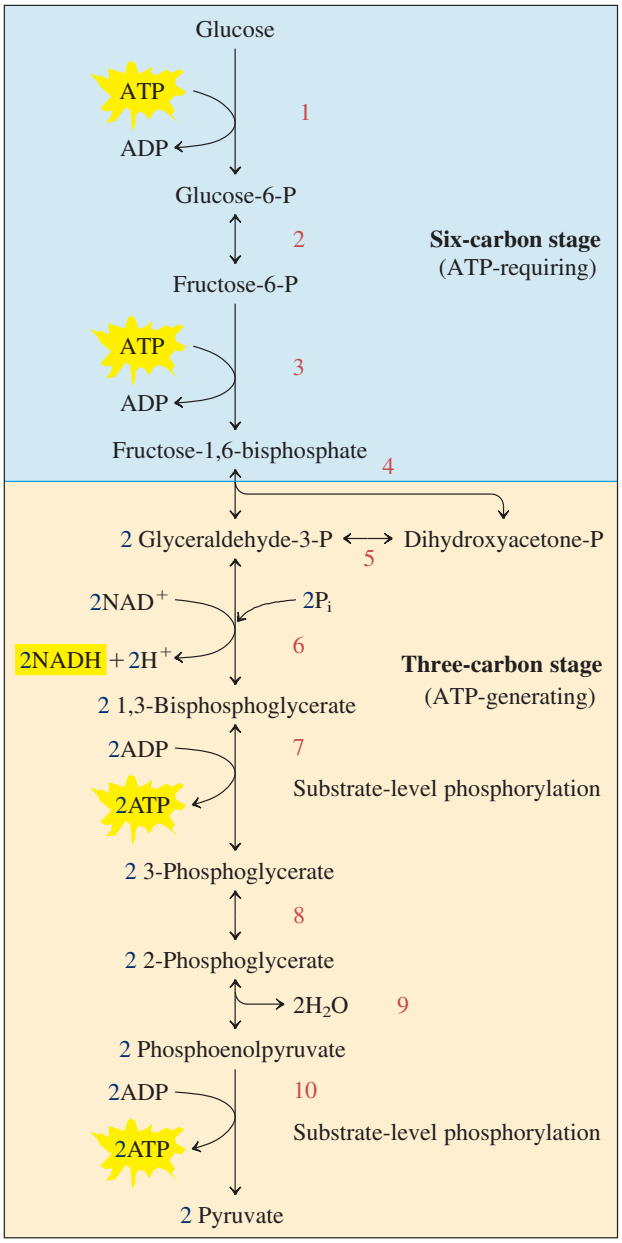


Figure 21.7
A summary of the reactions of glycolysis. These reactions occur in the cell cytoplasm.

from the cytoplasm into the mitochondria. Here they enter an electron transport system for the generation of ATP by **oxidative phosphorylation.** Under anaerobic conditions, NADH is used as a source of electrons in fermentation reactions.

- **Two pyruvate molecules.** At the end of glycolysis the six-carbon glucose molecule has been converted into two three-carbon pyruvate molecules. The fate of the pyruvate also depends on whether the reactions are occurring in the presence or absence of oxygen. Under aerobic conditions it is used to produce acetyl CoA destined for the citric acid cycle and complete oxidation. Under anaerobic conditions it is used as an electron acceptor in fermentation reactions.

In any event these last two products must be used in some way so that glycolysis can continue to function and produce ATP. There are two reasons for this. First, if pyruvate were allowed to build up, it would cause glycolysis to stop, thereby stopping the production of ATP. Thus pyruvate must be used in some kind of follow-up reaction, aerobic or anaerobic. Second, in step 6, glyceraldehyde-3-phosphate is oxidized and NAD^+ is reduced (accepts the hydride anion). The cell has only a small supply of NAD^+. If all the NAD^+ is reduced, none will be available for this reaction, and glycolysis will stop. Therefore NADH must be reoxidized so that glycolysis can continue to produce ATP for the cell.

Reactions of Glycolysis

Learning Goal 3 Learning Goal 4

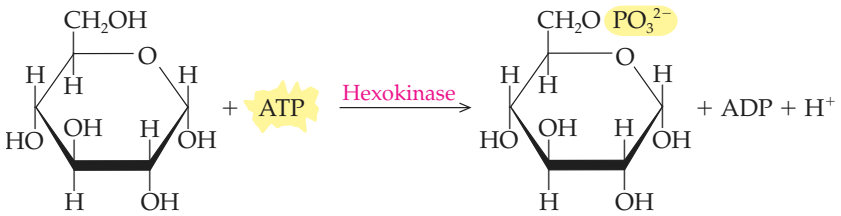
The structures of the intermediates of glycolysis are seen in Figure 21.8, along with a concise description of the reactions that occur at each step and the names of the enzymes that catalyze each reaction.

Glycolysis can be divided into two major segments. The first is the investment of ATP energy. Without this investment, glucose would not have enough energy for glycolysis to continue, and there would be no ATP produced. This segment includes the first five reactions of the pathway. The second major segment involves the remaining reactions of the pathway (steps 6–10), those that result in a net energy yield.

The enzyme name can tell us a lot about the reaction (see Section 20.1). The suffix *-kinase* tells us that the enzyme is a transferase that will transfer a phosphoryl group, in this case from an ATP molecule to the substrate. The prefix *hexo-* gives us a hint that the substrate is a six-carbon sugar. Hexokinase predominantly phosphorylates the six-carbon sugar glucose.

Reaction 1

The substrate, glucose, is phosphorylated by the enzyme *hexokinase* in a coupled phosphorylation reaction. The source of the phosphoryl group is ATP. At first this reaction seems contrary to the overall purpose of catabolism, the *production* of ATP. The expenditure of ATP in these early reactions must be thought of as an "investment." The cell actually goes into energy "debt" in these early reactions, but this is absolutely necessary to get the pathway started.

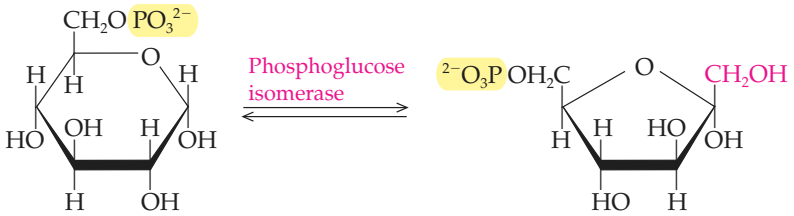


Glucose Glucose-6-phosphate

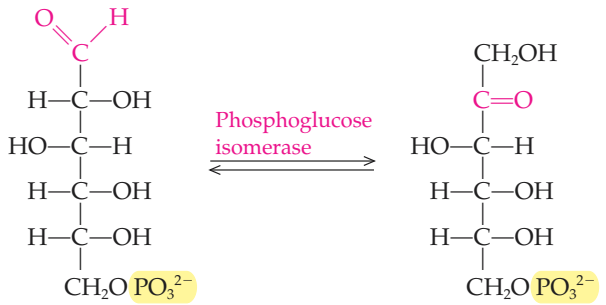
The enzyme name, phosphoglucose isomerase, provides clues to the reaction that is being catalyzed (Section 20.1). *Isomerase* tells us that the enzyme will catalyze the interconversion of one isomer into another. *Phosphoglucose* suggests that the substrate is a phosphorylated form of glucose.

Reaction 2

The glucose-6-phosphate formed in the first reaction is rearranged to produce the structural isomer fructose-6-phosphate. The enzyme *phosphoglucose isomerase* catalyzes this isomerization. The result is that the C-1 carbon of the six-carbon sugar is exposed; it is no longer part of the ring structure. Examination of the open-chain structures reveals that this isomerization converts an aldose into a ketose.



Glucose-6-phosphate Fructose-6-phosphate



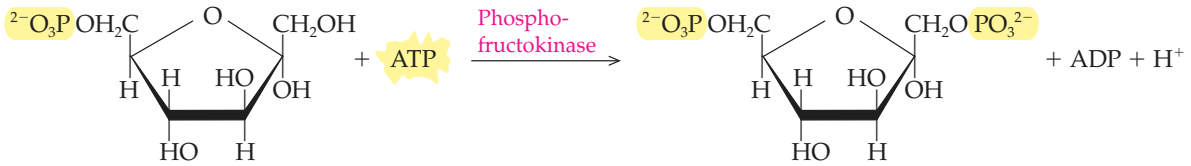
Glucose-6-phosphate (an aldose) — Fructose-6-phosphate (a ketose)

This is an enediol reaction. It occurs through exactly the same steps as the conversion of fructose to glucose that we discussed in Section 17.4.

Reaction 3

A second energy "investment" is catalyzed by the enzyme *phosphofructokinase.* The phosphoanhydride bond in ATP is hydrolyzed, and a phosphoester linkage between the phosphoryl group and the C-1 hydroxyl group of fructose-6-phosphate is formed. The product is fructose-1,6-bisphosphate.

The suffix *-kinase* in the name of the enzyme once again tells us that this is a coupled reaction in which ATP is hydrolyzed and a phosphoryl group is released and transferred to another molecule. The prefix *phosphofructo-* indicates that the substrate that will be phosphorylated is a phosphorylated form of fructose.



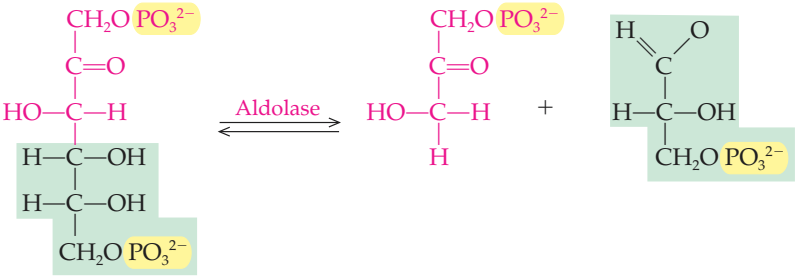
Fructose-6-phosphate — Fructose-1,6-bisphosphate

Reaction 4

Fructose-1,6-bisphosphate is split into two three-carbon intermediates in a reaction catalyzed by the enzyme *aldolase.* The products are glyceraldehyde-3-phosphate (G3P) and dihydroxyacetone phosphate.

In aldol condensation, aldehydes and ketones react to form a larger molecule (Section 14.4). This reaction is a reverse aldol condensation. The large ketone sugar fructose-1,6-bisphosphate is broken down into dihydroxyacetone phosphate (a ketone) and glyceraldehyde-3-phosphate (an aldehyde).

The double reaction arrows tell us that this is a reversible reaction. The reverse reaction is an aldol condensation (Section 14.4) that we will study in the pathway for glucose synthesis called gluconeogenesis (Section 21.6).

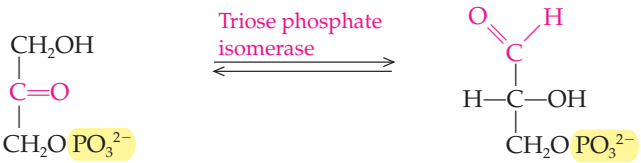


Fructose-1,6-bisphosphate — Dihydroxyacetone phosphate — Glyceraldehyde-3-phosphate

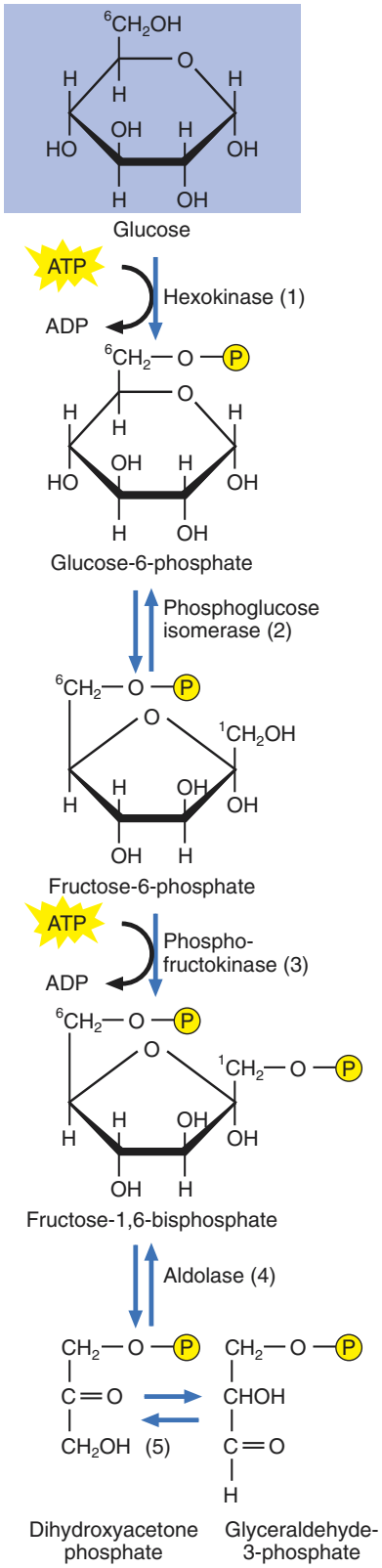
Reaction 5

Because G3P is the only substrate that can be used by the next enzyme in the pathway, the dihydroxyacetone phosphate is rearranged to become a second molecule of G3P. The enzyme that mediates this isomerization is *triose phosphate isomerase.*

The enzyme name hints that two isomers of a phosphorylated three-carbon sugar are going to be interconverted (Section 20.1). The ketone dihydroxyacetone phosphate and its isomeric aldehyde, phosphoglyceraldehyde-3-phosphate are interconverted through an enediol intermediate.



Dihydroxyacetone phosphate — Glyceraldehyde-3-phosphate



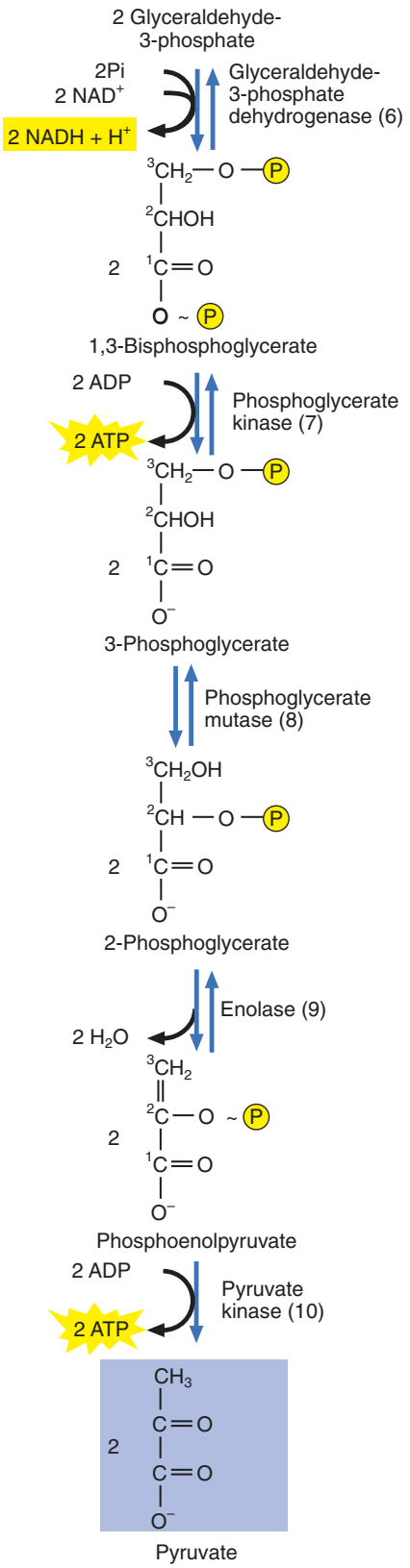
1. Glucose is phosphorylated at the expense of ATP to produce glucose-6-phosphate.

2. Glucose-6-phosphate is rearranged to produce fructose-6-phosphate.

3. Fructose-6-phosphate is phosphorylated to produce fructose-1,6-bisphosphate at the expense of another ATP. The expenditure of 2 ATP represents an energy investment to "activate" the glucose for its eventual oxidation.

4 and 5. Aldolase cleaves the six-carbon fructose-1,6-bisphosphate into two nonidentical three-carbon molecules, dihydroxyacetone phosphate and glyceraldehyde-3-phosphate. The dihydroxyacetone phosphate is converted to glyceraldehyde-3-phosphate by the enzyme triose phosphate isomerase.

Figure 21.8
The intermediates and enzymes of glycolysis.



6. Glyceraldehyde-3-phosphate is oxidized and NADH is produced. An inorganic phosphate group is transferred to the carboxylate group to produce 1,3-bisphosphoglycerate.

7. ATP is produced in the first substrate level phosphorylation in the pathway. The phosphoryl group is transferred from the substrate to ADP to produce ATP.

8. The C-3 phosphoryl group of 3-phosphoglycerate is transferred to the second carbon.

9. Dehydration of 2-phosphoglycerate generates the energy-rich molecule phosphoenolpyruvate.

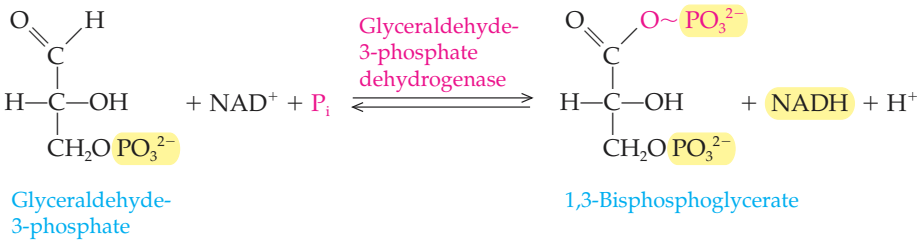
10. The final substrate level phosphorylation produces ATP and pyruvate.

The enzyme is glyceraldehyde-3-phosphate dehydrogenase. This tells us that the substrate glyceraldehyde-3-phosphate is going to be oxidized. Recall that in organic (and biochemical) reactions, oxidation is typically recognized as a gain of oxygen or a loss of hydrogen (Section 13.6). In this reaction, we see that the aldehyde group has been oxidized to a carboxylate group (Section 14.4).

Actually the intermediate of the oxidation reaction is a high-energy thioester formed between the enzyme and the substrate (Section 15.4). When this bond is hydrolyzed, enough energy is released to allow the formation of a bond between an oxygen atom of an inorganic phosphate group and the substrate.

Reaction 6

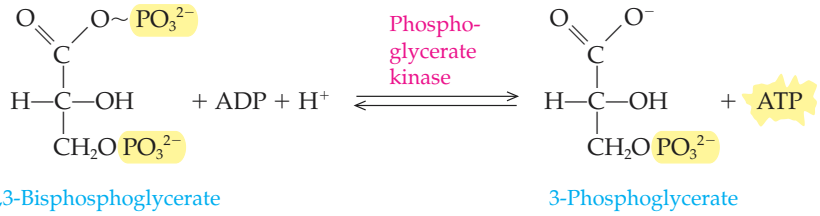
In this reaction the aldehyde glyceraldehyde-3-phosphate is oxidized to a carboxylic acid in a reaction catalyzed by *glyceraldehyde-3-phosphate dehydrogenase.* This is the first step in glycolysis that harvests energy, and it involves the reduction of the coenzyme nicotinamide adenine dinucleotide (NAD^+). This reaction occurs in two steps. First, NAD^+ is reduced to NADH as the aldehyde group of glyceraldehyde-3-phosphate is oxidized to a carboxyl group. Second, an inorganic phosphate group is transferred to the carboxyl group to give 1,3-bisphosphoglycerate. Notice that the new bond is denoted with a squiggle (~), indicating that this is a high-energy bond. This, and all remaining reactions of glycolysis, occur twice for each glucose because each glucose has been converted into two molecules of glyceraldehyde-3-phosphate.



Once again, the enzyme name reveals a great deal about the reaction. The suffix *-kinase* tells us that a phosphoryl group will be transferred. In this case, a phosphoester bond in the substrate 1,3-bisphosphoglycerate is hydrolyzed and ADP is phosphorylated. Note that this is a reversible reaction.

Reaction 7

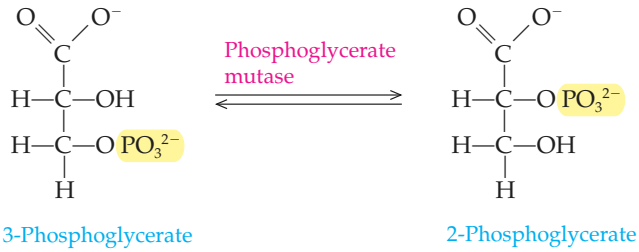
In this reaction, energy is harvested in the form of *ATP.* The enzyme *phosphoglycerate kinase* catalyzes the transfer of the phosphoryl group of 1,3-bisphosphoglycerate to ADP. This is the first substrate-level phosphorylation of glycolysis, and it produces ATP and 3-phosphoglycerate. It is a coupled reaction in which the high-energy bond is hydrolyzed and the energy released is used to drive the synthesis of ATP.



The suffix *-mutase* indicates another type of isomerase. Notice that the chemical formulas of the substrate and reactant are the same. The only difference is in the location of the phosphoryl group.

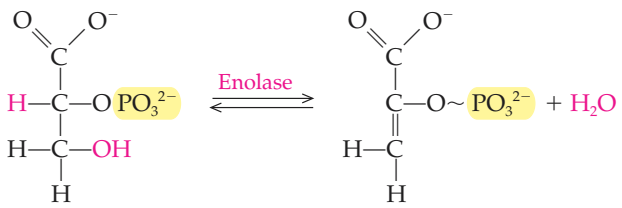
Reaction 8

3-Phosphoglycerate is isomerized to produce 2-phosphoglycerate in a reaction catalyzed by the enzyme *phosphoglycerate mutase.* The phosphoryl group attached to the third carbon of 3-phosphoglycerate is transferred to the second carbon.



Reaction 9

In this step the enzyme *enolase* catalyzes the dehydration (removal of a water molecule) of 2-phosphoglycerate. The energy-rich product is phosphoenolpyruvate, the highest energy phosphorylated compound in metabolism.

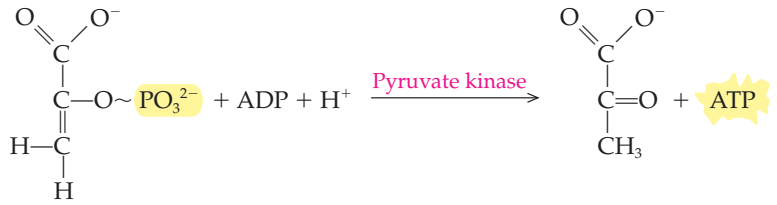


In Section 14.4 we learned that aldehydes and ketones exist in an equilibrium mixture of two tautomers called the keto and enol forms. The dehydration of 2-phosphoglycerate produces the molecule phosphoenolpyruvate, which is in the enol form. In this case, the enol is extremely unstable. Because of this instability, the phosphoester bond in the product is a high-energy bond; in other words, a great deal of energy is released when this bond is broken.

Reaction 10

Here we see the final substrate-level phosphorylation in the pathway, which is catalyzed by *pyruvate kinase.* Phosphoenolpyruvate serves as a donor of the phosphoryl group that is transferred to ADP to produce ATP. This is another coupled reaction in which hydrolysis of the phosphoester bond in phosphoenolpyruvate provides energy for the formation of the phosphoanhydride bond of ATP. The final product of glycolysis is pyruvate.

The enzyme name indicates that a phosphoryl group will be transferred (*kinase*) and that the product will be pyruvate. Pyruvate is a keto tautomer and is much more stable than the enol (Section 14.4).



It should be noted that reactions 6 through 10 occur twice per glucose molecule, because the starting six-carbon sugar is split into two three-carbon molecules. Thus in reaction 6, two NADH molecules are generated, and a total of four ATP molecules are made (steps 7 and 10). The net ATP gain from this pathway is, however, only two ATP molecules because there was an energy investment of two ATP molecules in the early steps of the pathway. This investment was paid back by the two ATP molecules produced by substrate-level phosphorylation in step 7. The actual energy yield is produced by substrate-level phosphorylation in reaction 10.

What is substrate-level phosphorylation? **Question 21.5**

What are the major products of glycolysis? **Question 21.6**

Describe an overview of the reactions of glycolysis. **Question 21.7**

How do the names of the first three enzymes of the glycolytic pathway relate to the reactions they catalyze? **Question 21.8**

Regulation of Glycolysis

Learning Goal 5

Energy-harvesting pathways, such as glycolysis, are responsive to the energy needs of the cell. Reactions of the pathway speed up when there is a demand for ATP. They slow down when there is abundant ATP to meet the energy requirements of the cell.

One of the major mechanisms for the control of the rate of the glycolytic pathway is the use of *allosteric enzymes.* In addition to the active site, which binds the

substrate, allosteric enzymes have an effector binding site, which binds a chemical signal that alters the rate at which the enzyme catalyzes the reaction. Effector binding may increase (positive allosterism) or decrease the rate of reaction (negative allosterism).

The chemical signals, or effectors, that indicate the energy needs of the cell include molecules such as ATP. If the ATP concentration is high, the cell must have sufficient energy. Similarly, ADP and AMP, which are precursors of ATP, are indicators that the cell is in need of ATP. In fact, all of these molecules are allosteric effectors that alter the rate of irreversible reactions catalyzed by enzymes in the glycolytic pathway.

The enzyme hexokinase, which catalyzes the phosphorylation of glucose, is allosterically inhibited by the product of the reaction it catalyzes, glucose-6-phosphate. A buildup of this product indicates that the reactions of glycolysis are not proceeding at a rapid rate, presumably because the energy demands of the cell are being met.

Phosphofructokinase, the enzyme that catalyzes the third reaction in glycolysis, is a key regulatory enzyme in the pathway. ATP is an allosteric inhibitor of phosphofructokinase, whereas AMP and ADP are allosteric activators. Another allosteric inhibitor of phosphofructokinase is citrate. As we will see in the next chapter, citrate is the first intermediate in the citric acid cycle. The citric acid cycle is a pathway that results in the complete oxidation of the pyruvate produced by glycolysis. A high concentration of citrate signals that sufficient substrate is entering the citric acid cycle. The inhibition of phosphofructokinase by citrate is an example of *feedback inhibition:* the product, citrate, allosterically inhibits the activity of an enzyme early in the pathway.

There are additional mechanisms that regulate the rate of glycolysis, but we will focus on those that involve principles studied previously (Section 20.9).

The last enzyme in glycolysis, pyruvate kinase, is also subject to allosteric regulation. In this case, fructose-1,6-bisphosphate is the allosteric activator. It is interesting that fructose-1,6-bisphosphate is the product of the reaction catalyzed by phosphofructokinase. Thus, activation of phosphofructokinase results in the activation of pyruvate kinase. This is an example of *feedforward activation* because the product of an earlier reaction causes activation of an enzyme later in the pathway.

21.4 Fermentations

Learning Goal 6

In the overview of glycolysis we noted that the pyruvate produced must be used up in some way so that the pathway will continue to produce ATP. Similarly, the NADH produced by glycolysis in step 6 (see Figure 21.8) must be reoxidized at a later time, or glycolysis will grind to a halt as the available NAD^+ is used up. If the cell is functioning under aerobic conditions, NADH will be reoxidized, and pyruvate will be completely oxidized by aerobic respiration. Under anaerobic conditions, however, different types of fermentation reactions accomplish these purposes. **Fermentations** are catabolic reactions that occur with no net oxidation. Pyruvate or an organic compound produced from pyruvate is reduced as NADH is oxidized. We will examine two types of fermentation pathways in detail: lactate fermentation and alcohol fermentation.

Aerobic respiration is discussed in Chapter 22.

Lactate Fermentation

Lactate fermentation is familiar to anyone who has performed strenuous exercise. If you exercise so hard that your lungs and circulatory system can't deliver enough oxygen to the working muscles, your aerobic (oxygen-requiring) energy-harvesting pathways are not able to supply enough ATP to your muscles. But the muscles still demand energy. Under these anaerobic conditions, lactate fermentation begins. In this reaction the enzyme *lactate dehydrogenase* reduces pyruvate to lactate. NADH is the reducing agent for this process (Figure 21.9). As pyruvate is reduced, NADH is oxidized, and NAD^+ is again available, permitting glycolysis to continue.

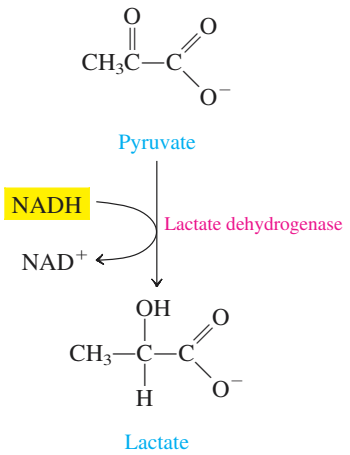


Figure 21.9
The final reaction of lactate fermentation.

The lactate produced in the working muscle passes into the blood. Eventually, if strenuous exercise is continued, the concentration of lactate becomes so high that this fermentation can no longer continue. Glycolysis, and thus ATP production, stops. The muscle, deprived of energy, can no longer function. This point of exhaustion is called the **anaerobic threshold.**

Of course, most of us do not exercise to this point. When exercise is finished, the body begins the process of reclaiming all of the potential energy that was lost in the form of lactate. The liver takes up the lactate from the blood and converts it back to pyruvate. Now that a sufficient supply of oxygen is available, the pyruvate can be completely oxidized in the much more efficient aerobic energy-harvesting reactions to replenish the store of ATP. Alternatively, the pyruvate may be converted to glucose and used to restore the supply of liver and muscle glycogen. This exchange of metabolites between the muscles and liver is called the *Cori Cycle*.

The Cori Cycle is described in Section 21.6 and shown in Figure 21.13.

A variety of bacteria are able to carry out lactate fermentation under anaerobic conditions. This is of great importance in the dairy industry, because these organisms are used to produce yogurt and some cheeses. The tangy flavor of yogurt is contributed by the lactate produced by these bacteria. Unfortunately, similar organisms also cause milk to spoil.

As we saw in A Human Perspective: Tooth Decay and Simple Sugars (Chapter 17), the lactate produced by oral bacteria is responsible for the gradual removal of calcium from tooth enamel and the resulting dental cavities.

Alcohol Fermentation

Alcohol fermentation has been appreciated, if not understood, since the dawn of civilization. The fermentation process itself was discovered by Louis Pasteur during his studies of the chemistry of winemaking and "diseases of wines." Under anaerobic conditions, yeast are able to ferment the sugars produced by fruit and grains. The sugars are broken down to pyruvate by glycolysis. This is followed by the two reactions of alcohol fermentation. First, *pyruvate decarboxylase* removes CO_2 from the pyruvate producing acetaldehyde (Figure 21.10). Second, *alcohol dehydrogenase* catalyzes the reduction of acetaldehyde to ethanol but, more important, reoxidizes NADH in the process. The regeneration of NAD^+ allows glycolysis to continue, just as in the case of lactate fermentation.

These applications and other fermentations are described in A Human Perspective: Fermentations: The Good, the Bad, and the Ugly.

The two products of alcohol fermentation, then, are ethanol and CO_2. We take advantage of this fermentation in the production of wines and other alcoholic beverages and in the process of breadmaking.

Question 21.9

How is the alcohol fermentation in yeast similar to lactate production in skeletal muscle?

A HUMAN PERSPECTIVE

Fermentations: The Good, the Bad, and the Ugly

In this chapter we have seen that fermentation is an anaerobic, cytoplasmic process that allows continued ATP generation by glycolysis. ATP production can continue because the pyruvate produced by the pathway is utilized in the fermentation and because NAD^+ is regenerated.

The stable end products of alcohol fermentation are CO_2 and ethanol. These have been used by humankind in a variety of ways, including the production of alcoholic beverages, bread making, and alternative fuel sources.

The production of bread, wine, and cheese depends on fermentation processes.

If alcohol fermentation is carried out by using fruit juices in a vented vat, the CO_2 will escape, and the result will be a still wine (not bubbly). But conditions must remain anaerobic; otherwise, fermentation will stop, and aerobic energy-harvesting reactions will ruin the wine. Fortunately for vintners (wine makers), when a vat is fermenting actively, enough CO_2 is produced to create a layer that keeps the oxygen-containing air away from the fermenting juice, thus maintaining an anaerobic atmosphere.

Now suppose we want to make a sparkling wine, such as champagne. To do this, we simply have to trap the CO_2 produced. In this case the fermentation proceeds in a sealed bottle, a very strong bottle. Both the fermentation products, CO_2 and ethanol, accumulate. Under pressure within the sealed bottle the CO_2 remains in solution. When the top is "popped," the pressure is released, and the CO_2 comes out of solution in the form of bubbles.

In either case the fermentation continues until the alcohol concentration reaches 12–13%. At that point the yeast "stews in its own juices"! That is, 12–13% ethanol kills the yeast cells that produce it. This points out a last generalization about fermentations. The stable fermentation end product, whether it is lactate or ethanol, eventually accumulates to a concentration that is toxic to the organism. Muscle fatigue is the early effect of lactate buildup in the working muscle. In the same way, continued accumulation of the fermentation product can lead to concentrations that are fatal if there is no means of getting rid of the

Question 21.10

Why must pyruvate be used and NADH be reoxidized so that glycolysis can continue?

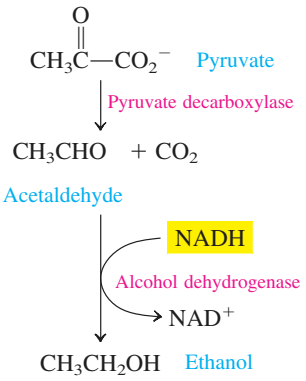


Figure 21.10
The final two reactions of alcohol fermentation.

toxic product or of getting away from it. For single-celled organisms the result is generally death. Our bodies have evolved in such a way that lactate buildup contributes to muscle fatigue that causes the exerciser to stop the exercise. Then the lactate is removed from the blood and converted to glucose by the process of gluconeogenesis.

Another application of alcohol fermentation is the use of yeast in bread making. When we mix the water, sugar, and dried yeast, the yeast cells begin to grow and carry out the process of fermentation. This mixture is then added to the flour, milk, shortening, and salt, and the dough is placed in a warm place to rise. The yeast continues to grow and ferment the sugar, producing CO_2 that causes the bread to rise. Of course, when we bake the bread, the yeast cells are killed, and the ethanol evaporates, but we are left with a light and airy loaf of bread.

Today, alcohol produced by fermentation is being considered as an alternative fuel to replace the use of some fossil fuels. Geneticists and bioengineers are trying to develop strains of yeast that can survive higher alcohol concentrations and thus convert more of the sugar of corn and other grains into alcohol.

Bacteria perform a variety of other fermentations. The propionibacteria produce propionic acid and CO_2. The acid gives Swiss cheese its characteristic flavor, and the CO_2 gas produces the characteristic holes in the cheese. Other bacteria, the clostridia, perform a fermentation that is responsible in part for the horrible symptoms of gas gangrene. When these bacteria are inadvertently introduced into deep tissues by a puncture wound, they find a nice anaerobic environment in which to grow. In fact, these organisms are *obligate anaerobes;* that is, they are killed by even a small amount of oxygen. As they grow, they perform a fermentation called the *butyric acid, butanol, acetone fermentation*. This results in the formation of CO_2, the gas associated with gas gangrene. The CO_2 infiltrates the local tissues and helps to maintain an anaerobic environment because oxygen from the local blood supply cannot enter the area of the wound. Now able to grow well, these bacteria produce a variety of toxins and enzymes that cause extensive tissue death and necrosis. In addition, the fermentation produces acetic acid, ethanol, acetone, isopropanol, butanol, and butyric acid (which is responsible, along with the necrosis, for the characteristic foul smell of gas gangrene). Certainly, the presence of these organic chemicals in the wound enhances tissue death.

Gas gangrene is very difficult to treat. Because the bacteria establish an anaerobic region of cell death and cut off the local circulation, systemic antibiotics do not infiltrate the wound and kill the bacteria. Even our immune response is stymied. Treatment usually involves surgical removal of the necrotic tissue accompanied by antibiotic therapy. In some cases a hyperbaric oxygen chamber is employed. The infected extremity is placed in an environment with a very high partial pressure of oxygen. The oxygen forced into the tissues is poisonous to the bacteria, and they die.

These are but a few examples of the fermentations that have an effect on humans. Regardless of the specific chemical reactions, all fermentations share the following traits:

- They use pyruvate produced in glycolysis.
- They reoxidize the NADH produced in glycolysis.
- They are self-limiting because the accumulated stable fermentation end product eventually kills the cell that produces it.

21.5 The Pentose Phosphate Pathway

Learning Goal 7

The **pentose phosphate pathway** is an alternative pathway for glucose oxidation. It provides the cell with energy in the form of reducing power for biosynthesis. Specifically, NADPH is produced in the oxidative stage of this pathway. NADPH is the reducing agent required for many biosynthetic pathways.

The details of the pentose phosphate pathway will not be covered in this text. But an overview of the key reactions will allow us to understand the importance of the pathway (Figure 21.11). We can consider the pathway in three stages. The first is the oxidative stage, which can be summarized as

$$\text{glucose-6-phosphate} + 2NADP^+ + H_2O \longrightarrow \text{ribulose-5-phosphate} + 2NADPH + CO_2$$

These reactions provide the NADPH required for biosynthesis.

The second stage involves isomerization reactions that convert ribulose-5-phosphate into ribose-5-phosphate or xylulose-5-phosphate. The pathway's name reflects the production of these phosphorylated five-carbon sugars (pentose phosphates).

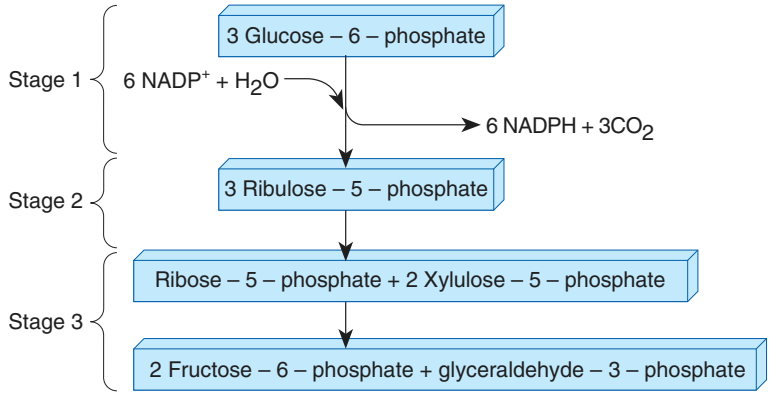


Figure 21.11
Summary of the major stages of the pentose phosphate pathway.

The third stage is a complex series of reactions involving C—C bond breakage and formation. The result of these reactions is the formation of two molecules of fructose-6-phosphate and one molecule of glyceraldehyde-3-phosphate from three molecules of pentose phosphate.

In addition to providing reducing power (NADPH), the pentose phosphate pathway provides sugar phosphates that are required for biosynthesis. For instance, ribose-5-phosphate is used for the synthesis of nucleotides such as ATP. The four-carbon sugar phosphate, erythrose-4-phosphate, produced in the third stage of the pentose phosphate pathway is a precursor of the amino acids phenylalanine, tyrosine, and tryptophan.

The pathway for fatty acid biosynthesis is discussed in Section 23.4.

The pentose phosphate pathway is most active in tissues involved in cholesterol and fatty acid biosynthesis. These two processes require abundant NADPH. Thus the liver, which is the site of cholesterol synthesis and a major site for fatty acid biosynthesis, and adipose (fat) tissue, where active fatty acid synthesis also occurs, have very high levels of pentose phosphate pathway enzymes.

21.6 Gluconeogenesis: The Synthesis of Glucose

Learning Goal 8

Under normal conditions we have enough glucose to satisfy our needs. However, under some conditions the body must make glucose. This is necessary following strenuous exercise to replenish the liver and muscle supplies of glycogen. It also occurs during starvation so that the body can maintain adequate blood glucose levels to supply the brain cells and red blood cells. Under normal conditions these two tissues use only glucose for energy.

Under extreme conditions of starvation the brain eventually switches to the use of ketone bodies. Ketone bodies are produced, under certain circumstances, from the breakdown of lipids (Section 23.3).

Glucose is produced by the process of **gluconeogenesis,** the production of glucose from noncarbohydrate starting materials (Figure 21.12). Gluconeogenesis, an anabolic pathway, occurs primarily in the liver. Lactate, all the amino acids except leucine and lysine, and glycerol from fats can all be used to make glucose. However, the amino acids and glycerol are generally used only under starvation conditions.

At first glance, gluconeogenesis appears to be simply the reverse of glycolysis (compare Figures 21.12 and 21.7), because the intermediates of the two pathways are identical. But this is not the case, because steps 1, 3, and 10 of glycolysis are irreversible, and therefore the reverse reactions must be carried out by other enzymes. In step 1 of glycolysis, hexokinase catalyzes the phosphorylation of glucose. In gluconeogenesis the dephosphorylation of glucose-6-phosphate is carried out by the enzyme *glucose-6-phosphatase,* which is found in the liver but not in muscle. Similarly, reaction 3, the phosphorylation of fructose-6-phosphate catalyzed by phosphofructokinase, is irreversible. That step is bypassed in gluconeogenesis by using the enzyme *fructose-1,6-bisphosphatase*. Finally, the phosphorylation of ADP

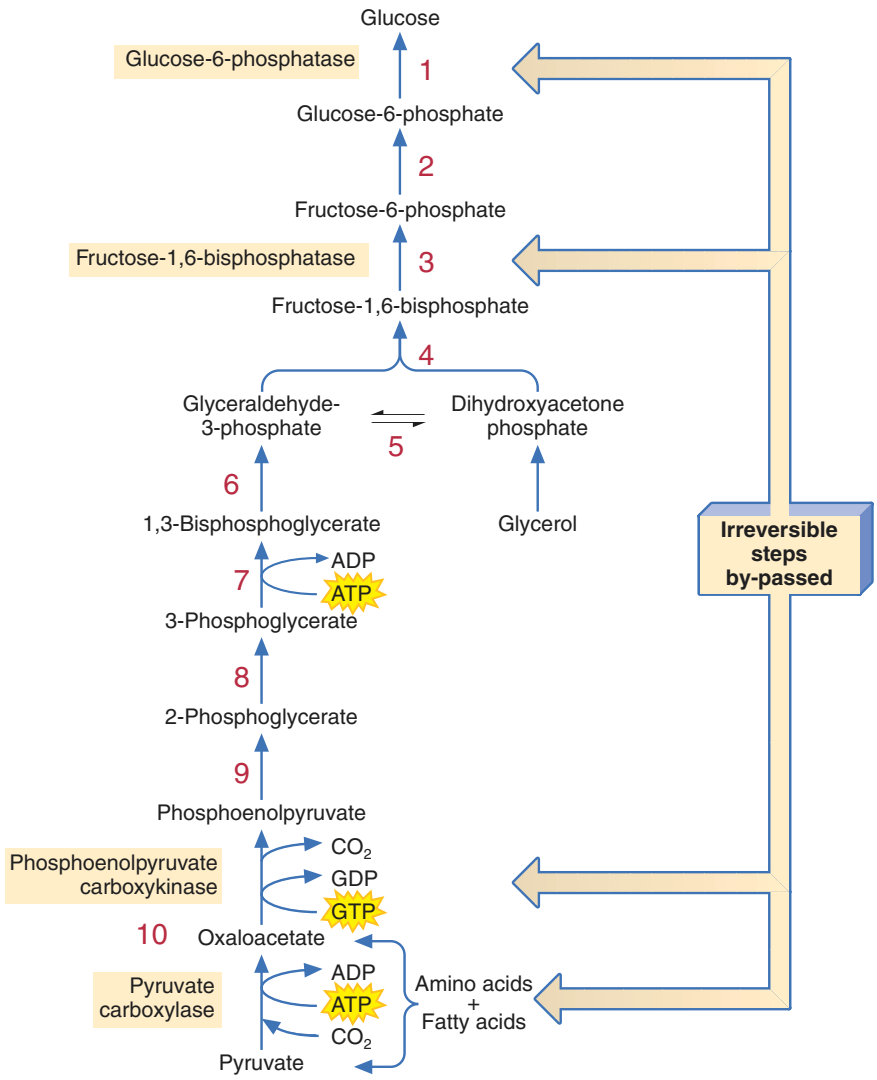


Figure 21.12
Comparison of the reactions of glycolysis and gluconeogenesis. All the reactions of glycolysis occur in the cytoplasm of the cell. However, in many human cells, pyruvate carboxylase is found in the mitochondria and phosphoenolpyruvate carboxykinase is located in the cytoplasm. Oxaloacetate, the product of the reaction catalyzed by pyruvate carboxylase, is shuttled out of the mitochondria and into the cytoplasm by a complex set of reactions.

catalyzed by pyruvate kinase, step 10 of glycolysis, cannot be reversed. The conversion of pyruvate to phosphoenolpyruvate actually involves two enzymes and some unusual reactions. First, the enzyme *pyruvate carboxylase* adds CO_2 to pyruvate. The product is the four-carbon compound oxaloacetate. Then *phosphoenolpyruvate carboxykinase* removes the CO_2 and adds a phosphoryl group. The donor of the phosphoryl group in this unusual reaction is **guanosine triphosphate (GTP).** This is a nucleotide like ATP, except that the nitrogenous base is guanine.

This last pair of reactions is complicated by the fact that pyruvate carboxylase is found in the mitochondria, whereas phosphoenolpyruvate carboxykinase is found in the cytoplasm. As we will see in Chapters 22 and 23, mitochondria are organelles in which the final oxidation of food molecules occurs and large amounts of ATP are produced. A complicated shuttle system transports the oxaloacetate produced in the mitochondria through the two mitochondrial membranes and into the cytoplasm. There, phosphoenolpyruvate carboxykinase catalyzes its conversion to phosphoenolpyruvate.

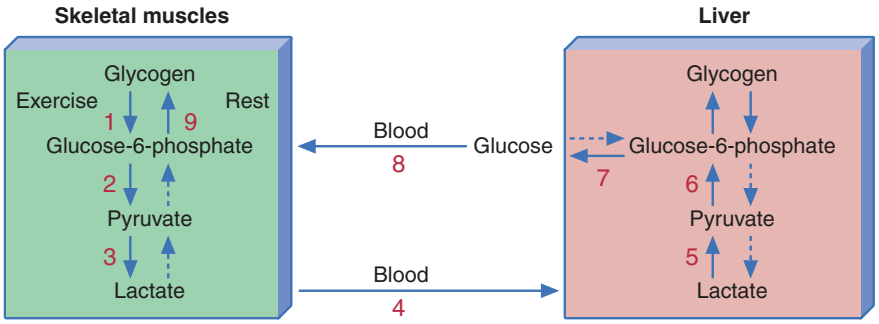


Figure 21.13
The Cori Cycle.

If glycolysis and gluconeogenesis were not regulated in some fashion, the two pathways would occur simultaneously, with the disastrous effect that nothing would get done. Three convenient sites for this regulation are the three bypass reactions. Step 3 of glycolysis is catalyzed by the enzyme phosphofructokinase. This enzyme is stimulated by high concentrations of AMP, ADP, and inorganic phosphate, signals that the cell needs energy. When the enzyme is active, glycolysis proceeds. On the other hand, when ATP is plentiful, phosphofructokinase is inhibited, and fructose-1,6-bisphosphatase is stimulated. The net result is that in times of energy excess (high concentrations of ATP), gluconeogenesis will occur.

As we have seen, the conversion of lactate into glucose is important in mammals. As the muscles work, they produce lactate, which is converted back to glucose in the liver. The glucose is transported into the blood and from there back to the muscle. In the muscle it can be catabolized to produce ATP, or it can be used to replenish the muscle stores of glycogen. This cyclic process between the liver and skeletal muscles is called the **Cori Cycle** and is shown in Figure 21.13. Through this cycle, gluconeogenesis produces enough glucose to restore the depleted muscle glycogen reservoir within forty-eight hours.

Question 21.11

What are the major differences between gluconeogenesis and glycolysis?

Question 21.12

What do the three irreversible reactions of glycolysis have in common?

21.7 Glycogen Synthesis and Degradation

Learning Goal 9

Glucose is the sole source of energy of mammalian red blood cells and the major source of energy for the brain. Neither red blood cells nor the brain can store glucose; thus a constant supply must be available as blood glucose. This is provided by dietary glucose and by the production of glucose either by gluconeogenesis or by **glycogenolysis,** the degradation of glycogen. Glycogen is a long-branched-chain polymer of glucose. Stored in the liver and skeletal muscles, it is the principal storage form of glucose.

The total amount of glucose in the blood of a 70-kg (approximately 150-lb) adult is about 20 g, but the brain alone consumes 5–6 g of glucose per hour. Breakdown of glycogen in the liver mobilizes the glucose when hormonal signals register a need for increased levels of blood glucose. Skeletal muscle also contains substantial stores of glycogen, which provide energy for rapid muscle contraction. However, this glycogen is not able to contribute to blood glucose because muscle cells do not have the enzyme glucose-6-phosphatase. Because glucose cannot be formed from the glucose-6-phosphate, it cannot be released into the bloodstream.

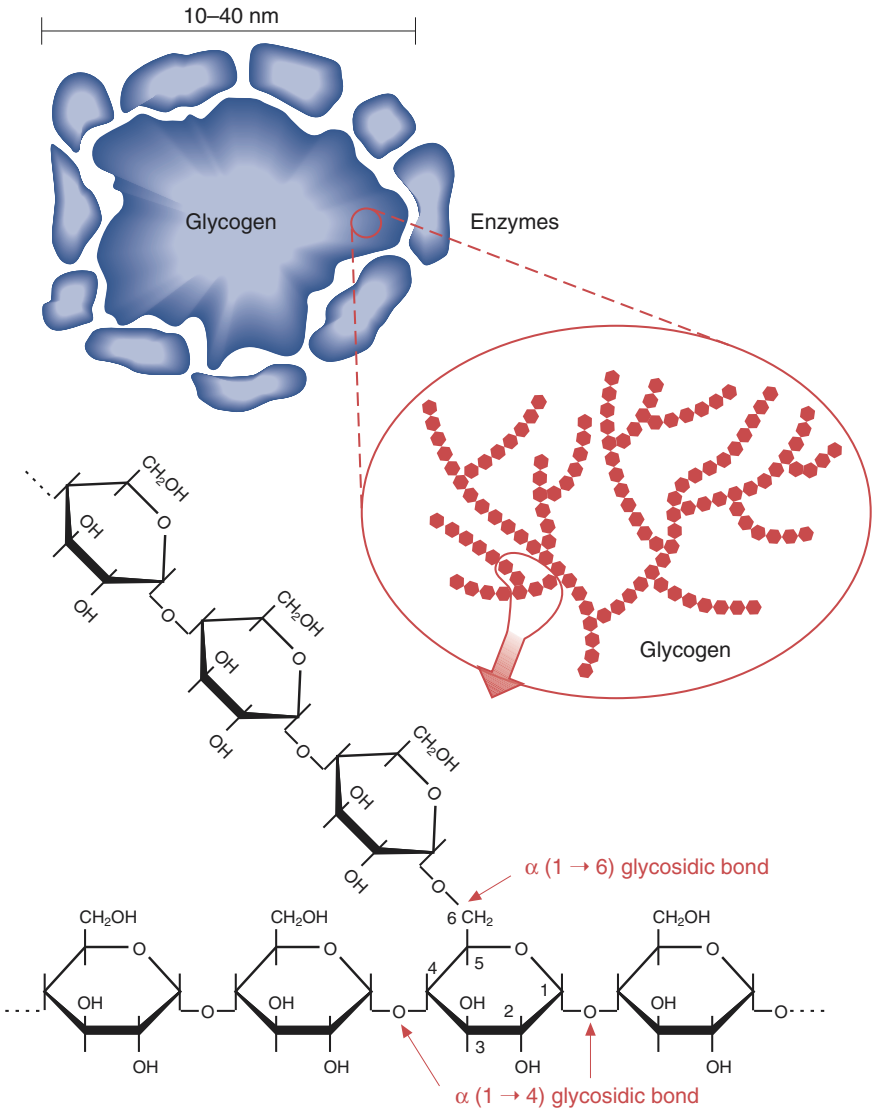


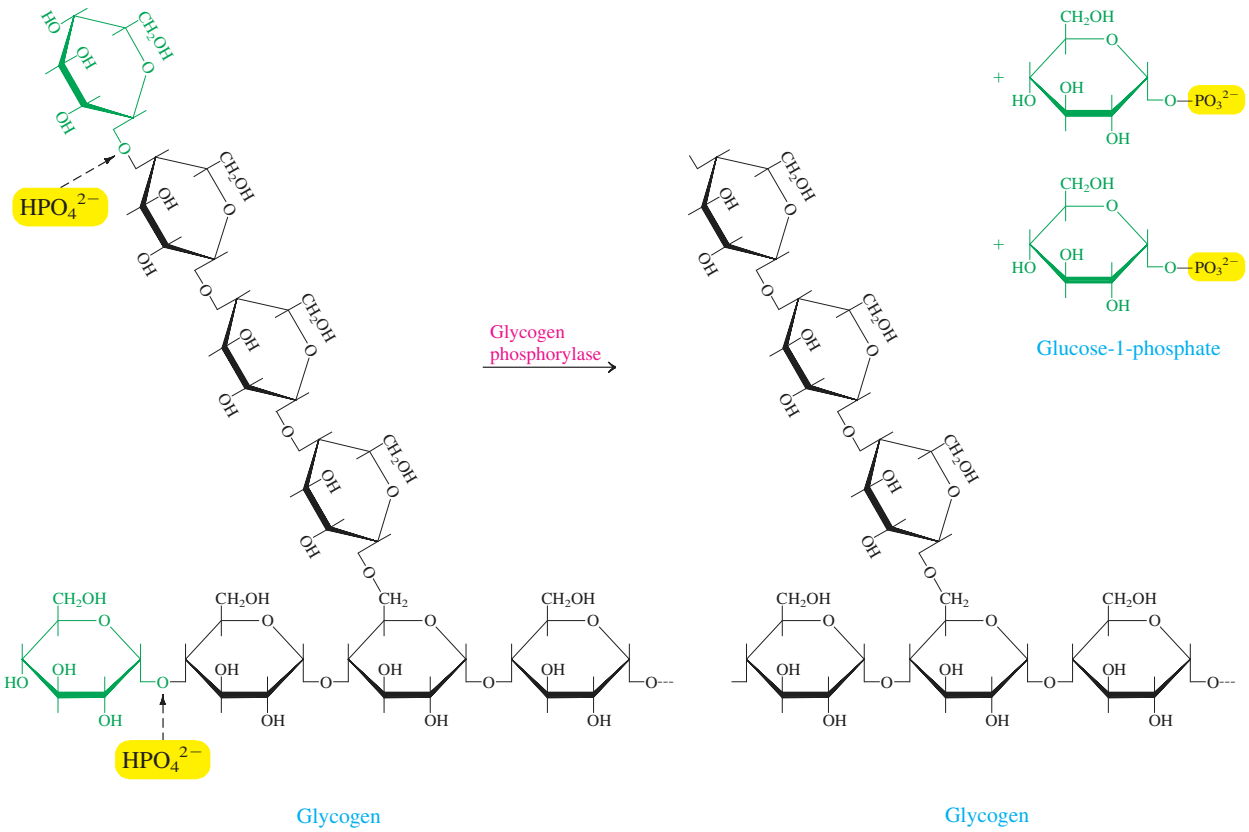
Figure 21.14
The structure of glycogen and a glycogen granule.

The Structure of Glycogen

Glycogen is a highly branched glucose polymer in which the "main chain" is linked by α (1 → 4) glycosidic bonds. The polymer also has numerous α (1 → 6) glycosidic bonds, which provide many branch points along the chain. This structure is shown schematically in Figure 21.14. **Glycogen granules** with a diameter of 10–40 nm are found in the cytoplasm of liver and muscle cells. These granules exist in complexes with the enzymes that are responsible for glycogen synthesis and degradation. The structure of such a granule is also shown in Figure 21.14.

Glycogenolysis: Glycogen Degradation

Two hormones control glycogenolysis, the degradation of glycogen. These are **glucagon,** a peptide hormone synthesized in the pancreas, and *epinephrine,* produced in the adrenal glands. Glucagon is released from the pancreas in response to low blood glucose, and epinephrine is released from the adrenal glands in response to a threat or a stress. Both situations require an increase in blood glucose, and both



General reaction:

$$\text{Glycogen (glucose)}_x + n\ HPO_4^{2-} \xrightarrow[\text{phosphorylase}]{\text{Glycogen}} \text{(glucose)}_{x-n} + n\ \text{glucose-1-phosphate}$$

Figure 21.15
The action of glycogen phosphorylase in glycogenolysis.

hormones function by altering the activity of two enzymes, glycogen phosphorylase and glycogen synthase. *Glycogen phosphorylase* is involved in glycogen degradation and is activated; *glycogen synthase* is involved in glycogen synthesis and is inactivated. The steps in glycogen degradation are summarized as follows.

Step 1. The enzyme glycogen phosphorylase catalyzes *phosphorolysis* of a glucose at one end of a glycogen polymer (Figure 21.15). The reaction involves the displacement of a glucose unit of glycogen by a phosphate group. As a result of phosphorolysis, glucose-1-phosphate is produced without using ATP as the phosphoryl group donor.

Step 2. Glycogen contains many branches bound to the α (1 → 4) backbone by α (1 → 6) glycosidic bonds. These branches must be removed to allow the complete degradation of glycogen. The extensive action of glycogen phosphorylase produces a smaller polysaccharide with a single glucose bound by an α (1 → 6) glycosidic bond to the main chain. The enzyme α *(1 → 6) glycosidase*, also called the *debranching enzyme*, hydrolyzes the α (1 → 6) glycosidic bond at a branch point and frees one molecule of glucose (Figure 21.16). This molecule of glucose can be phosphorylated and utilized in glycolysis, or it may be released into the bloodstream for use elsewhere. Hydrolysis of the branch bond liberates another stretch of α(1 → 4)-linked glucose for the action of glycogen phosphorylase.

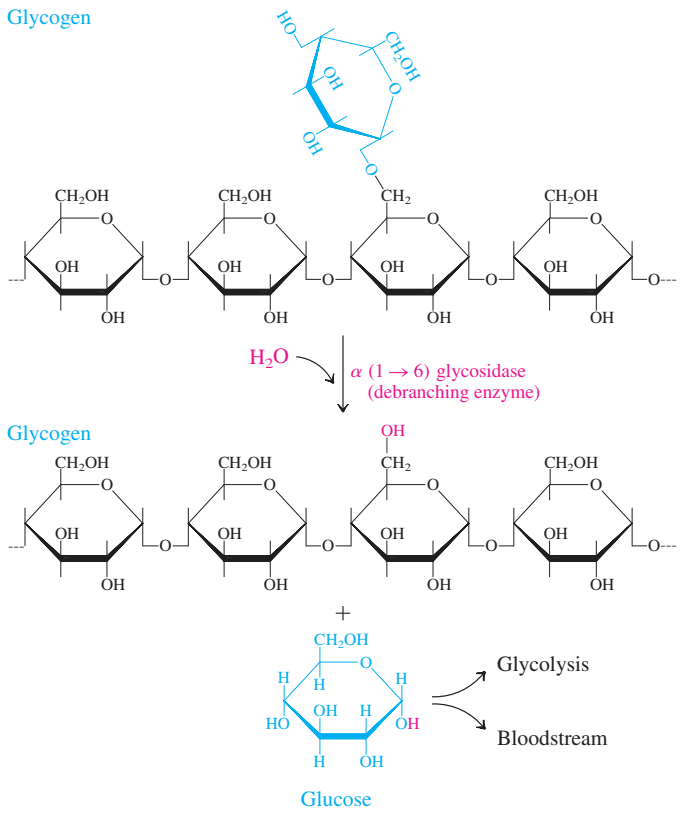


Figure 21.16
The action of α (1 → 6) glycosidase (debranching enzyme) in glycogen degradation.

Step 3. Glucose-1-phosphate is converted to glucose-6-phosphate by *phosphoglucomutase* (Figure 21.17). Glucose originally stored in glycogen enters glycolysis through the action of phosphoglucomutase. Alternatively, in the liver and kidneys it may be dephosphorylated for transport into the bloodstream.

Question 21.13

Explain the role of glycogen phosphorylase in glycogenolysis.

Question 21.14

How does the action of glycogen phosphorylase and phosphoglucomutase result in an energy savings for the cell if the product, glucose-6-phosphate, is used directly in glycolysis?

Glycogenesis: Glycogen Synthesis

The hormone **insulin,** produced by the pancreas in response to high blood glucose levels, stimulates the synthesis of glycogen, **glycogenesis.** Insulin is perhaps one of the most influential hormones in the body because it directly alters the metabolism and uptake of glucose in all but a few cells of the body.

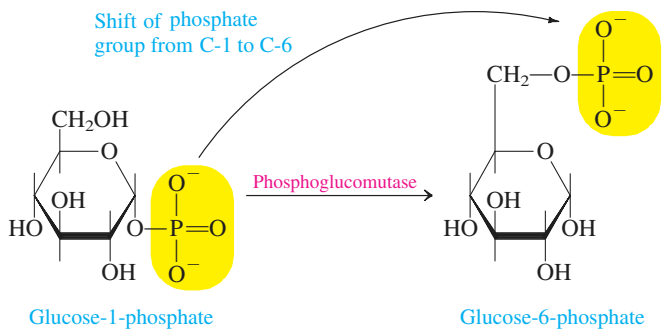


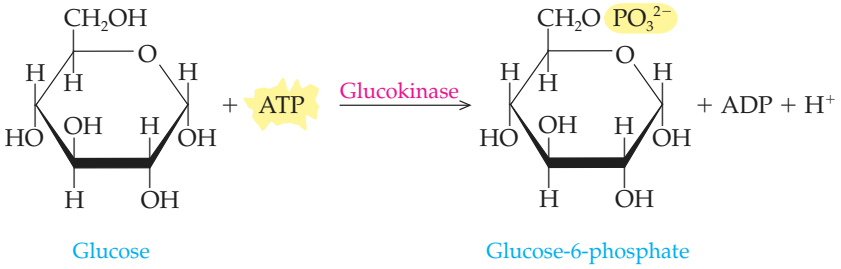
Figure 21.17
The action of phosphoglucomutase in glycogen degradation.

When blood glucose rises, as after a meal, the beta cells of the pancreas secrete insulin. It immediately accelerates the uptake of glucose by all the cells of the body except the brain and certain blood cells. In these cells the uptake of glucose is insulin-independent. The increased uptake of glucose is especially marked in the liver, heart, skeletal muscle, and adipose tissue.

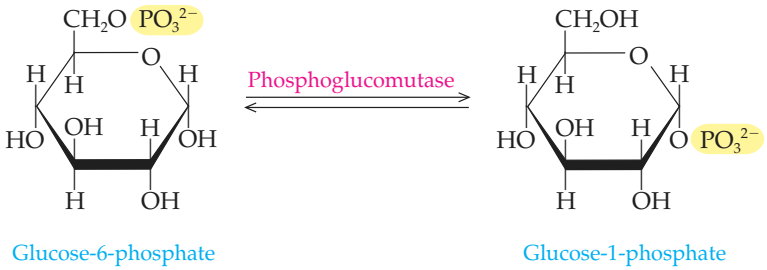
In the liver, insulin promotes glycogen synthesis and storage by inhibiting glycogen phosphorylase, thus inhibiting glycogen degradation. It also stimulates glycogen synthase and glucokinase, two enzymes that are involved in glycogen synthesis.

Although glycogenesis and glycogenolysis share some reactions in common, the two pathways are not simply the reverse of one another. Glycogenesis involves some very unusual reactions, which we will now examine in detail.

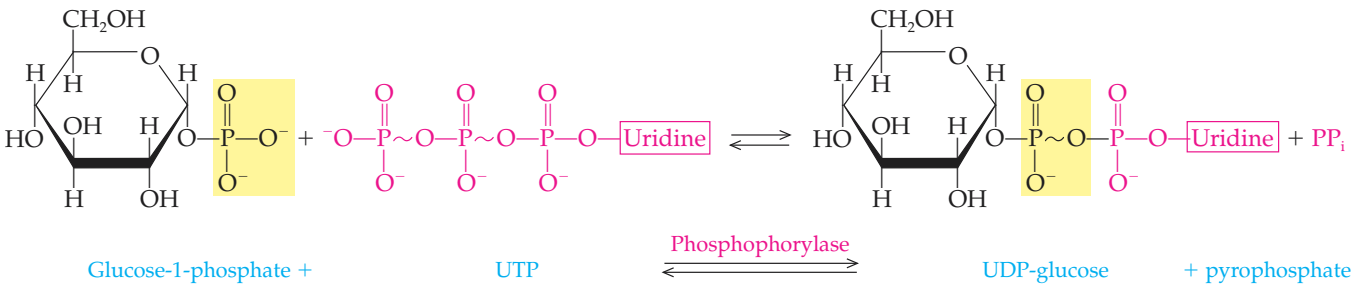
The first reaction of glycogen synthesis in the liver traps glucose within the cell by phosphorylating it. In this reaction, catalyzed by the enzyme *glucokinase*, ATP serves as a phosphoryl donor, and glucose-6-phosphate is formed:



The second reaction of glycogenesis is the reverse of one of the reactions of glycogenolysis. The glucose-6-phosphate formed in the first step is isomerized to glucose-1-phosphate. The enzyme that catalyzes this step is phosphoglucomutase:



The glucose-1-phosphate must now be activated before it can be added to the growing glycogen chain. The high-energy compound that accomplishes this is the nucleotide **uridine triphosphate (UTP).** In this reaction, mediated by the enzyme *pyrophosphorylase*, the C-1 phosphoryl group of glucose is linked to the α phosphoryl group of UTP to produce UDP-glucose:



This is accompanied by the release of a pyrophosphate group (PP_i). The structure of UDP-glucose is seen in Figure 21.18.

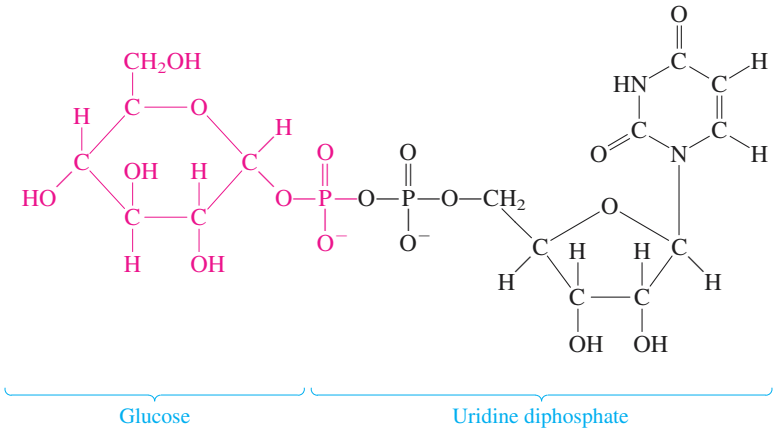
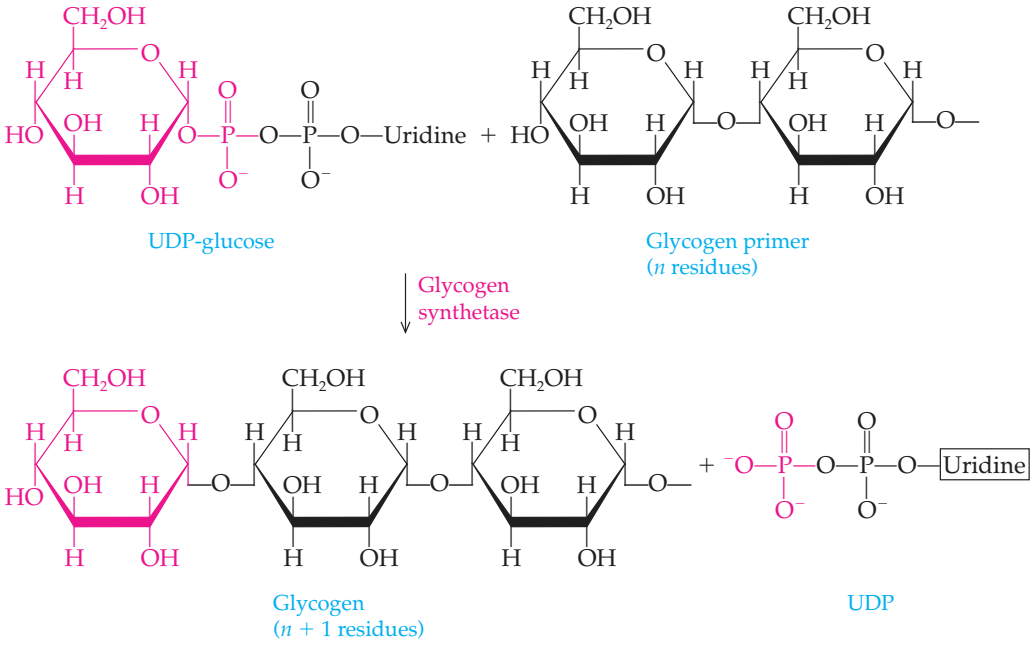


Figure 21.18
The structure of UDP-glucose.

The UDP-glucose can now be used to extend glycogen chains. The enzyme glycogen synthase breaks the phosphoester linkage of UDP-glucose and forms an α (1 → 4) glycosidic bond between the glucose and the growing glycogen chain. UDP is released in the process.



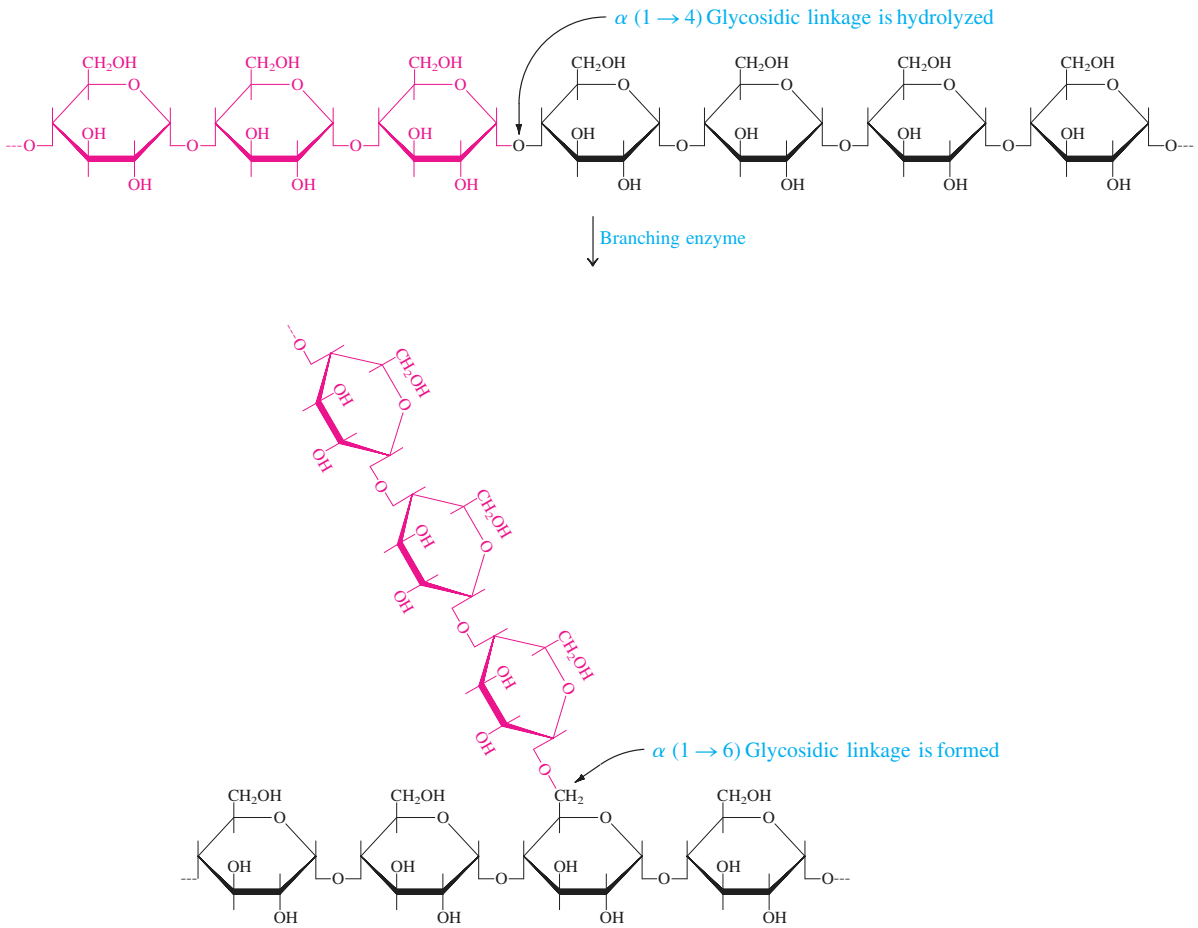


Figure 21.19
The action of the branching enzyme in glycogen synthesis.

Finally, we must introduce the α (1 → 6) glycosidic linkages to form the branches. The branches are quite important to proper glycogen utilization. As Figure 21.19 shows, the *branching enzyme* removes a section of the linear α (1 → 4) linked glycogen and reattaches it in α (1 → 6) glycosidic linkage elsewhere in the chain.

Question 21.15 Describe the way in which glucokinase traps glucose inside liver cells.

Question 21.16 Describe the reaction catalyzed by the branching enzyme.

Compatibility of Glycogenesis and Glycogenolysis

As was the case with glycolysis and gluconeogenesis, it would be futile for the cell to carry out glycogen synthesis and degradation simultaneously. The results achieved by the action of one pathway would be undone by the other. This problem is avoided by a series of hormonal controls that activate the enzymes of one pathway while inactivating the enzymes of the other pathway.

A CLINICAL PERSPECTIVE

Diagnosing Diabetes

When diagnosing diabetes, doctors take many factors and symptoms into consideration. However, there are two primary tests that are performed to determine whether an individual is properly regulating blood glucose levels. First and foremost is the fasting blood glucose test. A person who has fasted since midnight should have a blood glucose level between 70 and 110 mg/dL in the morning. If the level is 140 mg/dL on at least two occasions, a diagnosis of diabetes is generally made.

The second commonly used test is the glucose tolerance test. For this test the subject must fast for at least ten hours. A beginning blood sample is drawn to determine the fasting blood glucose level. This will serve as the background level for the test. The subject ingests 50–100 g of glucose (40 g/m^2 body surface), and the blood glucose level is measured at thirty minutes, and at one, two, and three hours after ingesting the glucose.

A graph is made of the blood glucose levels over time. For a person who does not have diabetes, the curve will show a peak of blood glucose at approximately one hour. There will be a reduction in the level, and perhaps a slight hypoglycemia (low blood glucose level) over the next hour. Thereafter, the blood glucose level stabilizes at normal levels.

An individual is said to have impaired glucose tolerance if the blood glucose level remains between 140 and 200 mg/dL two hours after ingestion of the glucose solution. This suggests that there is a risk of the individual developing diabetes and is reason to prescribe periodic testing to allow early intervention.

If the blood glucose level remains at or above 200 mg/dL after two hours, a tentative diagnosis of diabetes is made. However, this result warrants further testing on subsequent days to rule out transient problems, such as the effect of medications on blood glucose levels.

It was recently suggested that the upper blood glucose level of 200 mg/dL should be lowered to 180 mg/dL as the standard to diagnose impaired glucose tolerance and diabetes. This would allow earlier detection and intervention. Considering the grave nature of long-term diabetic complications, it is thought to be very beneficial to begin treatment at an early stage to maintain constant blood glucose levels. For more information on diabetes, see A Clinical Perspective: Diabetes Mellitus and Ketone Bodies, in Chapter 23.

When the blood glucose level is too high, a condition known as **hyperglycemia,** insulin stimulates the uptake of glucose via a transport mechanism. It further stimulates the trapping of the glucose by the elevated activity of glucokinase. Finally, it activates glycogen synthase, the last enzyme in the synthesis of glycogen chains. To further accelerate storage, insulin *inhibits* the first enzyme in glycogen degradation, glycogen phosphorylase. The net effect, seen in Figure 21.20, is that glucose is removed from the bloodstream and converted into glycogen in the liver. When the glycogen stores are filled, excess glucose is converted to fat and stored in adipose tissue.

Glucagon is produced in response to low blood glucose levels, a condition known as **hypoglycemia,** and has an effect opposite to that of insulin. It stimulates glycogen phosphorylase, which catalyzes the first stage of glycogen degradation. This accelerates glycogenolysis and release of glucose into the bloodstream. The effect is further enhanced because glucagon inhibits glycogen synthetase. The opposing effects of insulin and glucagon are summarized in Figure 21.20.

This elegant system of hormonal control ensures that the reactions involved in glycogen degradation and synthesis do not compete with one another. In this way they provide glucose when the blood level is too low, and they cause the storage of glucose in times of excess.

Explain how glucagon affects the synthesis and degradation of glycogen. **Question 21.17**

How does insulin affect the storage and degradation of glycogen? **Question 21.18**

A HUMAN PERSPECTIVE

Glycogen Storage Diseases

Glycogen metabolism is important for the proper function of many aspects of cellular metabolism. Many diseases of glycogen metabolism have been discovered. Generally, these are diseases that result in the excessive accumulation of glycogen in the liver, muscle, and tubules of the kidneys. Often they are caused by defects in one of the enzymes involved in the degradation of glycogen.

One example is an inherited defect of glycogen metabolism known as *von Gierke's disease*. This disease results from a defective gene for glucose-6-phosphatase, which catalyzes the final step of gluconeogenesis and glycogenolysis. People who lack glucose-6-phosphatase cannot convert glucose-6-phosphate to glucose. As we have seen, the liver is the primary source of blood glucose, and much of this glucose is produced by gluconeogenesis. Glucose-6-phosphate, unlike glucose, cannot cross the cell membrane, and the liver of a person suffering from von Gierke's disease cannot provide him or her with glucose. The blood sugar level falls precipitously low between meals. In addition, the lack of glucose-6-phosphatase also affects glycogen metabolism. Because glucose-6-phosphatase is absent, the supply of glucose-6-phosphate in the liver is large. This glucose-6-phosphate can also be converted to glycogen. A person suffering from von Gierke's disease has a massively enlarged liver as a result of enormously increased stores of glycogen.

Defects in other enzymes of glycogen metabolism also exist. *Cori's disease* is caused by a genetic defect in the debranching enzyme. As a result, individuals who have this disease cannot completely degrade glycogen and thus use their glycogen stores very inefficiently.

On the other side of the coin, *Andersen's disease* results from a genetic defect in the branching enzyme. Individuals who have this disease produce very long, unbranched glycogen chains. This genetic disorder results in decreased efficiency of glycogen storage.

A final example of a glycogen storage disease is *McArdle's disease*. In this syndrome the muscle cells lack the enzyme glycogen phosphorylase and cannot degrade glycogen to glucose. Individuals who have this disease have little tolerance for physical exercise because their muscles cannot provide enough glucose for the necessary energy-harvesting processes. It is interesting to note that the liver enzyme glycogen phosphorylase is perfectly normal, and these people respond appropriately with a rise of blood glucose levels under the influence of glucagon or epinephrine.

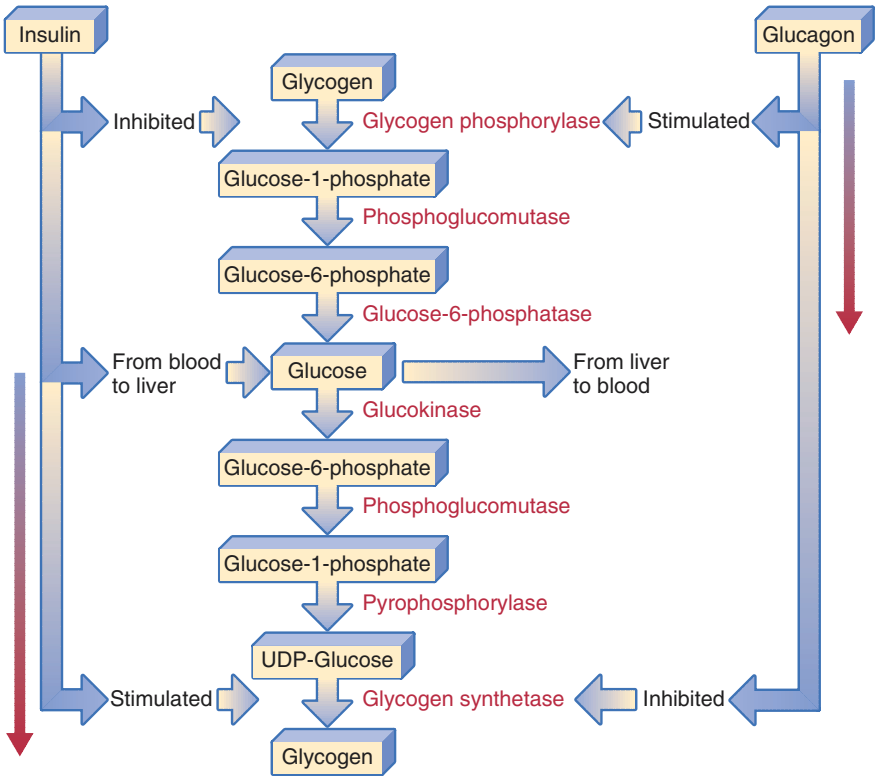


Figure 21.20
The opposing effects of the hormones insulin and glucagon on glycogen metabolism.

Summary

21.1 ATP: The Cellular Energy Currency

Adenosine triphosphate, ATP, is a *nucleotide* composed of adenine, the sugar ribose, and a triphosphate group. The energy released by the hydrolysis of the phosphoanhydride bond between the second and third phosphoryl groups provides the energy for most cellular work.

21.2 Overview of Catabolic Processes

The body needs a supply of ATP to carry out life processes. To provide this ATP, we consume a variety of energy-rich food molecules: carbohydrates, lipids, and proteins. In the digestive tract these large molecules are degraded into smaller molecules (monosaccharides, glycerol, fatty acids, and amino acids) that are absorbed by our cells. These molecules are further broken down to generate ATP.

21.3 Glycolysis

Glycolysis is the pathway for the *catabolism* of glucose that leads to pyruvate. It is an anaerobic process carried out by enzymes in the cytoplasm of the cell. The net harvest of ATP during glycolysis is two molecules of ATP per molecule of glucose. Two molecules of NADH are also produced. The rate of glycolysis responds to the energy demands of the cell. The regulation of glycolysis occurs through the allosteric enzymes hexokinase, phosphofructokinase, and pyruvate kinase.

21.4 Fermentations

Under anaerobic conditions the NADH produced by glycolysis is used to reduce pyruvate to lactate in skeletal muscle (lactate *fermentation*) or to convert acetaldehyde to ethanol in yeast (alcohol fermentation).

21.5 The Pentose Phosphate Pathway

The *pentose phosphate pathway* is an alternative pathway for glucose degradation that is particularly abundant in the liver and adipose tissue. It provides the cell with a source of NADPH to serve as a reducing agent for biosynthetic reactions. It also provides ribose-5-phosphate for nucleotide synthesis and erythrose-4-phosphate for biosynthesis of the amino acids tryptophan, tyrosine, and phenylalanine.

21.6 Gluconeogenesis: The Synthesis of Glucose

Gluconeogenesis is the pathway for glucose synthesis from noncarbohydrate starting materials. It occurs in mammalian liver. Glucose can be made from lactate, all the amino acids except lysine and leucine, and glycerol. Gluconeogenesis is not simply the reversal of glycolysis. Three steps in glycolysis in which ATP is produced or consumed are bypassed by different enzymes in gluconeogenesis. All other enzymes in gluconeogenesis are shared with glycolysis.

21.7 Glycogen Synthesis and Degradation

Glycogenesis is the pathway for the synthesis of glycogen, and *glycogenolysis* is the pathway for the degradation of glycogen. The concentration of blood glucose is controlled by the liver. A high blood glucose level causes secretion of *insulin.* This hormone stimulates glycogenesis and inhibits glycogenolysis. When blood glucose levels are too low, the hormone *glucagon* stimulates gluconeogenesis and glycogen degradation in the liver.

Key Terms

adenosine triphosphate (ATP) (21.1)
anabolism (21.1)
anaerobic threshold (21.4)
catabolism (21.1)
Cori Cycle (21.6)
fermentation (21.4)
glucagon (21.7)
gluconeogenesis (21.6)
glycogen (21.7)
glycogenesis (21.7)
glycogen granule (21.7)
glycogenolysis (21.7)
glycolysis (21.3)
guanosine triphosphate (GTP) (21.6)
hyperglycemia (21.7)
hypoglycemia (21.7)
insulin (21.7)
nicotinamide adenine dinucleotide (NAD^+) (21.3)
nucleotide (21.1)
oxidative phosphorylation (21.3)
pentose phosphate pathway (21.5)
substrate-level phosphorylation (21.3)
uridine triphosphate (UTP) (21.7)

Questions and Problems

ATP: The Cellular Energy Currency

21.19 What molecule is primarily responsible for conserving the energy released in catabolism?
21.20 Describe the structure of ATP.
21.21 Write a reaction showing the hydrolysis of the terminal phosphoanhydride bond of ATP.
21.22 What is meant by the term *high-energy bond?*

Glycolysis

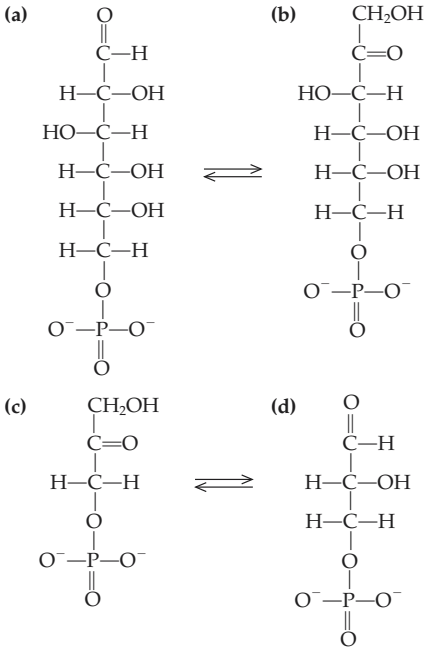
21.23 Why does glycolysis require a supply of NAD^+ to function?
21.24 Why must the NADH produced in glycolysis be reoxidized to NAD^+?
21.25 What is the net energy yield of ATP in glycolysis?
21.26 How many molecules of ATP are produced by substrate-level phosphorylation during glycolysis?
21.27 Explain how muscle is able to carry out rapid contraction for prolonged periods even though its supply of ATP is sufficient only for a fraction of a second of rapid contraction.
21.28 Where in the muscle cell does glycolysis occur?
21.29 Write the balanced chemical equation for glycolysis.

21.30 Write a chemical equation for the transfer of a phosphoryl group from ATP to fructose-6-phosphate.

21.31 Which glycolysis reactions are catalyzed by each of the following enzymes?
- **a.** Hexokinase
- **b.** Pyruvate kinase
- **c.** Phosphoglycerate mutase
- **d.** Glyceraldehyde-3-phosphate dehydrogenase

21.32 Fill in the blanks:
- **a.** _____ molecules of ATP are produced per molecule of glucose that is converted to pyruvate.
- **b.** Two molecules of ATP are consumed in the conversion of _____ to fructose-1,6-bisphosphate.
- **c.** NAD^+ is _____ to NADH in the first energy-releasing step of glycolysis.
- **d.** The second substrate-level phosphorylation in glycolysis is phosphoryl group transfer from phosphoenolpyruvate to _____.

21.33 Examine the following pair of reactions and use them to answer Questions 21.33–21.36. What type of enzyme would catalyze each of these reactions?



21.34 To which family of organic molecules do (a) and (d) belong? To which family of organic molecules do (b) and (c) belong?

21.35 What is the name of the type of intermediate formed in each of these reactions?

21.36 Draw the intermediate that would be formed in each of these reactions.

21.37 When an enzyme has the term *kinase* in the name, what type of reaction do you expect it to catalyze?

21.38 What features do the reactions catalyzed by hexokinase and phosphofructokinase share in common?

21.39 What is the role of NAD^+ in a biochemical oxidation reaction?

21.40 Write the equation for the reaction catalyzed by glyceraldehyde-3-phosphate dehydrogenase. Highlight the chemical changes that show this to be an oxidation reaction.

21.41 The enzyme that catalyzes step 9 of glycolysis is called enolase. What is the significance of that name?

21.42 Draw the enol tautomer of pyruvate.

21.43 What is the importance of the regulation of glycolysis?

21.44 Explain the role of allosteric enzymes in control of glycolysis.

21.45 What molecules serve as allosteric effectors of phosphofructokinase?

21.46 What molecule serves as an allosteric inhibitor of hexokinase?

21.47 Explain the role of citrate in the feedback inhibition of glycolysis.

21.48 Explain the feedforward activation mechanism that results in the activation of pyruvate kinase.

Fermentations

21.49 Write a balanced chemical equation for the conversion of acetaldehyde to ethanol.

21.50 Write a balanced chemical equation for the conversion of pyruvate to lactate.

21.51 After running a 100-m dash, a sprinter had a high concentration of muscle lactate. What process is responsible for production of lactate?

21.52 If the muscle of an organism had no lactate dehydrogenase, could anaerobic glycolysis occur in those muscle cells? Explain your answer.

21.53 What food products are the result of lactate fermentation?

21.54 Explain the value of alcohol fermentation in bread making.

21.55 What enzyme catalyzes the reduction of pyruvate to lactate?

21.56 What enzymes catalyze the conversion of pyruvate to ethanol and carbon dioxide?

21.57 A child was brought to the doctor's office suffering from a strange set of symptoms. When the child exercised hard, she became giddy and behaved as though drunk. What do you think is the metabolic basis of these symptoms?

21.58 A family started a batch of wine by adding yeast to grape juice and placing the mixture in a sealed bottle. Two weeks later, the bottle exploded. What metabolic reactions—and specifically, what product of those reactions—caused the bottle to explode?

The Pentose Phosphate Pathway

21.59 Describe the three stages of the pentose phosphate pathway.

21.60 Write an equation to summarize the pentose phosphate pathway.

21.61 Of what value are the ribose-5-phosphate and erythrose-4-phosphate that are produced in the pentose phosphate pathway?

21.62 Of what value is the NADPH that is produced in the pentose phosphate pathway?

Gluconeogenesis

21.63 What organ is primarily responsible for gluconeogenesis?

21.64 What is the physiological function of gluconeogenesis?

21.65 Lactate can be converted to glucose by gluconeogenesis. To what metabolic intermediate must lactate be converted so that it can be a substrate for the enzymes of gluconeogenesis?

21.66 L-Alanine can be converted to pyruvate. Can L-alanine also be converted to glucose? Explain your answer.

21.67 Explain why gluconeogenesis is not simply the reversal of glycolysis.

21.68 In step 10 of glycolysis, phosphoenolpyruvate is converted to pyruvate, and ATP is produced by substrate-level phosphorylation. How is this reaction bypassed in gluconeogenesis?

21.69 Which steps in the glycolysis pathway are irreversible?

21.70 What enzymatic reactions of gluconeogenesis bypass the irreversible steps of glycolysis?

Glycogen Synthesis and Degradation

21.71 What organs are primarily responsible for maintaining the proper blood glucose level?

21.72 Why must the blood glucose level be carefully regulated?
21.73 What does the term *hypoglycemia* mean?
21.74 What does the term *hyperglycemia* mean?
21.75 **a.** What enzymes involved in glycogen metabolism are stimulated by insulin?
b. What effect does this have on glycogen metabolism?
c. What effect does this have on blood glucose levels?
21.76 **a.** What enzyme is stimulated by glucagon?
b. What effect does this have on glycogen metabolism?
c. What effect does this have on blood glucose levels?
21.77 Explain how a defect in glycogen metabolism can cause hypoglycemia.
21.78 What defects of glycogen metabolism would lead to a large increase in the concentration of liver glycogen?

Critical Thinking Problems

1. An enzyme that hydrolyzes ATP (an ATPase) bound to the plasma membrane of certain tumor cells has an abnormally high activity. How will this activity affect the rate of glycolysis?
2. Explain why no net oxidation occurs during anaerobic glycolysis followed by lactate fermentation.
3. A certain person was found to have a defect in glycogen metabolism. The liver of this person could (a) make glucose-6-phosphate from lactate and (b) synthesize glucose-6-phosphate from glycogen but (c) could not synthesize glycogen from glucose-6-phosphate. What enzyme is defective?
4. A scientist added phosphate labeled with radioactive phosphorus (^{32}P) to a bacterial culture growing anaerobically (without O_2). She then purified all the compounds produced during glycolysis. Look carefully at the steps of the pathway. Predict which of the intermediates of the pathway would be the first one to contain radioactive phosphate. On which carbon of this compound would you expect to find the radioactive phosphate?
5. A two-month-old baby was brought to the hospital suffering from seizures. He deteriorated progressively over time, showing psychomotor retardation. Blood tests revealed a high concentration of lactate and pyruvate. Although blood levels of alanine were high, they did not stimulate gluconeogenesis. The doctor measured the activity of pyruvate carboxylase in the baby and found it to be only 1% of the normal level. What reaction is catalyzed by pyruvate carboxylase? How could this deficiency cause the baby's symptoms and test results?