CHAPTER

3

CARBOHYDRATES: ENERGY, METABOLISM, AND MORE

HERE'S WHERE YOU HAVE BEEN:

1. Digestion is a complex synergy of the physical actions of chewing, mixing, and moving and the chemical actions of saliva, enzymes, and emulsifiers.
2. Absorption refers to the movement of nutrients from the digestive tract into the blood or lymphatic circulations, whereas the concept of bioavailability also includes the uptake and utilization of a nutrient by cells or tissues.
3. Perceptions of hunger and satiety involve multiple hormonal and neurologic signals, including cholecystokinin, neuropeptide Y, ghrelin, obestatin, insulin, and leptin.
4. Different types of bacteria are found along the length of the digestive tract, depending on the environmental conditions of the segment and the properties of the bacterial species, with the highest concentration found in the colon.

HERE'S WHERE YOU ARE GOING:

1. Carbohydrates are a class of nutrients that includes sugars, starches, fibers, and related molecules such as glycosaminoglycans, amino sugars, and more.
2. Key differences in covalent bonding make some carbohydrates more digestible than others.
3. Carbohydrates are absorbed as monosaccharides that circulate to tissue and are taken up by special glucose transporters.
4. Circulating glucose and stored glycogen are principal energy sources for most cells and tissue and are mandatory for others, such as red blood cells, as well as the brain under normal conditions.
5. Carbohydrate metabolism is regulated by hormones such as insulin, epinephrine, glucagon, and cortisol.

Introduction

How much carbohydrate and what type to eat is a consideration for many people as they plan their diet. For instance, some weight loss diet programs may restrict carbohydrates, whereas others may provide carbohydrates as more than 50% of total energy. Meanwhile, endurance athletes may derive a large portion of their total energy consumption from carbohydrates to optimize performance and recovery.

Although both myths and truths abound in relation to how much carbohydrate we need, it remains the greatest contributor to human energy intake, both in developed and underdeveloped countries worldwide. Moreover, the importance of carbohydrate is not limited simply to supplying energy. For instance, most dietary **fibers** are classified as carbohydrates. Although dietary fiber does indeed provide a limited amount of energy to the body, its role in digestive operations and disease prevention is much more significant. Meanwhile, carbohydrates such as glycosaminoglycans play structural roles, especially in connective tissue.

Because carbohydrate can be used for energy by all cells or be assimilated into energy stores or converted to other molecules, humans have several overlapping carbohydrate metabolic pathways, which also integrate with those for other nutrients, such as fatty acids and amino acids. This chapter describes and details the different types of carbohydrates and their properties, food sources, digestion, and metabolism.

Carbohydrate Types and Characteristics

The term *carbohydrate* was coined long ago as scientists observed a consistent pattern in the chemical formula of most carbohydrates. Not only were they composed of only carbon, hydrogen, and oxygen, but also the ratio of carbon to water was typically one to one ($C:H_2O$). Thus, *carbohydrate* literally means "carbon with water." To create energy-providing carbohydrates from the non-energy-providing molecules H_2O and carbon dioxide (CO_2) is a talent bestowed only on plants and a select few microorganisms. In photosynthesis, plants couple H_2O and CO_2 by harnessing solar energy. Along with carbohydrates, molecular oxygen (O_2) is also a product of this reaction:

$$H_2O + CO_2 \xrightarrow{\textbf{Photosynthesis}} C_6H_{12}O_6 + O_2$$

Chemically, carbohydrates are defined as polyhydroxy aldehydes and ketones and their derivatives. Carbohydrates can vary from simpler three- to seven-carbon single-unit molecules to very complex branching polymers. Although hundreds of different carbohydrates exist in nature, this text takes the simplest approach and groups them into just a few broad categories, namely, sugars (monosaccharides and disaccharides), oligosaccharides, and polysaccharides (**Figure 3.1**).

Monosaccharides

The **monosaccharides** that are relevant to human nutrition may be classified based on carbon number and include the trioses, tetroses, pentoses, and hexoses. Both aldoses (aldehydes) and ketoses (ketones) are present (**Figure 3.2**). The six-carbon hexoses are the most common form of monosaccharides in the human diet. These include glucose, galactose, and fructose. Glucose is the principal carbohydrate found in human circulation and is often referred to as blood sugar.

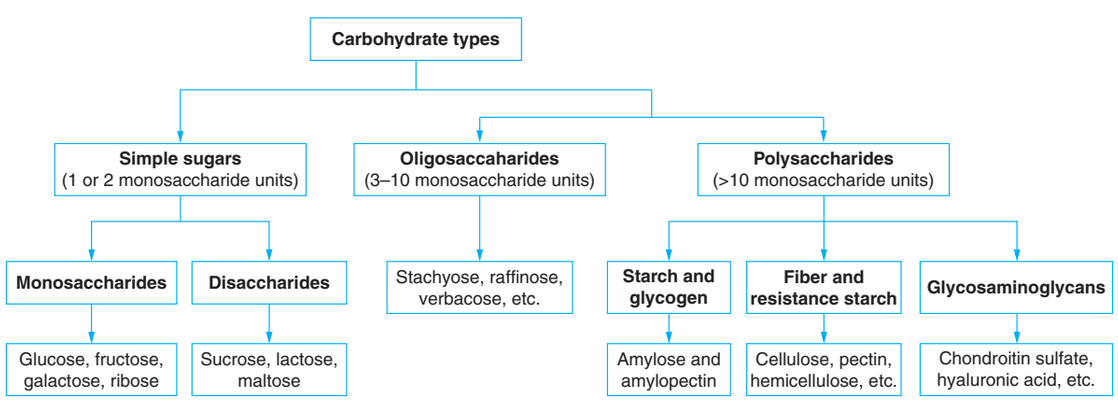


FIGURE 3.1 Classification System of Carbohydrates. Carbohydrates can be subclassified as sugars, oligosaccharides, and polysaccharides.

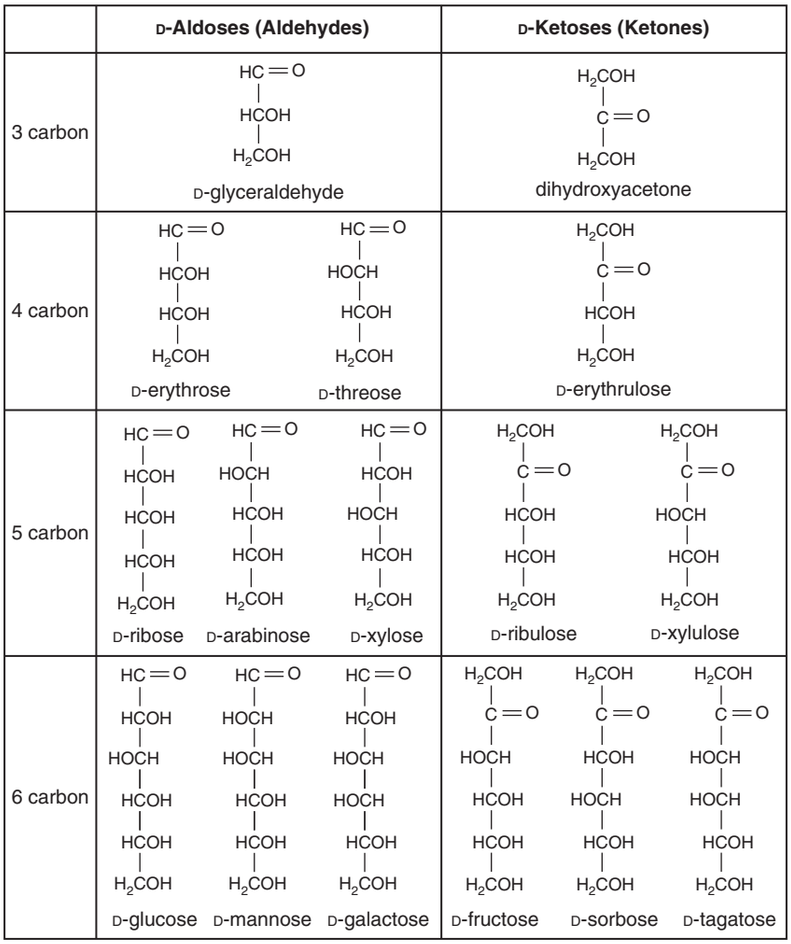


FIGURE 3.2 **Examples of D-Aldoses and D-Ketones Having Three to Six Carbons**

Three-carbon trioses such as glyceraldehyde and dihydroxyacetone are generally found as intermediary products of metabolic pathways (e.g., glycolysis). Four-carbon tetroses include erythrose, threose, and erythrulose. Five-carbon pentoses include the aldoses (xylose, ribose, and arabinose) and the ketoses (xylulose and ribulose). Of specific interest is ribose, which is a component of the nucleic acids (DNA and RNA); its alcohol derivative, ribitol, is found as a component of the water-soluble vitamin riboflavin. Also, **high-energy phosphate** compounds such as adenosine triphosphate (ATP), adenosine diphosphate (ADP), and adenosine monophosphate (AMP), as well as dinucleotides such as nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), all contain ribose as part of their chemical makeup. The other pentoses, especially xylose, are common in some fiber types, such as hemicellulose. **Figure 3.3** presents several of the more common monosaccharides.

Monosaccharide Structures

Although it is common to represent monosaccharides as straight-chain structures, in an aqueous environment there is a reaction between the aldehyde group (COOH) of carbon 1 and the hydroxyl group (OH) of carbon 5 (see Figure 3.3). This produces a hemiacetal group that allows for a cyclic structure, which naturally occurs almost all of the time. Many carbohydrates have the same chemical formula but vary in structure, making them isomers. For instance, **glucose**, **fructose**, **galactose**, and mannose have different structures but the same formula: $C_6H_{12}O_6$.

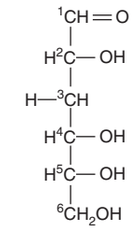
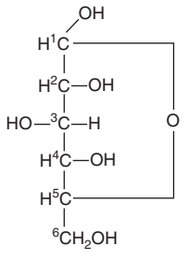
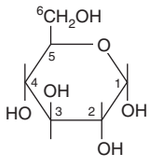
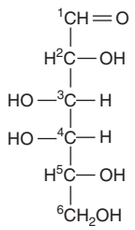
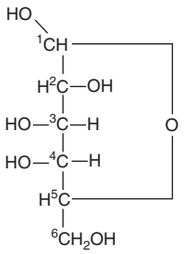
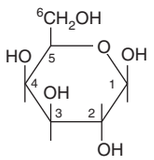
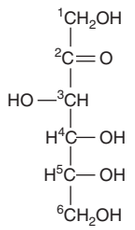
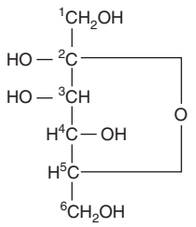
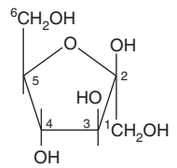
Hexose	Chemical Formula	Fisher Projection	Cyclized Fisher Projection	Haworth
α-D-glucose	$C_6H_{12}O_6$			
β-D-galactose	$C_6H_{12}O_6$			
β-D-fructose	$C_6H_{12}O_6$			

FIGURE 3.3 **Basic Structures of Nutritionally Significant Monosaccharides**

Monosaccharide epimers have differences in their configuration around only one carbon. A good example of this is the difference between glucose and galactose: their composition and molecular weights are the same, but the OH (hydroxyl) group on carbon 4 of the two compounds is different (**Figure 3.4**). In contrast, galactose and mannose are not epimers because they have differences in their OH positioning at two carbons. Another example of monosaccharide epimers is compounds with a difference in configuration around the carbonyl carbon; these are referred to as anomers. If the OH group around the carbonyl carbon is in the "down" position in a monosaccharide in the cyclic configuration, the epimer is given an α (alpha) designation. If the carbonyl carbon is in the "up" position, it is designated the β (beta) version. The difference between the α and β epimers becomes especially important in the bonding between monosaccharides and has a profound effect on the ability of human-produced enzymes to digest these carbohydrates.

Monosaccharide D and L Series

When looking at a monosaccharide as a straight chain, the position of the hydroxyl group on the asymmetric

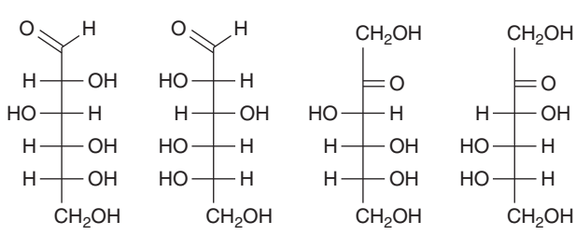


FIGURE 3.4 **Carbohydrate D and L Isomers**

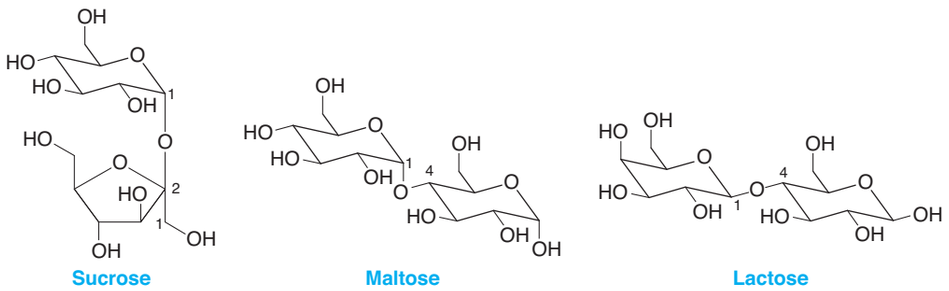


FIGURE 3.5 Common Disaccharides

carbon farthest away from the carbonyl group (C=O) is used to designate the D and L isomer series. Specifically, if the OH group is on the right side, then the monosaccharide is classified within the D series, as shown in Figure 3.4. If the OH group is on the left side, the monosaccharide is classified within the L series. One of the most important distinctions in nutrition between the D and L series is that the D isomers are the predominant naturally occurring form, whereas the L series isomers tend to result from chemical synthesis. These types of isomers are often referred to as enantiomers, because the D and L molecules look like mirror images. Enzymes called racemases are able to interconvert between the two series.

Monosaccharide Derivatives

Although monosaccharides are an important food and circulating carbohydrate, almost all of the carbohydrate present within cells—or as a component of cellular structure—is in the form of more complex carbohydrates and monosaccharide derivatives. Some other monosaccharide derivatives present within cells are amino sugars, acetyl amino sugars, uronic acids, glyconic acids, and sugar alcohols.

Disaccharides

Disaccharides are composed of two monosaccharides covalently linked by acetal (also known as *glyco*sidic bonds because they occur in carbohydrates), as shown in **Table 3.1** and **Figures 3.5** and **3.6**. The glycosidic bonds are formed between hydroxyl groups of adjacent monosaccharides, typically between carbon 1 and either carbon 4 or 6 in the polymer. Thus, specific bond designations, such as α1–4, α1–6, and β1–4, are used to describe the bond and explain the necessary specificity of disaccharidase enzymes.

TABLE 3.1 Most Prevalent Food Disaccharides and Their Monosaccharide Building Blocks

Disaccharide	Monosaccharide Components
Lactose	Glucose + galactose
Sucrose	Glucose + fructose
Maltose	Glucose + glucose

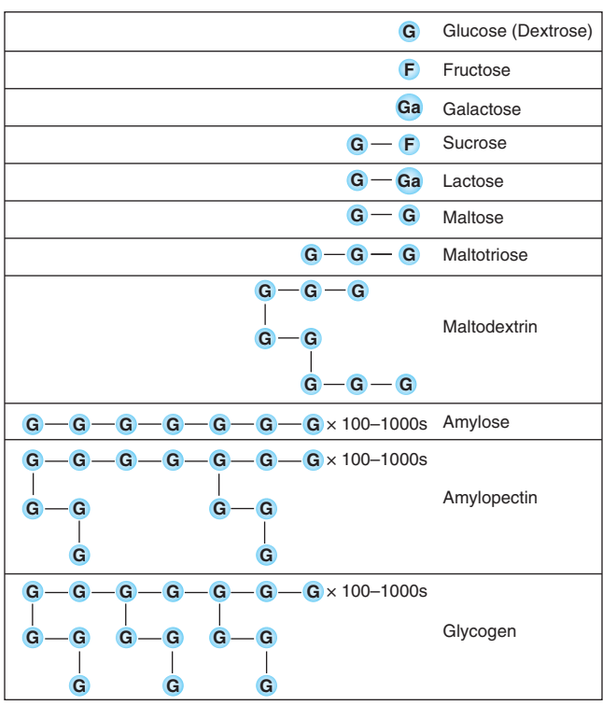


FIGURE 3.6 Overview of Carbohydrate and Monosaccharide Building Blocks

The three most common disaccharides are sucrose, lactose, and maltose. **Sucrose**, which is composed of fructose and glucose, is commonly referred to as "cane sugar," "beet sugar," or "table sugar." **Lactose**, or "milk sugar," is composed of glucose and galactose; this sugar contributes energy to mammalian milk, aids in the absorption of calcium, and supports the growth of beneficial bacteria in the large intestine. **Maltose** is composed of two glucose units. Maltose is found only for a brief time in the life of a plant, usually in the seed; however, it is also an intermediate product of the digestion of more complex carbohydrates (starch) in the gut as well as the partial hydrolysis of starch in ingredient processing and production of some foods, such as beer and malt liquors.

Of the disaccharides mentioned previously, only lactose is derived from animals. The remaining two disaccharides are derived from plants. The term *sugar* is often applied to monosaccharides and disaccharides. These carbohydrates have a sweet taste, with fructose being the sweetest. **Table 3.2** presents the relative sweetness of the sugars, along with common natural and artificial sweeteners, such as stevia and sucralose, respectively.

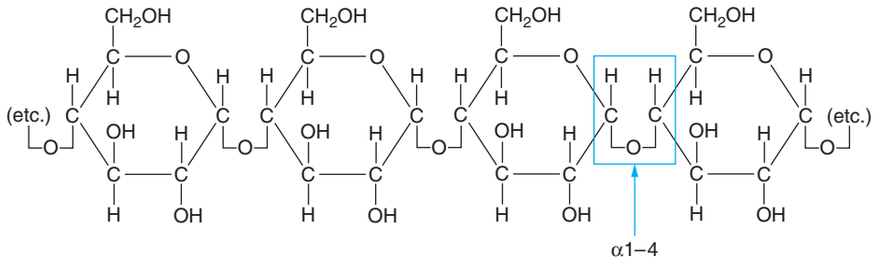
Polysaccharides

Polysaccharides are composed of repeating monosaccharide units, most commonly glucose (Figure 3.6). Although their length may vary, they are rather long, and the covalent bonds in the primary structure are found between carbons 1 and 4. For branched polysaccharides, a bond is typically found between carbons 1 and 6 if hexoses are the monosaccharides involved. These bond types are depicted in **Figure 3.7**. The position of the bonds, known as either the α or β configuration, determines the properties and digestive fate of these compounds because of the ability of digestive enzymes to recognize

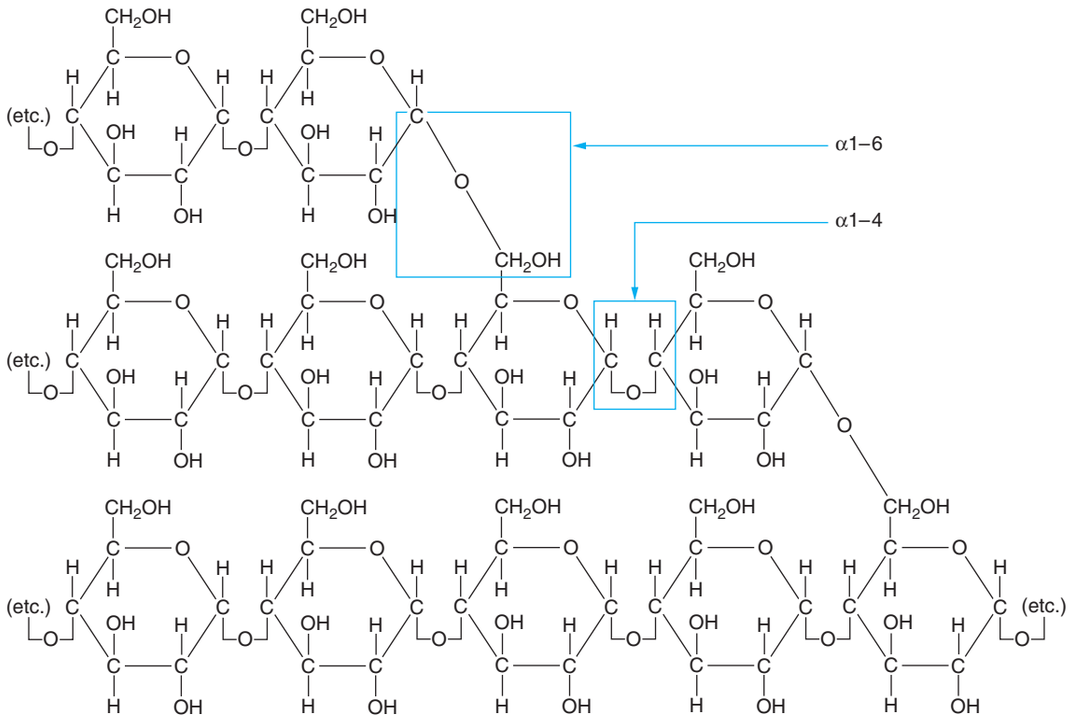
TABLE 3.2 Sweetness of Sugars and Alternative Sweeteners

Type of Sweetener	Relative Sweetness Compared with Sucrose (Table Sugar)	Typical Dietary Sources
Sugars		
Lactose	0.2	Dairy
Maltose	0.4	Sprouted seeds
Glucose	0.7–0.8	Corn syrup, fruits
Sucrose	1.0	Table sugar, fruits
Fructose	1.4	Fruits, honey
HFCS	1.2–1.6	Soft drinks, beverages
Sugar alcohols		
Sorbitol	60	Dietetic candies, sugarless gum
Mannitol	70	Dietetic candies
Erythritol	70	Sugarless candies, supplements, sweetener
Xylitol	90	Sugarless gum
Natural sweeteners		
Stevia	300	Sweetener used in tabletop packs and in foods and supplements
Artificial sweeteners		
Aspartame (NutraSweet)	180	Diet soft drinks and fruit drinks, powdered sweetener
Acesulfame-K	200	Sugarless gum, diet drink mixes, powdered sweetener, gelatin and puddings
Saccharin	300	Diet soft drinks, powdered sweetener
Sucralose	600	Beverages, baked goods, candies, breakfast and protein bars

HFCS, high-fructose corn syrup.



Amylose



Amylopectin

FIGURE 3.7 **α1–4 and α1–6 Links Between Glucose of Starch Components Such as Amylopectin**

only a particular configuration. There are several types of polysaccharides, which are simplified here into several categories: oligosaccharides, starch, glycogen, glycosaminoglycans, and fiber (see Figure 3.1).

Oligosaccharides

Oligosaccharides are composed of 3 to 10 monosaccharides linked by glycosidic bonds between the OH groups of adjacent monomeric units (see Figure 3.7). Stachyose, verbascose, and raffinose are oligosaccharides whose metabolic fate is somewhat different from other oligosaccharides in that they are primarily fermented by bacteria in the colon. This property has resulted in their claim to fame as flatulence producers. Legumes (beans) have appreciable levels of these oligosaccharides.

Plant Starch

One of the most common polysaccharides on the planet is starch, which serves primarily as a storage form of carbohydrate in plants. Starch can be one long chain or can be branched. Starch is referred to as a homopolysaccharide because it contains only glucose monomers linked via α1–4 and α1–6 glycosidic linkages. Starch is also referred to as a glucan because it only yields glucose when it is broken down.

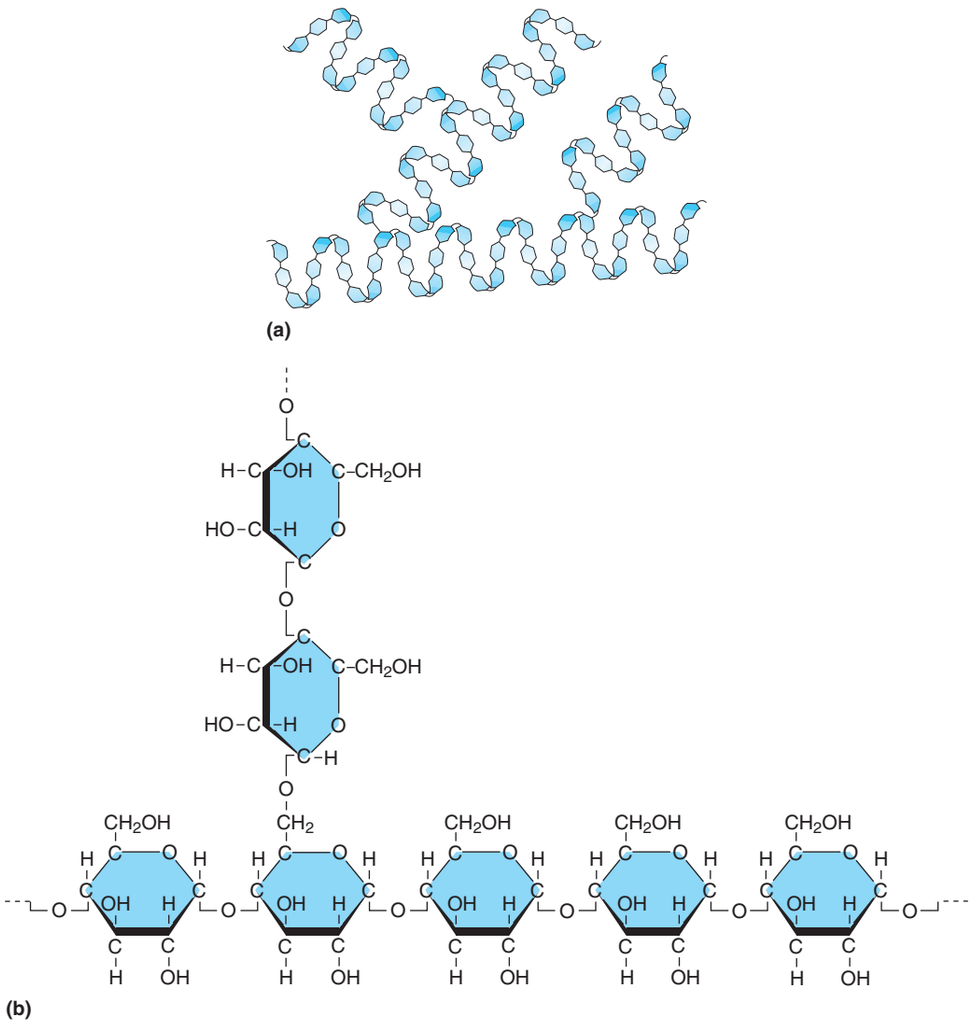


FIGURE 3.8 **Three-Dimensional Structure of Glycogen (a) and α1–4 and α1–6 Linkages Between Glucose Residues in Glycogen (b)**

Amylose is a straight-chain glucose polymer with α1–4 linkages (see Figure 3.7). It is present as a helical coil and forms hydrated micelles. Meanwhile, **amylopectin** is a branched-chain polymer, as shown in Figure 3.7. The α1–6 branches occur approximately every 24 to 30 glucose monomers. All other bonds between glucose monomers are α1–4 links; however, because of branching, amylopectin does not coil effectively and tends to form colloidal suspensions in water.

Animal Glycogen

Glycogen in animal tissue is also a homopolysaccharide. It is often referred to as "animal starch" because it contains repeating glucose units. However, glycogen differs from starch in that the branching occurs every 8 to 12 residues. Glycogen is a large branched polymer consisting of D-glucose linked by α1–4 bonds in straight portions and α1–6 linkages at branch points (**Figure 3.8**). Glycogen from animal flesh is not a significant source of dietary carbohydrate because it is depleted shortly after slaughter. However, it is very important as a carbohydrate storage form, particularly in the liver and muscle tissue. The glycogen concentration is 1% to 2% of skeletal muscle, and it can reach up to 8% to 10% of the weight of the liver. Meanwhile, adipose tissue is less than 1% glycogen by weight.

Glycosaminoglycans

Another class of polysaccharides is the **glycosaminoglycans**, which are sometimes called mucopolysaccharides. Glycosaminoglycans are characterized by their content of amino sugars and uronic acids, which occur in combination with proteins in body secretions and structures. These polysaccharides are responsible for the viscosity of body mucous secretions. They are components of extracellular amorphous ground substances surrounding collagen and elastin fibers and cells of connective tissues and bone. These molecules hold onto large amounts of water and occupy space, which allows for some cushioning and lubrication. Some examples of glycosaminoglycans are hyaluronic acid and chondroitin sulfate.

Dietary Fiber

Dietary **fiber** is plant material, both polysaccharide and lignin, that is resistant to human digestive enzymes. Another descriptor used for these molecules is nonstarch polysaccharides (NSPs); however, this categorization would not include lignin. Dietary fiber has long been classified as either soluble or insoluble, based on its propensity to dissolve in water. Soluble fibers include pectin (pectic substances), gums, and mucilages. Insoluble fibers are composed of cellulose, hemicellulose, lignin, and modified cellulose. In addition, some fibers have been grouped together as functional fibers based on whether they have been isolated, extracted, or manufactured and potentially promote health when consumed in regularly and at efficacious levels. More recently, the classification of fibers has shifted to either dietary fiber or functional fiber as described in Chapter 4.

BEFORE YOU GO ON . . .

1. What are the key differences between monosaccharides, disaccharides, and polysaccharides?
2. Which monosaccharides are found in the different disaccharides, oligosaccharides, and starch?
3. How does plant starch differ from animal glycogen, and why is this important?
4. What is the nature of the links (chemical bonds) between monosaccharides in disaccharides and polysaccharides, and why is this significant?
5. What are glycosaminoglycans, and where are they found in the human body and in other life forms?

Carbohydrate Intake, Food Sources, and Recommendations

Carbohydrate consumption has become one of the principal dietary issues for many people, ranging from athletes to people trying to lose weight or to control blood sugar levels. Carbohydrate in the form of glucose serves as the most basic energy source for all cells in the body. Foods high in carbohydrates include breads, pastas, potatoes, rice, and fruits. Legumes are also a good source of carbohydrate. Legumes are plants that have a single row of seeds in their pods. The foods commonly called legumes, such as peas, green beans, lima beans, pinto beans, black-eyed peas, garbanzo beans, lentils, and soybeans, are often the seeds of legume plants. Dairy foods and vegetables are also good sources of carbohydrates, whereas meats, eggs, and plant oils are not.

Carbohydrate Consumption

During preagricultural times, carbohydrate intake largely came by way of fruits, vegetables, leaves, and tubers. Today, industrial processing has increased the consumption of cereal grains, especially milled grains, as well as refined sugar cane through the mass production of sucrose (table sugar). Within many developed countries, the 20th century heralded changes in the types of carbohydrates consumed as well as carbohydrate's contribution to total energy intake. In the United States, carbohydrate consumption was approximately 500 grams daily at the beginning of the 20th century; it declined to 374 grams in the 1960s largely because of a decrease in consumption of cereal grains. From there, carbohydrate consumption increased steadily during the last four decades of the 20th century to about the same level as seen nearly 100 years earlier. However, much of the carbohydrate that returned to the diet was in the form of refined carbohydrates, such as sugary products, and thus was lacking fiber and many other beneficial nutrients. Today the caloric contribution of carbohydrate to the adult diet is roughly 50% and is derived from a variety of foods. **Table 3.3** lists the general carbohydrate content (by weight) of select foods.

TABLE 3.3 Carbohydrate Content of Select Foods[a]

Food	Carbohydrate (%)
Table sugar*	>98[b]
Ice cream, cake, pie	20–40
Fruits/vegetables	5–20
Nuts	10–15
Peanut butter	~20
Milk	5
Cheese	2–5
Shellfish (e.g., crab, lobster)	<1
Fish	<1
Butter	0
Oil	0

[a]Percentage based on weight.
[b]Remaining mass is moisture.

Monosaccharides and Disaccharides

Glucose is found in some foods in a free form, especially in ripening fruits and vegetables, although the majority of the glucose in the human diet is derived from the digestion of disaccharides and starch. Galactose is also found free in some foods, but to a relatively small degree. Most of the galactose in the human diet is derived from the digestion of the disaccharide lactose, which is found in milk and dairy foods. Fructose is found naturally in fruits and honey and is also derived from the disaccharide sucrose.

Fruits may be somewhat deceiving; according to Table 3.3, their carbohydrate content is roughly 5% to 20%. However, because water makes up most of the remaining weight, carbohydrate is the major nonwater content of fruits. Cereal grains and products such as rice, oats, pastas, and breads also have a relatively high carbohydrate content, whereas animal foods such as meats, fish, and poultry (and eggs) contain very little. Animal flesh (skeletal muscle) does contain a little carbohydrate, primarily as glycogen; however, this is lost during the processing of the meat. Milk and some dairy products (e.g., yogurt, ice cream) are the only significant animal-derived sources of carbohydrate.

Ripened fruits contain mostly monosaccharides and disaccharides, namely, fructose and glucose, as well as some sucrose. For example, a medium apple contains about 8 grams of fructose and 3 grams of both glucose and sucrose. Meanwhile, a medium banana contains between 5 and 6 grams of both fructose and glucose and 2 grams of sucrose. One tablespoon of honey contains 8 grams of fructose and 7 grams of glucose and less than 1 gram of sucrose, galactose, and maltose combined.

Sugars and Caloric Sweeteners

Caloric sweeteners (added sugars) include glucose, sucrose, corn starch, and **high-fructose corn syrup** (HFCS). The U.S. Department of Agriculture (USDA) estimated the consumption of caloric sweeteners at 153 pounds per adult at the turn of the 21st century. Sugar can be considered the number one food additive; it is found in many foods, such as pizza, bread, hot dogs, boxed mixed rice, soup, crackers, spaghetti sauce, lunch meat, canned vegetables, fruit drinks, flavored yogurt, ketchup, salad dressing, mayonnaise, and some peanut butters. Carbonated sodas provided more than one-fifth (22%) of the added sugars in the American food supply in 2000, compared with 16% in 1970. Fructose is also provided in the human diet in the form of the popular food sweetening agent HFCS, which tends to be more than 60% fructose. As dietary consumption of fructose has increased over the past several decades there is growing concern that higher consumption of fructose might be partly responsible for the increasing incidence of obesity worldwide.

Cereal Grains

Grains are among the richest sources of starch, as are legumes. In cereal grains, most of the starch is found within the endosperm compartment, as depicted in **Figure 3.9**. About 15% to 20% of the starch in the American diet is attributed to amylose. Amylopectin constitutes about 80% to 85% of the starch in the American diet. As mentioned previously, the level of consumption of cereal grains decreased in the 20th century.

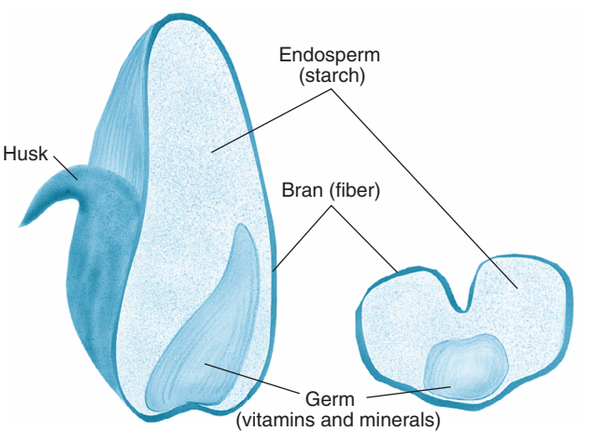


FIGURE 3.9 Structure of a Grain of Wheat and Some of the Major Nutrients Found in Different Regions

Fiber

The amount of fiber present within the human diet can vary geographically as well as by gender. In some developed countries, such as the United States, fiber consumption is relatively lower than in other societies. The average intake of fiber in the United States is only about 12 and 18 grams daily for women and men, respectively, which is well below recommendations. Americans consume a diet in which less than one-half of their carbohydrate intake comes from fruits, vegetables, and whole grains. Meanwhile, some African societies consume as much as 50 grams of fiber daily.

Carbohydrate Recommendations

As part of the Dietary Reference Intakes (DRIs), the Acceptable Macronutrient Distribution Range (AMDR) for carbohydrate intake in the United States and Canada is 45% to 65% of total energy. The range allows for different people to plan their dietary carbohydrate level based on different lifestyles and ability to metabolize food carbohydrates. Individuals are also advised to derive more of the carbohydrate they consume from more nutrient-dense sources such as whole grain products, legumes, lower-fat dairy foods, and fruits and vegetables. These foods provide vitamins, minerals, fiber, and **phytochemicals** that promote health and wellness.

The DRI for carbohydrate energy has been set at 130 grams per day for all people older than 1 year. This would provide 520 calories of energy, which is important to the central nervous system, red blood cells, and other tissue dependent on glucose as its primary energy source. The DRI for carbohydrate energy would be adequate to prevent **ketosis** in most people. It is important to note that the DRI recommendation does not take into consideration exercise and the additional calorie needs of working muscle.

As part of the DRIs it is recommended that the intake of added sugar not exceed 25% of calories. However, some healthcare professionals would like to see the level lowered because of the link between diets higher in added sugars and excessive calorie consumption and obesity. The USDA recommends that for an average adult woman consuming 2,000 calories, the amount that would support weight maintenance, the level of added sugar not exceed 40 grams. That level of added sugar (roughly 10 teaspoons) is the amount of sugar in 12 to 16 ounces of some soft drinks.

Dietary Fiber

The current Adequate Intake (AI) recommendation for total fiber intake for adults who are 50 years old and younger is 38 grams per day for men and 25 grams per day for women. For adults older than 50 years, the recommendation is 30 grams per day for men and 21 grams per day for women, or 14 grams per 1,000 calories consumed. Meanwhile, the World Health Organization recommends 25 to 40 grams of fiber daily for adults.

BEFORE YOU GO ON . . .

1. How has the intake of carbohydrate changed over the last 100 years, and what are the current trends?
2. What foods provide different types of carbohydrates, and how much carbohydrate do they contain?
3. What is the current recommended limit for added sugar, and what types of foods contain it?
4. What is the AMDR for carbohydrate intake in the United States and Canada, and how could it be applied to different people?
5. How does the average intake of fiber by American adults compare with recommendations, and what impact might that have on health?

Carbohydrate Digestion and Absorption

The objective of carbohydrate digestion is to liberate monosaccharides from disaccharides and more complex polymers. This activity begins in the mouth, because salivary secretions contain an amylase enzyme. The digestive impact of salivary amylase is short-lived, yet significant. After oral contents are swallowed, they traverse the esophagus and depot in the stomach. The optimal pH range for amylase activity is approximately 6.6 to 6.8. Therefore, once the swallowed contents are thoroughly mixed with the highly acidic gastric juice, amylase activity ceases. Virtually no carbohydrate digestion occurs in the gastric juice. Although some acid hydrolysis of sucrose may occur, it is not considered physiologically significant. Carbohydrate digestion picks up in the small and large intestines, with most of the monosaccharides being absorbed in the small intestine. **Figure 3.10** provides an overview of the carbohydrate digestion events taking place in the different parts of the digestive tract.

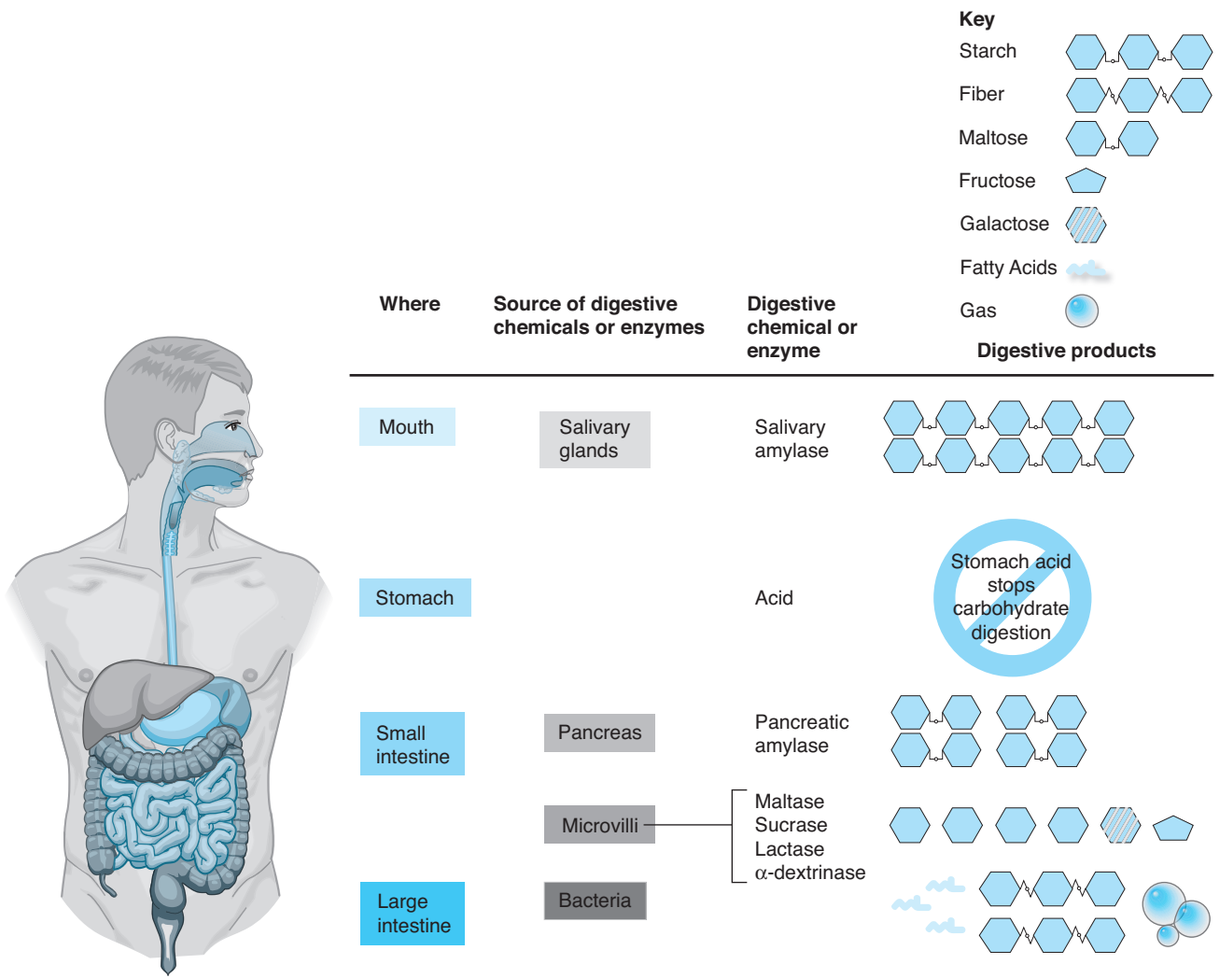


FIGURE 3.10 **Key Events Involved in Carbohydrate Digestion in Different Parts of the Digestive Tract**

Starch and Disaccharides

The major carbohydrate digestive enzyme in the small intestine is α-amylase, which is secreted by acinar cells of the pancreas. Both salivary and pancreatic amylase hydrolyze the α1–4 glycosidic linkages such that the starch consumed in a diet is converted sequentially to maltose, maltotrioses, α-dextrins, and some trace glucose. With respect to branched starch, a mixture of dextrins is generated, averaging six glucose residues per molecule and containing α1–6 linkages. These linkages are hydrolyzed by a brush border enzyme referred to as α-dextrinase or isomaltase.

The reaction that breaks down starch into α-dextrins, maltose, and maltotrioses occurs in the intestinal lumen. The remainder of carbohydrate digestion is believed to occur along the intestinal surface. When the sugars are hydrolyzed to monosaccharides, the products are therefore in close proximity to the transport proteins. Enterocytes lining the villi of the small intestine contain disaccharidases, namely **maltase, lactase**, and **sucrase**, as well as α-dextrinase. These enzymes are associated with microvilli plasma membranes, as shown in **Figure 3.11**.

Disaccharidases may not always be present in sufficient amounts to handle the digestion of disaccharides in the gut. This leads to an accumulation of the undigested disaccharide and the potential for disaccharide intolerance, with symptoms including diarrhea resulting from the increased osmotic pressure in the lumen of the gut. Furthermore, bacterial fermentation of the disaccharides can result in common symptoms such as flatulence, nausea, and bloating. This is the case in lactose intolerance (see **Special Feature 3.1**).

SPECIAL FEATURE 3.1

Lactose Intolerance

Any medical situation that damages the intestinal mucosa by preventing cell proliferation of the enterocytes, such as protein energy malnutrition or celiac disease, can produce a brush border enzyme deficiency. The most well-known and widespread disaccharidase deficiency condition is lactase deficiency, which produces lactose intolerance. Lactase deficiency has been reported in approximately 55% of Mexican American males, 74% of adult Mexicans from rural Mexico, 45% of Greeks, 56% of Cretans and 66% of Greek Cypriots, 68.8% of Jewish individuals living in North America, 50% of Indian adults and 20% of Indian children, 45% of African American children, and 80% of Alaskan Eskimos. Caucasians and those of Scandinavian descent normally have a lower prevalence of lactose intolerance than Asian adults. In fact, there are more individuals who are lactose intolerant than lactose tolerant.

Lactase begins to be synthesized in fetal life and is at its maximal activity at birth. At the time of weaning, lactase activity may have dropped to about 90% of the level of activity at birth. The decline in lactase activity is not a function of lactose in the diet, as was once popularly believed. It is more likely a genetically controlled event. Individuals who are tolerant are thought to have inherited the gene as a dominant gene from a genetic mutation. Those individuals who have the enzyme are descendants of some African and Middle Eastern tribes and Northern Europeans. Also the genetic adaptation is thought to be related to the development of dairy farming in these regions.

Despite the problem of lactose intolerance, milk consumption need not be discouraged in susceptible populations. In most studies, 250 milliliters (approximately 1 cup) of milk, which normally contains 12 grams of lactose, does not cause adverse effects. The drinking of milk by children should not be discouraged unless it causes severe diarrhea. Dairy products in which the lactose is prehydrolyzed, or in which *Lactobacillus acidophilus* was added during processing to hydrolyze the lactose, are available. Lactase enzyme tablets can also be added to milk to help digest the lactose. Fermented foods such as yogurt have bacteria that can digest lactose. Foods such as cottage cheese and aged cheddar cheese contain low levels of lactose and are not likely to produce problems.

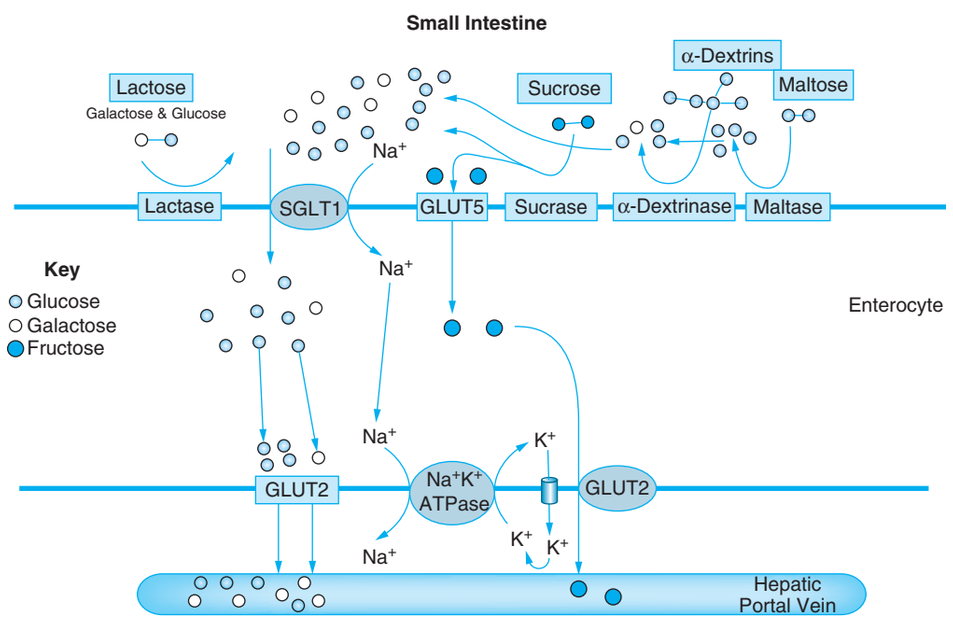


FIGURE 3.11 Absorption of Glucose and Galactose Across the Small Intestinal Mucosa. Both glucose and galactose bind to a transmembrane protein (SGLT1) that also binds sodium. The energy from sodium moving down its concentration gradient is sufficient to transport glucose into the cell against its concentration gradient. Sodium is then pumped out of the cell by adenosine triphosphatase (ATPase).

Absorption of Monosaccharides

The absorptive cells of the small intestinal lining absorb some hexoses at a greater rate than others. Galactose and glucose are known to be actively absorbed against a concentration gradient, whereas others, such as fructose, are not (**Figure 3.11**). Apparently, the basic requirement for active transport is based on the presence of the six-carbon structure and an intact OH group at position 2. Oxygen and sodium are required, and selective metabolic inhibitors can block the active transport. Absorption takes place against a concentration gradient, and the transport is selective, with some sugars transported at a greater rate than others. With glucose transport serving as the reference standard (1.0), the rate of galactose transport appears to be slightly greater (1.1), whereas the transport rates of fructose (0.4), mannose (0.2), xylose (0.15), and arabinose (0.10) are lower.

Glucose and galactose seem to compete with one another for absorption aboard a common transporter called SGLT1 (**S**odium/**Gl**ucose co**T**ransporter 1). As mentioned, both of these monosaccharides are absorbed by active transport, as will be discussed soon. However, fructose is absorbed by facilitative diffusion utilizing **GLUT5** (**Glu**cose **T**ransporter 5). Thus, fructose needs to bind to a membrane protein carrier, as well as move down a concentration gradient. Mannose, xylose, and arabinose are also absorbed by passive diffusion.

SGLT1, sodium, and energy in the form of ATP are required for active transport of glucose and galactose. The sodium-gradient hypothesis states that glucose or galactose will associate with SGLT1 on the microvilli membrane, which also has a binding site for sodium (see Figure 3.11). The energy released by sodium moving down its concentration gradient into the cell is sufficient to also move glucose into the cell against its concentration gradient. Sodium is subsequently pumped out of the cell by ATPase to maintain the gradient. Two sodium ions are required for each monosaccharide transported.

Once inside the cell, 15% of the monosaccharides leak back out through the brush border, 25% diffuse through the basolateral membrane, and 60% leave on the serosal side through a carrier mechanism; all of these mechanisms are independent of sodium. Because of these multiple exit avenues, monosaccharides such as glucose and galactose do not accumulate within enterocytes at significant levels. Most of the absorption of monosaccharides occurs in the upper portion of the small intestine. The trioses and tetrasaccharides are absorbed through passive diffusion.

BEFORE YOU GO ON . . .

1. Where are the primary locations of carbohydrate digestion and absorption?
2. What are the key carbohydrate digestion enzymes, and where are they produced?
3. What are the key mechanisms involved in the absorption of monosaccharides?
4. What is the cause of lactose intolerance?
5. What makes fructose different from glucose and galactose with regard to the mechanism of absorption?

Carbohydrate Circulation and Cellular Uptake

All cells can use glucose for energy purposes. This means that glucose must have a means of crossing the plasma membrane. Also, because carbohydrate can be used as an immediate source of energy, stored as glycogen or fat, or used to make certain amino acids or other molecules, several factors must direct its use inside of cells. This section provides an overview of the major metabolic pathways involved in carbohydrate metabolism.

Blood Glucose Regulation

Glucose must continuously circulate in the blood in order to serve as a fuel resource for cells. A blood glucose concentration of 70 to 110 milligrams per 100 milliliters is typical in a fasting state. This would equate to roughly 5 grams of glucose in circulation given a total blood volume of 5.5 liters. However, the level of circulating glucose can increase after eating a meal or decrease during fasting based on changes in supply and demand. Several hormones are employed to control blood glucose levels, with the most significant being insulin, glucagon, epinephrine, and cortisol.

Insulin promotes cellular events that work to lower blood glucose level when it is elevated (**hyperglycemia**). Meanwhile, glucagon, epinephrine, and cortisol coordinate tissue operations in an attempt to raise blood glucose level when it declines (**hypoglycemia**), such as during fasting and times of increased glucose demand (e.g., exercise, stress). By and large, these hormones and other factors control blood glucose levels by regulating metabolic pathways involved in glycogen production and

breakdown, glucose utilization for energy, and glucose production from other energy molecules. The term **euglycemia** is used to denote the achievement and maintenance of an optimal fasting blood glucose level despite changing nutrition and metabolic states.

Glycemic Index

Glycemic index has become an important concept in general nutrition. Simply put, **glycemic response** refers to the degree and duration to which blood glucose level is elevated after consuming a portion of food that would provide 50 grams of digestible (available) carbohydrates and measured (the area under the curve [AUC]) for the next 2 hours following the meal (**Figure 3.12**). The **glycemic index** of a food is simply the comparison of its glycemic response to a food standard based on studies of healthy people. Glucose and white bread are used as the standards. For instance, if a food raises blood glucose level to 50% of the rise caused by glucose, then the glycemic index of that food is 50. **Table 3.4** lists the glycemic index of several foods.

Because there are obvious differences between white bread and pure glucose, glycemic indexes determined for foods using these different standards can vary. The glycemic index scale is 0 to 100 when using glucose as the standard; this scale is more common because it is easier to understand and apply. Meanwhile, when white bread is used as the standard, the scale can be a little less user-friendly, because some foods, such as baked potatoes, rice cakes, and many breakfast cereals, will have a glycemic index exceeding 100.

The glycemic index of a food is influenced by several factors, including carbohydrate type and other nutrients that can influence rate of digestion or absorption. Because only half of the monosaccharide units in lactose and sucrose are glucose, whereas all of the monosaccharides in starch are glucose, this suggests that "starchy" foods such as a baked potato might have a higher glycemic index than milk and dairy foods and many "sugary" foods such as candies. Fruits and honey with high fructose content only have a moderate impact on blood glucose. Meanwhile, the level of protein, fat, and fiber in a food can lower the glycemic index of a food by slowing the rate of digestion and absorption of monosaccharides. If monosaccharides are absorbed more slowly, there is more opportunity for the liver to remove them before they reach the general circulation. This helps explain why whole wheat bread can have a lower glycemic index than white bread.

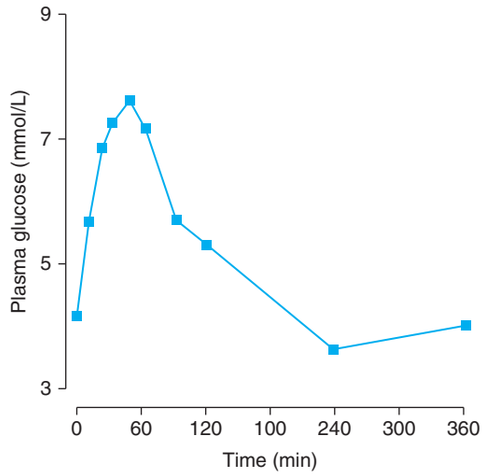


FIGURE 3.12 Typical Glucose Tolerance Curve to Measure Glycemic Response. The area under the curve (AUC) represents the rise and subsequent lowering of blood glucose levels by insulin and tissue processing after consuming a 50-gram glucose source.

Glycemic Load

The concept of glycemic index is simple to grasp; however, it is not always easy to apply to how people tend to eat. One issue with glycemic index is that the amount of food used to determine it is not the amount typically consumed by people. For instance, boiled carrots have a glycemic index of about 90; however, it would take over 10 cups of carrots to achieve the 50 grams of carbohydrate needed for the glycemic index test. For this and other reasons, a second glycemic measure more appropriate for the real world, called **glycemic load**, is used.

Glycemic load is basically glycemic index normalized to serving standards. A food's glycemic load is derived by multiplying a food's glycemic index by the amount of digestible carbohydrate in a serving and then dividing by 100. For instance, carrots have a glycemic index of 90, which, multiplied by 4 (the grams of digestible carbohydrate in 1 cup) and divided by 100, gives one a glycemic load of roughly 4. See Table 3.4 for a listing of the glycemic loads of common foods relative to their glycemic index.

Foods with a higher glycemic index (and, more applicably, glycemic load) may be undesirable food choices for people with chronic hyperglycemia (e.g., diabetes mellitus). First, the higher glycemic index food can worsen a hyperglycemic state. Second, further elevation of circulating glucose could lead to an increase in the level of

TABLE 3.4 Glycemic Index and Glycemic Load Levels

Level	Glycemic Index	Glycemic Load	Glycemic Load/Day
Low	≤55	≤10	<80
Medium	56–69	11–19	80–120
High	≥70	≥20	>120

Food	Glycemic Index	Glycemic Load	Food	Glycemic Index	Glycemic Load
All-bran cereal	42	8	Peanuts	14	1
Apple juice	40	11	Pears	38	4
Apples	38	6	Pineapple	59	7
Bananas	52	12	Pinto beans	39	10
Beets	64	5	Popcorn	72	8
Buckwheat	54	16	Potatoes (new)	57	12
Cantaloupe	65	4	Potatoes (Russet, baked)	85	26
Carrots	47	3	Rice, white	64	23
Cheerios cereal	74	15	Rice, wild	57	18
Corn Flakes cereal	81	21	Sourdough wheat bread	54	15
Couscous	65	23	Spaghetti	42	20
Fettuccini	40	18	Strawberries	40	1
Grapes	46	8	Sucrose (table sugar)	68	7
Green peas	48	3	Shredded Wheat cereal	67	13
Kidney beans	28	7	Sweet corn	54	9
Life cereal	66	16	Sweet potatoes	61	17
Linguine	52	23	Watermelon	72	4
Macaroni	47	23	Whole wheat flour bread	71	9
Navy beans	38	12	White wheat flour bread	70	10

circulating insulin (**hyperinsulinemia**). For many hyperglycemic people, insulin may already be circulating at normal or elevated levels relative to the blood glucose concentration. Chronic hyperinsulinemia is associated with elevated blood lipids (hypercholesterolemia and hypertriglyceridemia), blood pressure, and body fat.

Glucose Transport into Cells

Glucose moves across human cell plasma membranes by facilitative diffusion via **glucose transport proteins** (**GLUT**). At least six glucose transport proteins have been described in detail at this time, each varying in its operational properties as well as the types of cells in which it is expressed (**Table 3.5**). GLUT1 is the most widely expressed isoform and provides most cells with their basal glucose requirements. GLUT1 is expressed in higher amounts in epithelial cells and the endothelium of barrier tissue such as the blood–brain barrier. GLUT2 is produced in higher amounts in hepatocytes, pancreatic β-cells, and the basolateral membranes of intestinal and renal epithelial cells. This glucose transport protein is a high-K_m isoform, meaning that it is most active when more glucose is available, such as during hyperglycemia. Meanwhile, GLUT3 is responsible for glucose transport in neurons and has a relatively low K_m to ensure glucose supply, even during hypoglycemia.

GLUT4 is expressed in insulin-sensitive cells such as adipocytes and cardiac and skeletal muscle cells and is primarily responsible for reducing elevated blood glucose levels (**Figure 3.13**). Here, insulin binds to its receptor and sets in play a series of phosphorylation steps that lead to the translocation of GLUT4 to the plasma membrane. GLUT5 is a fructose transporter expressed

TABLE 3.5 Major Glucose Transport (GLUT) Proteins in Tissue

Protein	Tissue	Properties/Characteristics
GLUT1	Most cells	Low K_m (1–2 mM) Ensures glucose uptake during hypoglycemia
GLUT2	Pancreatic β-cells, renal tubular cells, small intestinal basolateral epithelial cells that transport glucose, liver cells, hypothalamus	High K_m (15–20 mM)
GLUT3	Expressed mostly in neurons, placenta, testes	Low K_m (1 mM) Very high affinity Probable main glucose transporter in neurons
GLUT4	Skeletal muscle fibers, adipose tissue, cardiac muscle cells	High K_m (5 mM) Insulin regulated to help regulate hyperglycemia
GLUT5	Mucosal surface of small intestine cells, hepatocytes, sperm, skeletal muscle fibers	Low K_m (1–2 mM) Fructose transporter
GLUT7	Hepatocytes	Transports glucose out of the endoplasmic reticulum after final step in gluconeogenesis

in greater amounts in spermatozoa and the apical membrane of intestinal enterocytes and, to a lesser degree, skeletal muscle. GLUT7 is a glucose transporter found on the endoplasmic reticulum membrane; it transports free glucose into the cytosol after the action of glucose-6-phosphatase upon glucose-6-phosphate. This is of particular importance to hepatocytes during glycogen breakdown because it allows for glucose liberation (from phosphate) for subsequent release into circulation.

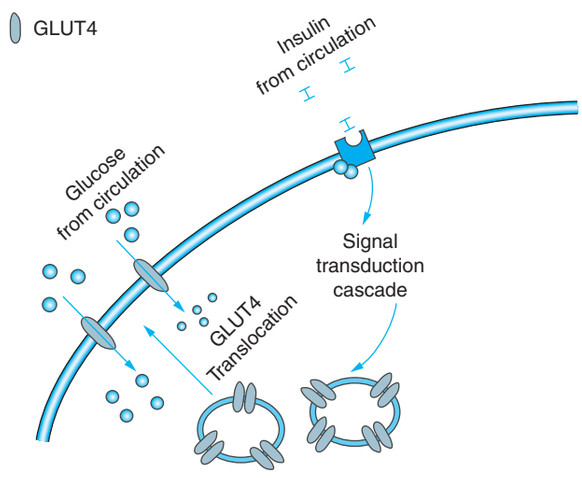


FIGURE 3.13 Insulin Interaction with Insulin Receptors and Translocation of GLUT4 to Cell Plasma Membranes to Bring Glucose into Cells. The binding of insulin to its receptor results in a series of phosphorylation of signaling factors that ultimately leads to the translocation of GLUT4 to the plasma membrane.

Glucose is the principal energy source of the brain. Delivery of glucose to brain tissue requires transport across the endothelial cells of the blood–brain barrier and then into neurons and glial cells (collectively referred to as glia). GLUT1 has been determined to be in higher concentration in the brain, with variations in the degree of glycosylation in neurons and in the blood–brain barrier. GLUT3 is also concentrated in neurons, and GLUT5 in microglia. GLUT2, GLUT4, and GLUT7 have also been detected in the brain, but at lower concentrations.

Glucose transport across the plasma membrane of muscle (skeletal and cardiac) has additional considerations beyond the presence of insulin and the mobilization of GLUT4 transporters. Glucose transport is increased by alterations in the metabolic condition of muscle cells. In the heart, glucose transport can be increased by more powerful contractions, increased levels of circulating epinephrine and growth hormone, and intracellular AMP and ADP. Meanwhile, skeletal muscle contraction leads to an augmentation in glucose transport that is independent of insulin. This is important because insulin release is dampened during moderate to intense exercise. Muscle cell contractile activities result in an increase in intracellular Ca^{2+} content, which has been suggested to be associated with the translocation of GLUT4 from the intracellular pool to the plasma membrane.

Monosaccharide Activation

Free monosaccharides are found in low concentration in cells because they are quickly utilized or assimilated into

stores. For a monosaccharide to be metabolized within a cell, it must be phosphorylated (i.e., have a phosphate attached). For example, glucose-6-phosphate is created in the first step of glycolysis from free glucose entering a cell. Not only does this serve to activate the monosaccharide, but also it "locks" the monosaccharides within certain cells, such as hepatocytes. Glucose-6-phosphate is readily active and tends not to accumulate within a cell.

BEFORE YOU GO ON . . .

1. What is glycemic index, and how is it measured?
2. How does glycemic load differ from glycemic index? How can both be applied to people and populations?
3. What are glucose transport proteins, and what cell types produce different isoforms?
4. What are the steps involved in GLUT4 movement to cell membranes?
5. What is the purpose of activating monosaccharides upon entering cells?

Major Hormones in Carbohydrate Metabolism

The metabolism of carbohydrate is regulated by individual hormone levels and their relative ratios. Among the most significant hormones are insulin, which tends to elicit an anabolic effect on carbohydrates, thus increasing cellular uptake and building stores; and glucagon, epinephrine, and cortisol, which tend to have an opposite effect.

Insulin

Insulin is a polypeptide produced in β-cells of pancreatic islets and consists of two chains (A and B) linked by disulfide bonds (**Figure 3.14**). The A chain consists of 21 amino acids, the B chain consists of 30 amino acids, and the disulfide bonds arising from cysteine residues are located at A7–B7 and A20–B19. A disulfide bond also exists between cysteine residues between A6 and A11. Although there is some variation in the insulin amino acid sequence between mammalian species, the positioning of the three disulfide bonds seems invariant.

Insulin Production

Insulin is synthesized (via protein translation) as preproinsulin, which has a molecular weight of 11,500. Posttranslational modification begins with the cleavage of the 23–amino acid pre- or leader sequence, resulting in proinsulin, which has a molecular weight of approximately 9,000. The cleaved leader sequence is necessary for guiding preproinsulin into the endoplasmic reticulum during synthesis. Cleavage of the leader group also allows for the appropriate conformation for the formation of disulfide linkages.

Proinsulin then moves to the Golgi apparatus. In the Golgi apparatus, proinsulin begins conversion to mature insulin, or simply insulin, which involves the removal of a stretch of amino acids in the central portion of the proinsulin polypeptide. The removed amino acid sequence is called C peptide, and the remaining, once flanking, amino acid sequences are the A chain and B chain, which are secured by disulfide bonds. This process continues after

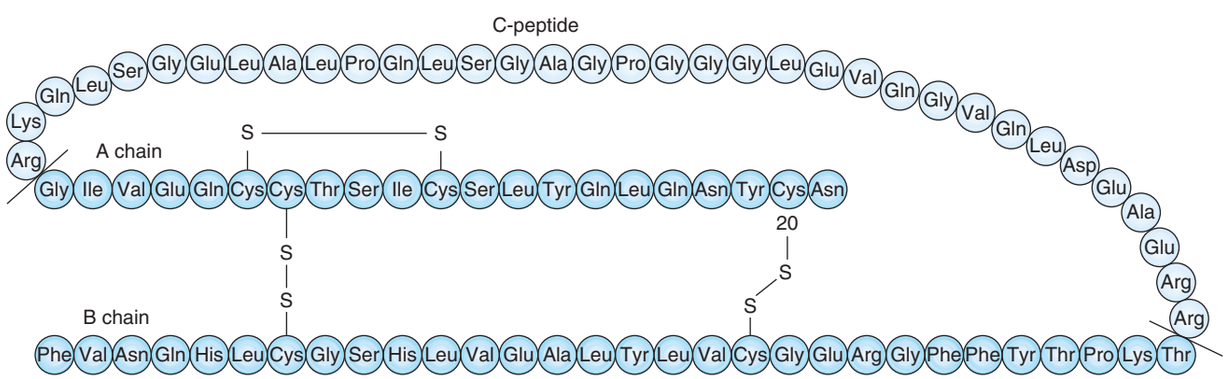
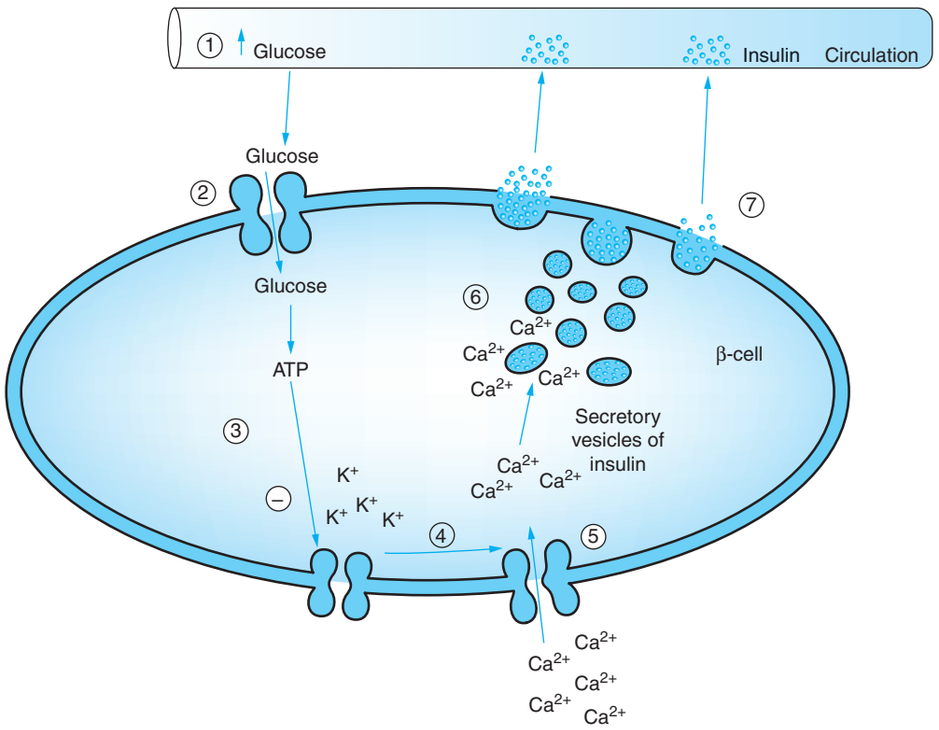


FIGURE 3.14 **Amino Acid Sequence of Insulin A and B Chains and Location of Disulfide Bonds**



① Blood glucose levels increase (e.g., meal)
② Glucose uptake via GluT2
③ ATP formation through glucose utilization inactivates potassium channels
④ β-cell membrane becomes depolarized due to accumulation of potassium ions
⑤ Calcium channel opens and calcium diffuses into cell
⑥ Calcium promotes fusing of insulin secretory vesicles with plasma membrane
⑦ Insulin diffuses into circulation

FIGURE 3.15 Release of Insulin from Pancreatic β-Cells via Fusion of Secretory Vesicles with Plasma Membrane

vesicles bud from the Golgi apparatus and traverse the cytoplasm toward the plasma membrane and conversion of proinsulin to insulin is typically about 95% complete. Upon stimulus, the secretory vesicles will fuse with the plasma membrane to release insulin into the intercellular space (**Figure 3.15**).

Insulin Secretion

Insulin and proinsulin combine with zinc within secretory granules and form hexamer structures. The secretory vesicles then fuse with the plasma membranes of β-cells, releasing insulin, proinsulin, and C peptide into the extracellular space. These molecules are then free to diffuse into the blood. Proinsulin has less than 5% of the bioactivity of insulin, and C peptide has none. The half-life of insulin is 3 to 5 minutes, whereas the half-life of proinsulin is much longer. Insulin is metabolized primarily in the liver, kidneys, and placenta. About 50% of circulating insulin is removed in a single pass through the liver.

On a daily basis, the adult pancreas secretes about 40 to 50 units of insulin, which represents about 15% to 20% of that which is available in secretory vesicles. A unit is equal to 45.5 micrograms of crystalline insulin. The release of insulin is an energy-dependent process, and the strongest stimulus is an elevation in plasma glucose concentration. The threshold concentration for secretion is

about 80 to 100 milligrams per 100 milliliters, and a maximal response occurs when blood glucose concentration is approximately 300 to 500 milligrams per 100 milliliters of blood.

Secretion of insulin via rising glucose levels can be influenced by several factors. For instance, α-adrenergic agonists such as norepinephrine via autonomic innervation and circulating epinephrine can dampen glucose stimulation of insulin release, which can be important for controlling blood glucose levels during more strenuous exercise and stressful events. In addition, insulin secretion is increased by chronic exposure to growth hormone, estrogens, and progestins. Thus, it is not surprising to find insulin secretion elevated during the last trimester of pregnancy.

Insulin-Mediated Glucose Uptake

Insulin promotes the lowering of blood glucose concentration by several means. In adipose tissue and skeletal muscle, which collectively constitute approximately 50% to 60% of the tissue in the adult body, insulin increases the number of glucose transporters at the plasma membrane face. These transporters, particularly GLUT4, are assumed to be mobilized from an inactive intracellular pool (see Figure 3.13). Increased glucose entry into hepatocytes appears to occur by increasing the activity of glucokinase. Once glucose enters hepatocytes (via GLUT1) it is quickly phosphorylated by glucokinase, thus maintaining a concentration gradient that favors further influx of free glucose from circulation. Similarly, the activity of skeletal muscle hexokinase II, which also catalyzes the phosphorylation of glucose, is increased due to insulin.

The actions of insulin on increased glucose entry are somewhat special to certain cell types, such as adipocytes, skeletal and cardiac myocytes, and hepatocytes. Most other cells in the body demonstrate a more consistent uptake of glucose from circulation based on their metabolic needs and glucose availability. This is explained by the variety of glucose transporter proteins. Insulin also promotes the uptake of certain amino acids into cells, especially muscle cells.

Metabolic Roles of Insulin

Insulin not only increases the uptake of glucose and amino acids into certain types of cells, but also strongly influences energy nutrient metabolic pathways within cells as well (**Table 3.6**). Insulin promotes increased activities of glycolysis, the pentose phosphate pathway, glycogen formation (glycogenesis), and fatty acid synthesis (lipogenesis). Insulin inhibits glucose formation via glycogen breakdown (glycogenolysis) and the conversion from noncarbohydrate molecules (gluconeogenesis). Furthermore, insulin inhibits fat breakdown (lipolysis) and fatty acid oxidation in adipocytes and hepatocytes, while at the same time supporting protein synthesis in skeletal muscle and other tissue. Generally, insulin influences the associated pathways by either activating or deactivating key enzymes or influencing events of transcription or translation or both. In these ways, insulin is believed to influence either the quantity or activity of at least 50 different enzymes.

TABLE 3.6 Actions of Insulin, Glucagon, Cortisol, and Epinephrine in Carbohydrate Metabolism

Hormone	Actions
Insulin	Increases the uptake of glucose by skeletal muscle and adipocytes Increases the synthesis of glycogen in skeletal muscle and liver hepatocytes Increases fatty acid synthesis from excessive dietary carbohydrate Decreases fat breakdown and mobilization from adipose tissue
Glucagon	Increases glycogen breakdown in liver Increases liver glycogen-derived glucose release into blood Increases glucose manufacturing in liver Increases fat breakdown and mobilization from adipocytes
Epinephrine (adrenalin)	Increases glycogen breakdown in liver hepatocytes and skeletal muscle Increases liver glycogen-derived glucose release into blood Increases fat breakdown and mobilization from adipocytes
Cortisol (stress hormone)	Increases skeletal muscle protein breakdown to amino acids (alanine and glutamine can circulate to the liver and be used for gluconeogenesis) Increases gluconeogenesis and liver glucose release into blood Increases fat breakdown and mobilization from fat tissue Increases glycogen content in liver

The net effect of insulin is to decrease the circulatory concentration of glucose. In this sense, insulin stands alone, and its general actions are opposed by several hormones, such as glucagon, epinephrine, and cortisol. The net effect of insulin is also to promote storage of diet-derived (exogenous) energy. Because the liver receives portal blood that has drained from the pancreas, it is exposed to insulin concentrations that can be 3 to 10 times greater than in the systemic circulation. The liver binds and removes a significant amount of insulin on this pass. The liver is also more sensitive to insulin, presumably because it also has greater receptor concentrations than other tissue.

Insulin Receptors

Insulin acts by first binding with an insulin receptor on the plasma membrane (see Figure 3.13), and its indirect actions can arise within seconds to minutes (nutrient transport, activation or inhibition of enzymes, RNA transcription) or hours (protein and DNA synthesis and cell growth). The insulin receptor is a heterodimer transmembrane glycoprotein. Its cytoplasmic region has tyrosine kinase activity and an autophosphorylation site. The insulin receptor gene is located on chromosome 19. Insulin receptors undergo constant turnover because their half-life is only 7 to 12 hours. Most human cells synthesize insulin receptors, with the average concentration being about 20,000 receptors per cell. This is because insulin not only governs metabolic activity but also is involved in cell growth and reproduction.

Once insulin binds to a receptor, there is a conformational change, the receptor is internalized, and one or more signals are produced. The internalization of receptors is important to regulate receptor concentration, which, in turn, helps regulate cell turnover and metabolic activities. In hyperinsulinemic situations, such as in obesity, there is reduced production of insulin receptors. Fewer receptors are produced, resulting in fewer receptors on the plasma membrane, and thus those cells become less sensitive to insulin. This results in hyperglycemia and is often the case in obesity-related type 2 diabetes mellitus.

Insulin elicits a second messenger action that culminates in a variety of intracellular events. These events begin with the activity of tyrosine kinase, which results in an increase in tyrosine phosphorylation in both the receptor itself as well as in key intracellular proteins. This generally activates key enzymes such as guanosine triphosphatases (GTPases), lipid kinases, and protein kinases, which mediate much of insulin's metabolic impact.

Glucagon

Glucagon is produced by α-cells of pancreatic islets. It is a single-chain polypeptide consisting of 29 amino acids. Like insulin, glucagon is also synthesized in a larger prohormone form. Glucagon circulates in the plasma unbound and has a half-life of about 5 minutes. The liver is the primary site of glucagon inactivation. Because pancreatic endocrine secretions drain into the hepatic portal vein, much of the secreted glucagon is actually metabolized without ever reaching the systemic circulation. Glucagon secretion is associated with hypoglycemia, and inhibition of secretion is associated with hyperglycemia. The exact inhibitory mechanisms are unclear. It could be a more direct inhibition via increased glucose reception, or a more indirect inhibition via insulin or insulin-related events, or a combination of these or associated events. Other stimulators may include some amino acids, particularly glucogenic amino acids such as alanine, serine, glycine, cysteine, and threonine. These amino acids are important sources of glucose via gluconeogenesis. This also means that a protein-containing meal can, in theory, stimulate glucagon release, concomitant to stimulating insulin release.

Whereas the influence of insulin is diverse, glucagon focuses its actions mainly on the liver and adipose tissue (see Table 3.6). The binding of glucagon to glucagon receptors on the plasma membrane of hepatocytes results in an increase in intracellular cAMP. The activation of phosphorylase by cAMP promotes glycogen degradation while also inhibiting glycogen synthesis. Furthermore, glucagon promotes the conversion of noncarbohydrate molecules to glucose in hepatocytes. In adipose tissue, glucagon promotes lipolysis principally by activating the enzyme hormone-sensitive lipase. As with hepatocytes, the binding of glucagon to receptors on the plasma membrane of adipocytes initiates a second messenger cascade that begins with the activation of adenylyl cyclase through a G-protein-linked mechanism and produces increased cAMP levels, as discussed later in this chapter.

Skeletal muscle cells do not make glucagon receptors. Thus, glycogenolysis in skeletal muscle is not influenced by glucagon; it is primarily influenced by epinephrine and to a lesser degree norepinephrine. In general, glucagon is gluconeogenic, glycogenolytic, and ketogenic in hepatocytes and lipolytic in adipocytes.

Insulin-to-Glucagon Molar Ratios

Because many aspects of energy nutrient metabolism promoted by either insulin or glucagon are antagonistic

in nature, the molar ratio of these two hormones is the dominating factor in determining net metabolic activity. For instance, in hepatocytes and skeletal muscle the synthesis of glycogen can and will occur concurrent with the breakdown of glycogen. However, the algebraic net effect is dictated largely by the relative influences of insulin and glucagon and, to a lesser degree, other hormones, such as epinephrine and cortisol. An insulin-to-glucagon ratio of 2.3:1 may be expected from the consumption of a balanced meal. Meanwhile, the infusion of arginine increases the secretion of both hormones, but more so for insulin, which results in a ratio approximating 3:1. Conversely, if a glucose solution is infused into circulation, a ratio of 25:1 can be expected.

Epinephrine

Epinephrine (adrenalin) is produced in the adrenal glands (adrenal medulla) from the amino acid tyrosine, which itself can be synthesized from the essential amino acid phenylalanine. Intermediates of the synthesis of epinephrine include dopa, dopamine, and norepinephrine (noradrenaline). Epinephrine, norepinephrine, and dopamine are important molecules in the response to stress. They are synthesized in chromaffin cells and stored in secretory granules. Epinephrine is the principal catecholamine synthesized in chromaffin cells of the adrenal medulla, constituting 80% of the total catecholamine production.

The conversion of dopamine to norepinephrine is catalyzed by the copper-containing enzyme dopamine β-hydroxylase (DBH). DBH requires ascorbate (an electron donor) and copper at the active site. Meanwhile, phenylethanolamine-*N*-methyltransferase (PNMT) catalyzes the production of epinephrine from norepinephrine (**Figure 3.16**). Synthesis of PNMT is induced by glucocorticoid hormones that reach the medulla, via a portal vein, from the adrenal cortex.

The incorporation of catecholamines into secretory granules is an ATP-dependent transport mechanism. The granules also contain ATP-Mg^{2+}, Ca^{2+}, and DBH. Once inside the granule, epinephrine complexes with ATP in a 4:1 ratio. Secretory granules fuse with the plasma membrane upon appropriate neural stimulation. β-Adrenergic and cholinergic agents stimulate fusion, whereas α-adrenergic agents inhibit it. Catecholamines circulate loosely bound to albumin and have a half-life of about 10 to 30 seconds. Catecholamines are metabolized by catechol-*O*-methyltransferase (COMT) and monoamine oxidase (MAO), which are found in many tissues.

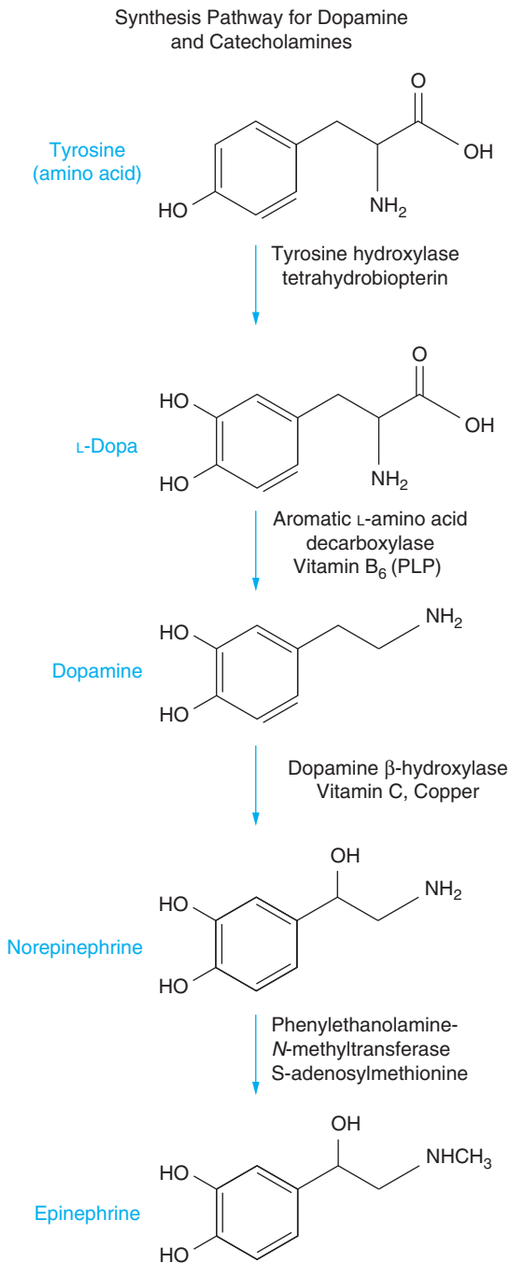


FIGURE 3.16 Steps Involved in the Production of Epinephrine and Norepinephrine

The effects of epinephrine are mediated via its reception by two classes of receptors. Alpha and β receptors are subdivided into α_1 and α_2 and β_1 and β_2. This classification system is based on binding affinity of the different receptors for catecholamines. When epinephrine binds

to β_1 on cardiac tissue, the force and rate of contraction are increased. Furthermore, the binding of epinephrine to β_2 receptors elicits smooth muscle relaxation and thus vasodilation in skeletal muscle and the liver. Meanwhile, the interaction with α_1 receptors results in contraction in some smooth muscle.

The effects of epinephrine include the breakdown of glycogen in skeletal muscle and the liver and fat breakdown in adipose tissue (see Table 3.6). This serves to make fuel available for skeletal muscle and the heart during times of increased activity.

Cortisol

Cortisol is produced in the adrenal cortex and is the principal glucocorticoid in humans. It is derived from cholesterol and circulates in the blood bound predominantly to corticosteroid-binding globulin (CBG), which is produced in the liver and to a minor degree loosely associated with albumin. The binding of cortisol to a plasma protein allows for a longer half-life (60 to 90 minutes) than the polypeptide hormones discussed previously. Cortisol is principally removed and metabolized by the liver.

Cortisol has widespread effects in the human body, and greater secretion is associated with stress and fasting, whereby it mediates adaptive processes. Cortisol then plays a significant role in carbohydrate, protein, fat, and nucleic acid metabolism. Cortisol and its structural analogues (e.g., hydrocortisone) are also used clinically as anti-inflammatory agents because they inhibit the migration of polymorphonuclear leukocytes, monocytes, and lymphocytes at the site of inflammation.

In the liver, the effects of cortisol are largely anabolic (see Table 3.6). Cortisol promotes gluconeogenesis in hepatocytes by binding to intracellular receptors and inducing the production of a number of enzymes involved in gluconeogenesis as well as amino acid transamination. Additionally, glucose-6-phosphatase activity is increased, allowing for more glucose to leave the liver to serve as fuel for other tissue. Cortisol also promotes glycogen synthesis in the liver. This effect most likely occurs to maintain at least basal levels of glycogen stores during times when it could easily become exhausted (i.e., extended fasting, stress). However, it should be noted that during hypoglycemia the impact of glucagon will supersede cortisol, and the net effect will be a breakdown of liver glycogen.

In peripheral tissue, cortisol-induced activity appears to antagonize insulin activity. Thus, cortisol works to reduce glucose and amino acid uptake in peripheral tissue, such as skeletal muscle, to preserve circulating glucose for other tissue with obligate demands, such as red blood cells and the brain. Meanwhile, protein and nucleic acid synthesis are inhibited and protein breakdown is promoted by cortisol in more sensitive tissue (i.e., skeletal muscle and connective tissue in the skin). Free amino acids in skeletal muscle, especially alanine, become resources for gluconeogenesis in the liver via the alanine–glucose cycle.

Cortisol also promotes lipolysis in adipose tissue, thereby allowing free fatty acids to be mobilized to serve as fuel for tissue throughout the body. Meanwhile, cortisol promotes an increase in total white blood cell count in circulation. However, this is a net effect, because although monocytes and polymorphonuclear leukocytes are increased, eosinophils, basophils, and lymphocytes are decreased.

BEFORE YOU GO ON . . .

1. What cells in what tissue produce insulin, and how and when is it released from those cells?
2. What role does insulin play in the metabolism of energy nutrients? Is it generally anabolic or catabolic?
3. Where is glucagon produced, and what roles does it play in carbohydrate and fat metabolism?
4. What cells produce cortisol, when is it released into circulation, and how does it affect carbohydrate, fat, and protein metabolism?
5. How is epinephrine produced, and what is its role in carbohydrate and fat metabolism?

Major Metabolic Pathways for Carbohydrate

The flux of glucose and other carbohydrates through metabolic pathways is regulated in several ways. First, hormonal influences such as insulin and glucagon can alter the activity of key enzymes by phosphorylation and dephosphorylation. Second, hormonal influences can either induce or repress transcription or translation or both of key enzymes. Third, intermediates and products of the metabolic reactions as well as other substances can elicit allosteric influences on the flux of metabolic pathways.

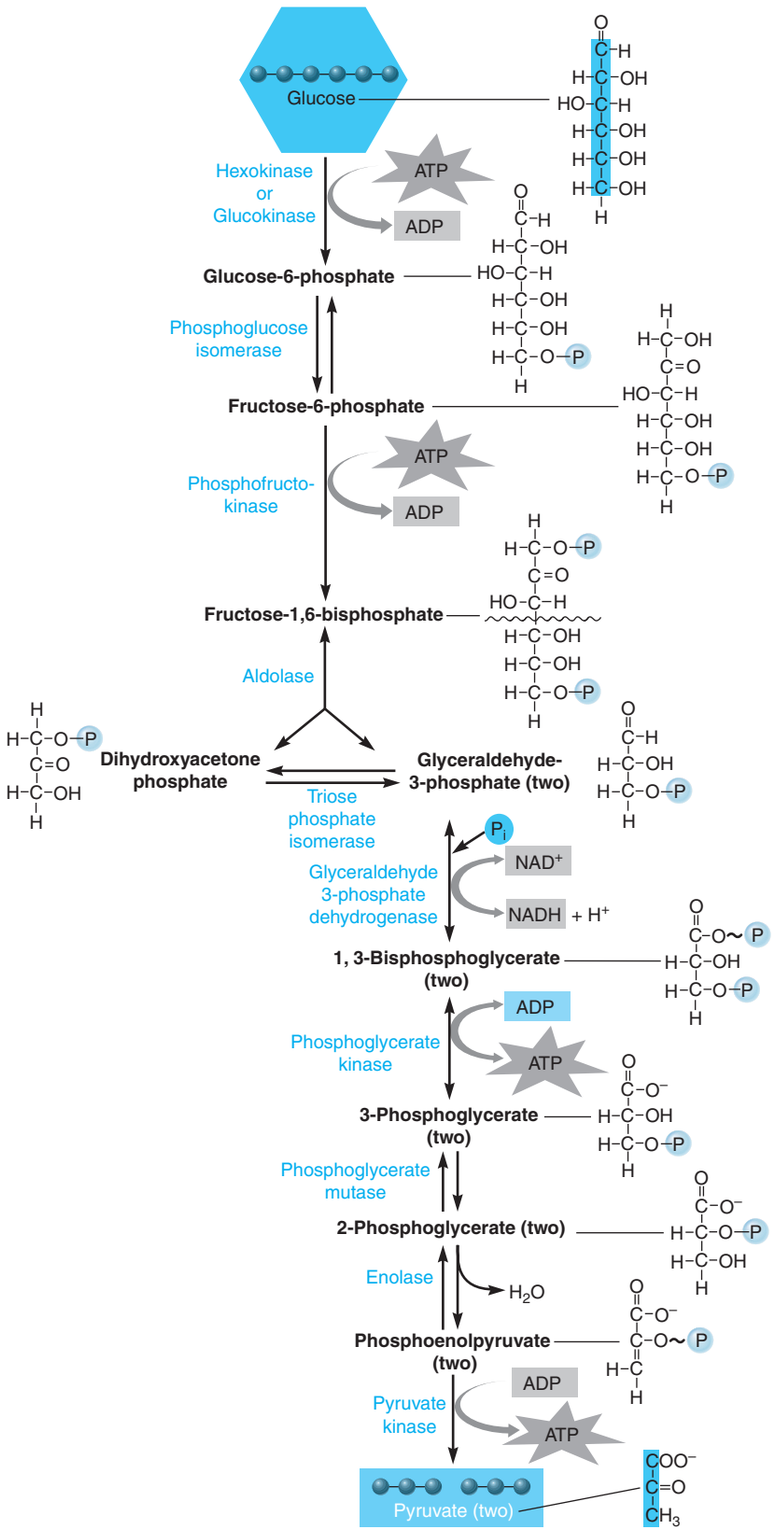


FIGURE 3.17 **Steps and Key Regulation of Glycolysis**

Most cells use more than one fuel source; red blood cells are the only true obligate glucose users. The brain is limited in its energy substrates, and under normal metabolic conditions derives nearly all of its energy from glucose as well. However, the brain can adapt to use more ketone bodies during starvation to spare blood glucose for other tissue. Conversely, tissues such as muscle, liver, and kidney are more omnivorous in their energy substrates. Here, substrate availability and hormonal influences are the greatest influential factors.

Glycolysis

Glycolysis is a series of 10 reactions that convert one six-carbon glucose molecule to two three-carbon pyruvate molecules (**Figure 3.17**). The net ATP yield of glycolysis is two ATP molecules, with the potential for two more via the glycerol phosphate shuttle, which allows for the reducing equivalents of the NADH generated in the cytosol to be transferred to mitochondrial $FADH_2$. Glycolysis also allows entry points for the catabolism of other monosaccharides, such as fructose and galactose. Glucose flux through glycolysis is regulated by several key enzymes, as described next.

Hexokinase and Glucokinase

The first influential enzymes in glucose metabolism in cells are hexokinase in all tissue and glucokinase in hepatocytes. Both enzymes phosphorylate glucose to produce glucose-6-phosphate. Hexokinase has a relatively low K_m, which allows it to operate despite a relatively low availability of glucose. However, hexokinase is inhibited by its product, glucose-6-phosphate. These regulations ensure glucose entry into all cells for glycolysis but allow it to proceed based on cell need.

In contrast, glucokinase, which is produced in hepatocytes as induced by insulin, has a relatively high K_m and is not inhibited by its product. Glucokinase allows for large quantities of glucose to enter hepatocytes during hyperglycemic states, such as a fed state. This makes sense, because the liver is a major metabolizing site for glucose during a fed state and about 50% of glucose is converted to energy in the liver, with the remaining carbohydrate converted to glycogen and fatty acids. Because both absorbed glucose from the digestive tract and insulin secreted from the pancreas perfuse the liver before entering the general, or systemic, circulation, a large portion of the absorbed glucose is transported into hepatocytes and never reaches the general circulation. This is a major point of control for blood glucose levels.

Phosphofructokinase

The activity of phosphofructokinase 1 (PFK1), which catalyzes the conversion of fructose-6-phosphate to fructose-1, 6-bisphosphate, is regulated by several factors (**Figure 3.18**). In the liver, one of the predominant factors is the activity of phosphofructokinase 2 (PFK2), an enzyme that catalyzes two opposite reactions depending on whether it is phosphorylated. PFK2 is phosphorylated when glucagon levels are elevated. Increased intracellular cAMP

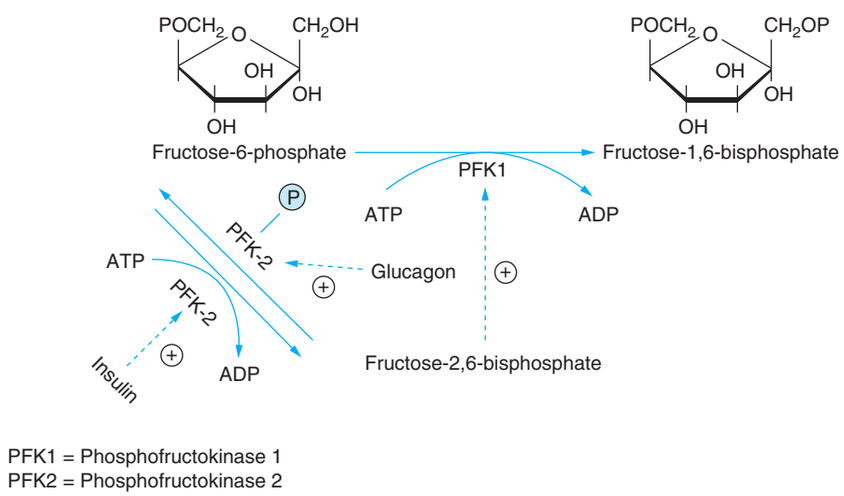


FIGURE 3.18 Activity of Phosphofructokinase 1 (PFK1). PFK1, which catalyzes the conversion of fructose-6-phosphate to fructose-1,6-bisphosphate, is regulated by several factors.

activates protein kinase A, which phosphorylates PFK2. Conversely, the phosphate group is removed, via intracellular phosphatases, when insulin levels are elevated.

The nonphosphorylated form of PFK2 catalyzes the conversion of fructose-6-phosphate to fructose-2, 6-bisphosphate, which has an activating effect on PFK1. This makes sense because elevations of both circulating insulin and hepatocyte intracellular fructose-6-phosphate occur in a fed state. The phosphorylated form of PFK2 catalyzes the conversion of fructose-2, 6-bisphosphate back to fructose-6-phosphate, thus removing the activating influence of fructose-2, 6-bisphosphate on PFK1.

As glycolysis continues, the six-carbon fructose-1, 6-bisphosphate molecule is split into two three-carbon molecules: dihydroxyacetone phosphate and glyceraldehyde-3-phosphate (Figure 3.18). Dihydroxyacetone can then be converted to glyceraldehyde-3-phosphate. Therefore, two glyceraldehyde-3-phosphate molecules can result from one molecule of fructose-1, 6-bisphosphate. The conversion of glyceraldehydate-3-phosphate to 1, 3-bisphosphoglycerate reduces NAD^+ to NADH. Therefore, two NADH molecules can be created in glycolysis from a single glucose molecule. In the next reaction, the phosphate at the number 1 position of 1, 3-bisphosphoglycerate is transferred to ADP to form ATP. This reaction can potentially happen twice for every glucose molecule that enters glycolysis. This reaction is catalyzed by phosphoglycerate kinase and produces two phosphoglycerate molecules, which are subsequently converted to phosphoenolpyruvate (PEP) by enolase.

Pyruvate Kinase

In the last reaction of glycolysis, PEP is converted to pyruvate by pyruvate kinase, which is activated by insulin. The binding of insulin to insulin receptors increases phosphatase activity, which dephosphorylates, and thus activates, pyruvate kinase. Conversely, the increased intracellular cAMP levels activate protein kinase A, which phosphorylates and deactivates pyruvate kinase. Increased cAMP can result from the binding of glucagon to glucagon receptors.

Fate of Pyruvate

Pyruvate is situated at a metabolic crossroad (**Figure 3.19**). Depending on the type of cell and hormonal and

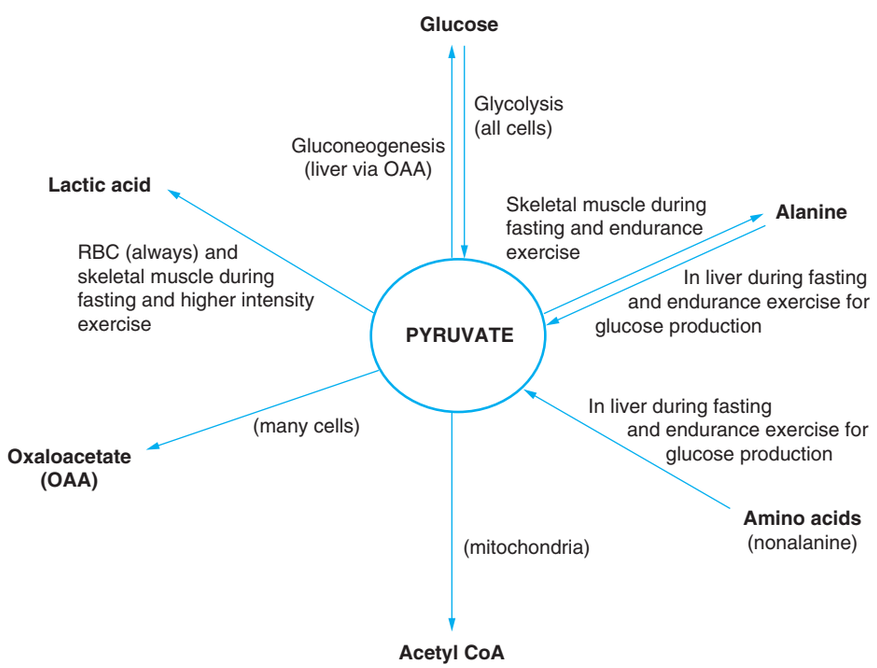


FIGURE 3.19 Pyruvate Sits at the Crossroads of Several Metabolic Pathways. Depending on the cell type and metabolic scenario, pyruvate can be used for fuel in mitochondria (via conversion to acetyl CoA), converted to lactate for exportation from a cell (e.g., red blood cell [RBC], skeletal muscle), or used to make glucose (in the liver) and the amino acid alanine (in skeletal muscle).

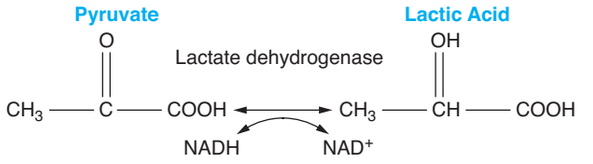


FIGURE 3.20 The Conversion of Pyruvate to Lactate. The conversion of pyruvate to lactate is a reduction reaction. In the process, NADH is oxidized to NAD^+.

metabolic influences, pyruvate can either be converted to the amino acid alanine or to lactate in the cytosol or enter mitochondria and be converted to acetyl CoA or oxaloacetate. The conversion of pyruvate to lactate is a reduction reaction, and in the process NADH is oxidized to NAD^+ (**Figure 3.20**). This negates the NADH created in glycolysis. This reaction is catalyzed in both directions by lactate dehydrogenase (LDH), which itself has five isoforms. LDH is composed of four subunits of either the heart (H) or muscle (M) type (i.e., MMMM, MMMH, MMHH, MHHH, HHHH), and different tissues express different forms. Lactate is produced in larger amounts in muscle and erythrocytes and can diffuse into the blood and serve as a gluconeogenic precursor in the liver or as an energy source for other cells.

Pyruvate in the mitochondria can be converted to acetyl CoA. Pyruvate dehydrogenase catalyzes this reaction, and NAD^+ is reduced to NADH in the process. NADH can then transfer electrons to the electron transport chain. Pyruvate dehydrogenase exists in either a phosphorylated (inactive) or dephosphorylated (active) form. The products of pyruvate dehydrogenase—acetyl CoA and NADH—activate the kinase that phosphorylates and inactivates pyruvate dehydrogenase. Conversely, CoASH (uncombined coenzyme A), NAD^+, and ADP inactivate the kinase, which keeps pyruvate dehydrogenase in an active state. Therefore, pyruvate dehydrogenase activity is controlled hormonally as well as by the metabolic state within the cell.

Glycogen Turnover

Like other bidirectional metabolic events, glycogen metabolism can be viewed as the algebraic net product of opposing operations: glycogen synthesis and glycogenolysis. It is possible, and often a reality, for these two mechanisms to operate at the same time. Thus, the governing factor becomes the relative influences of all the factors related to these operations. Some of the influences, such as metabolic products and intracellular factors (e.g., AMP, Ca^{2+}) may primarily exert their influence on only one of the two pathways, whereas others, such as hormones, can exert their influence on both pathways. For example, AMP increases glycogen degradative operations only, whereas epinephrine and glucagon both activate mechanisms involved in glycogen breakdown as well as inactivate mechanisms involved in glycogen synthesis.

Glycogen contains more branching than plant starch, with points of branching occurring every 8 to 10 residues (see Figure 3.8). One glucose unit with an exposed anomeric carbon is located at the reducing end of each glycogen molecule, and this monomer is attached to the protein glycogenin. This glucose unit functions as perhaps the anchoring and initiating point for the glycogen molecule, and it is believed that this glucose molecule is not readily available. The straight-chain oligosaccharide that extends from the reducing glucose monomer is the glycogen primer. The glucose monomers at the ends of the initial straight chain as well as branch chains are called nonreducing units; these serve as points of attachment for new monomers during synthesis and as points of removal during glycogen breakdown.

Glycogen Synthesis

Glycogen is found in several types of tissue, with the highest concentration being in hepatocytes of the liver and muscle cells (especially type II muscle fibers). The building block for glycogen is uridine diphosphate glucose (UDP-glucose), which is formed from glucose-1-phosphate, which itself is synthesized from glucose-6-phosphate (**Figure 3.21**). Insulin activates glycogen synthase, which is the key regulatory enzyme in this process. When a growing straight chain contains 11 or more glucose monomers, another enzyme, called branching enzyme or glucosyl 4:6 transferase, relocates an oligomer of about 6 to 8 monomers and reattaches it via an α1–6 linkage at what becomes a branch point.

Glycogen Degradation

Glycogen degradation (glycogenolysis) is catalyzed by the active phosphorylase (phosphorylase a) enzyme (**Figure 3.22**). This enzyme is activated by epinephrine and increased intracellular AMP levels in muscle cells. The increased presence of AMP is mostly associated with muscle cell contraction and the hydrolysis of ATP

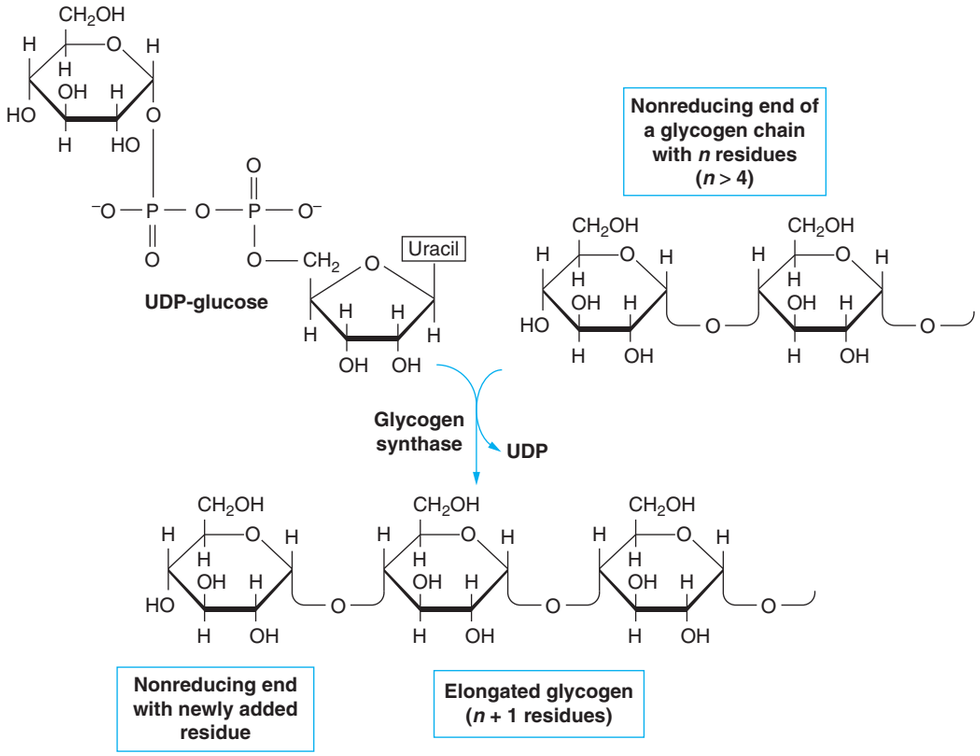


FIGURE 3.21 **Glycogen Synthesis.** The building block for glycogen is uridine diphosphate glucose (UDP-glucose), which is attached to the nonreducing end of a glycogen chain by glycogen synthase.

to ADP. As a means of regenerating ATP, a phosphate from one ADP can be transferred to another ADP via adenylate kinase, producing ATP and AMP. Meanwhile, glucagon and epinephrine both participate in the activation of phosphorylase in hepatocytes. As mentioned earlier, both epinephrine and glucagon elicit a second messenger cascade that culminates in an increased intracellular concentration of cAMP. In a chain of events, cAMP activates cAMP-dependent protein kinase, which, in turn, activates phosphylase kinase by converting it from inactive phosphorylase kinase b to the phosphorylated active phosphorylase kinase a form. Phosphorylase kinase a then can (1) activate phosphorylase (phosphorylase a), which can break down glycogen, and (2) inactivate glycogen synthase to inhibit counterproductive glycogen synthesis.

Phosphorylase a, with the assistance of vitamin B_6, detaches glucose monomers from glycogen, forming glucose-1-phosphate, which is subsequently converted to glucose-6-phosphate by phosphoglucomutase. Phosphorylase a can liberate about 90% of glucose residues from glycogen as it splits the α1–4 links (straight chain). Glucose-6-phosphate in hepatocytes can be dephosphorylated by glucose-6-phosphatase in the endoplasmic reticulum. Glucose is transported out of the endoplasmic reticulum by GLUT7 and can diffuse from the hepatocyte via GLUT2 and enter circulation. A debranching enzyme is responsible for the liberation of glucose units at branch points (approximately 10% of total glucose). The product of this activity is free glucose that can be transported out of the cell in the liver, again by GLUT2.

Pentose Phosphate Pathway

The primary importance of the **pentose phosphate pathway** (Figure 3.23) is the reduction of $NADP^+$ to NADPH, which can be used for reducing equivalents for

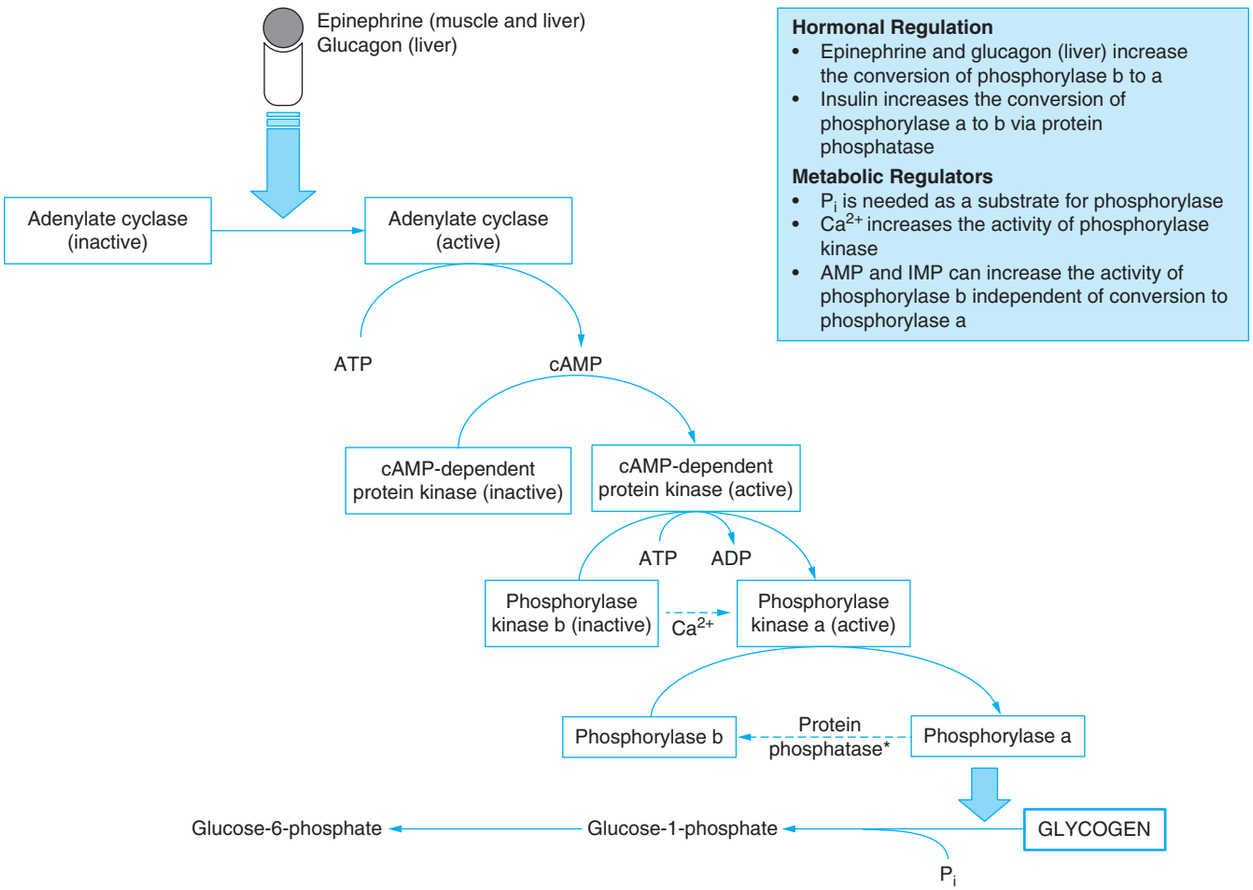


FIGURE 3.22 **Glycogenolysis.** Glycogen degradation, or glycogenolysis, begins with activation of phosphorylase. Phosphorylase activity is increased by the binding of epinephrine to receptors in skeletal muscle and liver cells (hepatocytes) and glucagon in the liver. The activation involves a cascade of steps. Phosphate (P_i), Ca^{2+}, adenosine monophosphate (AMP), and inosine monophosphate (IMP) all can increase the activity of phosphorylase, either directly or by increasing the activity of phosphorylase kinase. Active phosphorylase kinase also inactivates glycogen synthase (not shown) to minimize counterproductive glycogen synthesis.

the synthesis of certain molecules (i.e., fatty acids), **glutathione** reduction, or other reactions. Also, this reaction pathway allows for the creation of ribulose-5-phosphate, which may be isomerized to ribose-5-phosphate and used in nucleotide biosynthesis. The reactions of the pentose phosphate pathway can be described as either oxidative or nonoxidative. The oxidative reactions include the conversion of glucose-6-phosphate to phosphogluconolactone via glucose-6-dehydrogenase and the conversion of 6-phosphogluconate to ribulose-5-phosphate. Both reactions reduce $NADP^+$ to NADPH, and the latter reaction also produces CO_2. The nonoxidative reactions allow for the regeneration of the glycolytic intermediates glyceraldehyde-3-phosphate and fructose-6-phosphate.

Krebs Cycle (Citric Acid Cycle)

The Krebs cycle or citric acid cycle (**Figure 3.24**), which occurs in the mitochondrial matrix, consists of eight key sequential reactions whereby the final reaction produces the reactant for the first reaction that forms citric acid, the first product and reactant in the second reaction in the pathway. Therefore, this pathway is considered cyclic. In the reaction, acetyl CoA, which can be derived from a variety

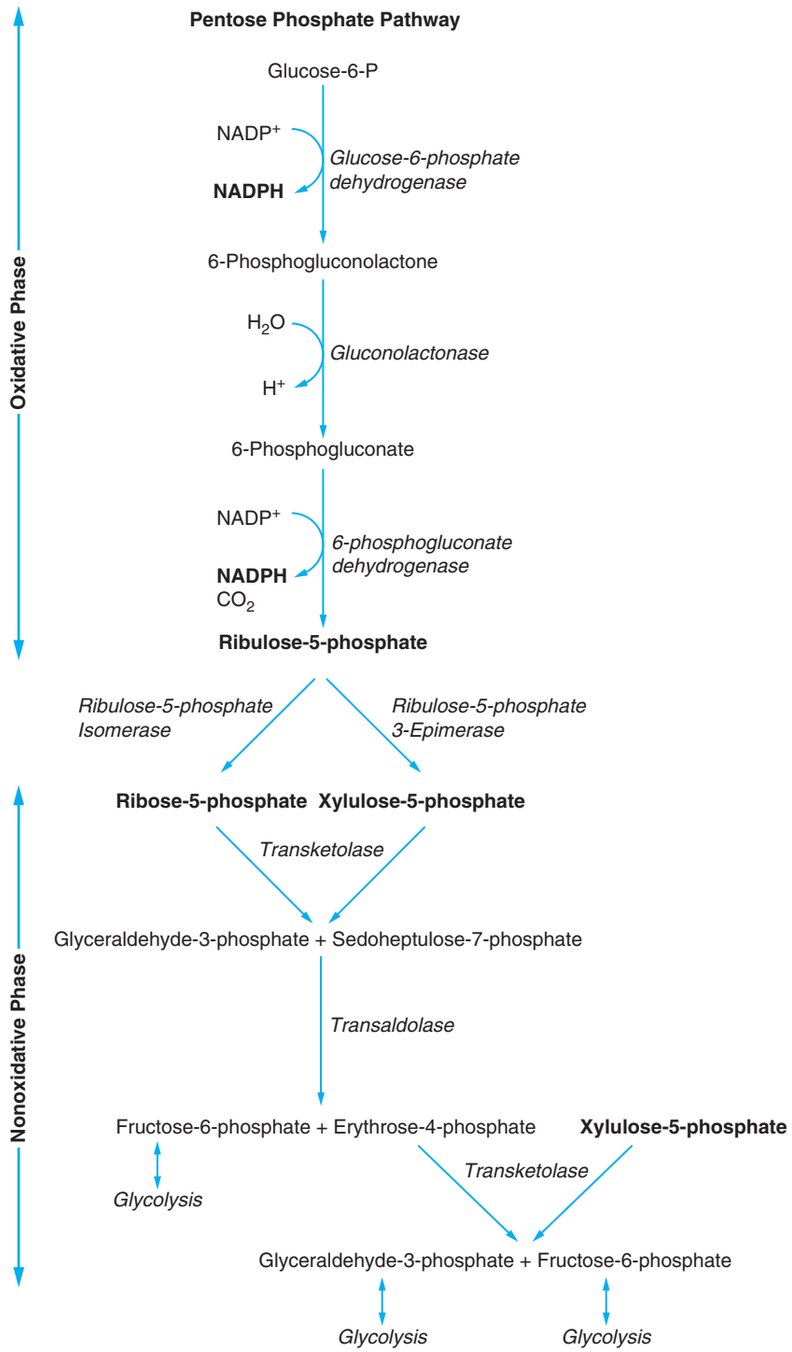


FIGURE 3.23 **The Pentose Phosphate Pathway.** This pathway is a principal means of reducing $NADP^+$ to NADPH, which can be used for reducing equivalents for the synthesis of certain molecules (i.e., fatty acids), glutathione reduction, or other reactions and for creating ribose-5-phosphate, as well as being used in nucleotide biosynthesis.

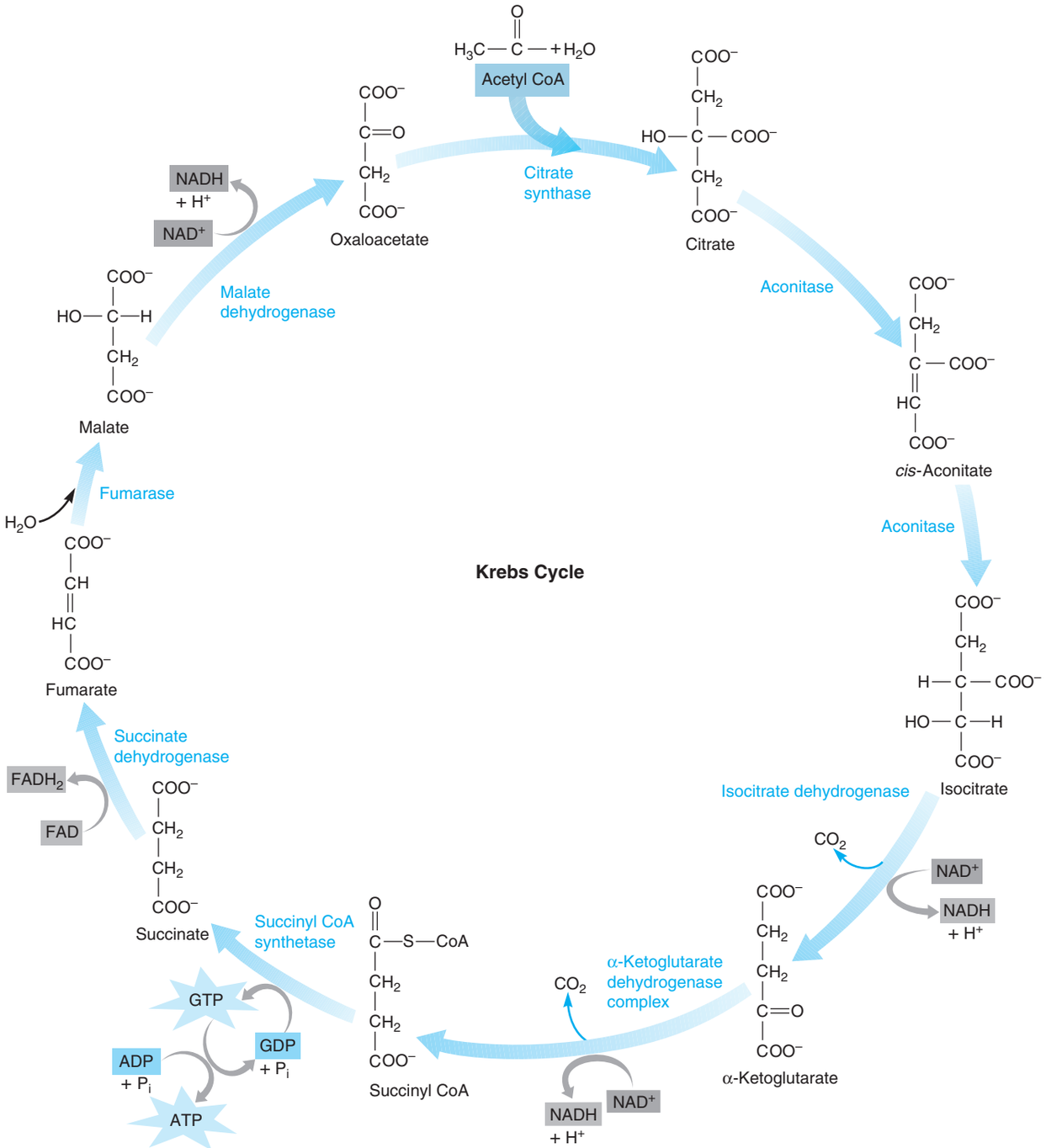


FIGURE 3.24 **The Krebs Cycle.** The Krebs (citric acid) cycle occurs in the mitochondrial matrix and consists of eight sequential reactions whereby the final reaction produces a potential reactant for the first reaction. NADH and $FADH_2$ can transfer electrons to the electron transfer chain to yield three and two ATP, respectively.

of sources, condenses with oxaloacetate, forming citrate. Citrate synthase is the catalyzing enzyme, and its activity is inhibited by its product. Aconitase catalyzes the conversion of citrate to isocitrate and has bidirectional activity, but favors citrate formation. Isocitrate dehydrogenase then converts isocitrate to α-ketoglutarate in the first oxidative reaction of the Krebs cycle. NAD^+ is reduced to NADH, and CO_2 is produced. The next reaction is also oxidative, because α-ketoglutarate is converted to succinyl CoA by α-ketoglutarate dehydrogenase. Here again, NAD^+ is reduced to NADH and CO_2 is produced.

In the next reaction, the energy liberated by the cleavage of the high-energy thioester bond of succinyl CoA to form succinate and coenzyme A is sufficient to phosphorylate GDP (guanosine diphosphate), forming GTP (guanosine triphosphate). Next, succinate is converted to fumarate by succinate dehydrogenase in the third oxidizing reaction of the Krebs cycle. However, here FAD is reduced to $FADH_2$. Then fumarate catalyzes the conversion of fumarate to malate. Malate is subsequently converted to oxaloacetate in the fourth oxidizing reaction, one that reduces NAD^+ to NADH. This is an equilibrium reaction that favors malate. The products of the Krebs cycle are three NADH, one $FADH_2$, and three CO_2 molecules. Thus, 12 ATP molecules can be generated from each citrate molecule formed in the initial reaction. So, in total, the complete oxidation of glucose can yield 36 to 38 ATP. Four total ATP are generated in substrate-level phosphorylation (2 each in glycolysis and the Krebs Cycle), while 10 NADH and 2 $FADH_2$ are generated via glycolysis in the cyptoplasm and the conversion of pyruvate to acetyl CoA and the Krebs Cycle in mitochondria. NADH and $FADH_2$ generated in the mitochondria yield 3 and 2 ATP via the electron transport chain, respectively, while NADH generated in the cytoplasm will yield either 2 or 3 ATP, depending on how it enters the mitochondria.

The events of the Krebs cycle are influenced primarily by the redox state of NAD^+:NADH, the cellular level of intermediates, and the energy level (ADP:ATP) of a cell. For instance, if the ratio of NADH to NAD^+ is high, then the activities of isocitrate dehydrogenase, α-ketoglutarate dehydrogenase, and malate dehydrogenase slow due to relative lack of a reactant. A high NADH:NAD^+ ratio dictates that the reversible malate dehydrogenase catalyzes in the direction of malate, thus reducing the concentration of oxaloacetate, a reactant in the first reaction. Also, inhibition of isocitrate dehydrogenase by increased NADH:NAD^+ ratio results in the accumulation of isocitrate, which is converted back to citrate by aconitase. Citrate inhibits citrate synthase, and thus citrate accumulates in the mitochondria. This will be important later when fatty acid synthesis is discussed.

Increased ADP:ATP ratio will speed up the Krebs cycle in general in two ways. Increased ADP indicates a need for cellular energy, and thus the electron transport chain will operate at a greater rate, thereby creating a higher NAD^+:NADH ratio. Second, ADP allosterically increases isocitrate dehydrogenase activity.

Gluconeogenesis

Gluconeogenesis (**Figure 3.25**), the production of glucose from noncarbohydrate substrates, occurs mainly in the liver. The major precursors are lactate, glycerol, and certain amino acids. Gluconeogenesis uses several reversible reactions of glycolysis but must create chemical reaction bypasses around several unidirectional reactions, in which the enzyme only catalyzes the reaction in the direction of glycolysis. Thus, gluconeogenesis cannot be viewed simply as the reversal of glycolysis.

Pyruvate cannot be made into phosphoenolpyruvate by a simple reversal of the reaction. The amino acid alanine and lactate are major gluconeogenic precursors, and both are converted to pyruvate in the liver. For pyruvate to be converted to phosphoenolpyruvate, pyruvate must first diffuse into the mitochondria and undergo conversion to oxaloacetate (OAA) and then malate. Pyruvate carboxylase catalyzes the conversion of pyruvate to OAA. Oxaloacetate is converted to malate by malate dehydrogenase. Malate can exit the mitochondria, but oxaloacetate cannot. Once the malate is in the cytoplasm, it is converted again to OAA by malate dehydrogenase. Finally, OAA is converted to phosphoenolpyruvate by the enzyme phosphoenolpyruvate carboxykinase (PEPCK).

Lipogenesis

Increased dietary carbohydrate intake may result in increased liver lipogenesis. Although insulin is released in response to carbohydrate intake and is well known for its lipogenic effects, some evidence suggests that glucose alone can enhance liver lipogenesis. Increased intake of carbohydrate can lead to gene expression of a variety of glycolytic and lipogenic pathways that play a role in converting glucose to fatty acids. Key enzymes that are upregulated in response to a high-carbohydrate diet include liver pyruvate kinase in glycolysis; acetyl-CoA carboxylase, the first enzyme in the biosynthesis of fatty acids;

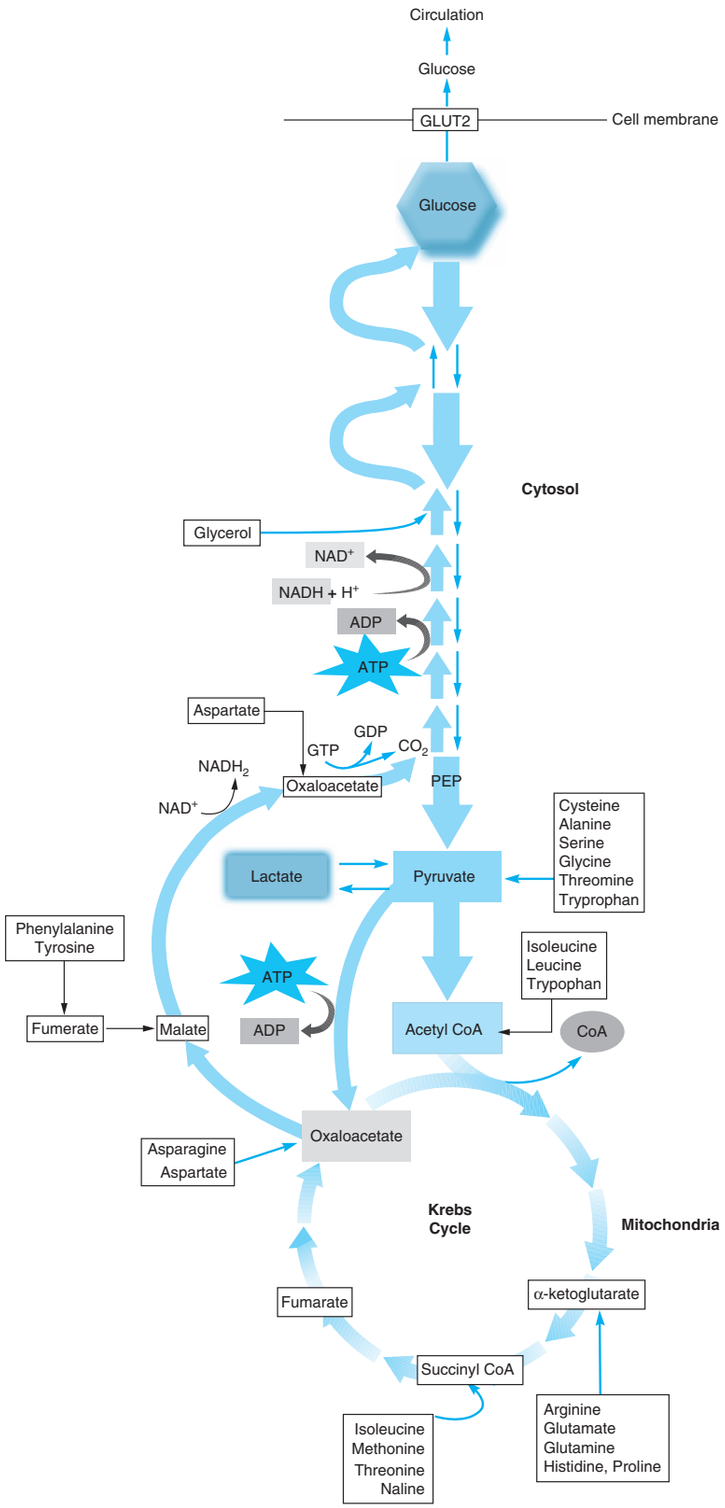


FIGURE 3.25 **Gluconeogenesis.** Gluconeogenesis, the production of glucose from noncarbohydrate substrates, occurs mainly in the liver. Lactate, glycerol, and alanine, as well as other amino acids, are major substrates in the liver. Glycerol is derived from fat breakdown in adipose tissue. Lactate is derived from RBCs and muscle during exercise. Most amino acids are derived from liver and muscle protein.

PEP, phosphoenolpyruvate; CoA, coenzyme A

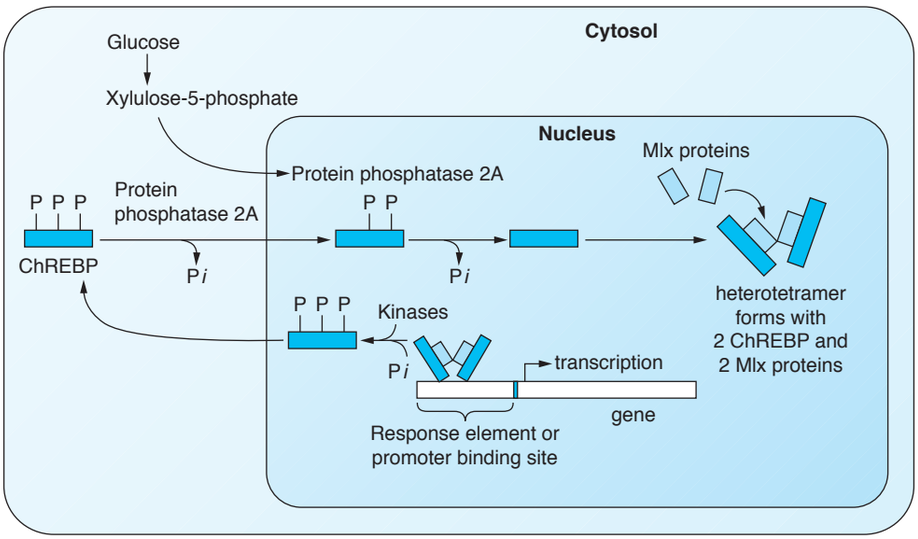


FIGURE 3.26 **Carbohydrate Response Element Binding Protein (ChREBP).** ChREBP regulates lipogenesis by binding to the promoters of genes to enhance transcription of genes involved with fat synthesis in response to glucose.

and fatty acid synthase, to name only a few. How does glucose up-regulate these genes independent of insulin? The mechanism by which these events occur is due to the transcription protein **carbohydrate response element binding protein** (**ChREBP**), which is activated by a high-carbohydrate diet. ChREBP was originally studied in the liver, because most glucose and lipid metabolism occurs in that organ, but other tissues also contain this protein, including adipose, intestine, kidney, and muscle tissue.

The promoters of enzymes involved in lipogenesis noted above have binding sites for ChREBP or response elements, which are nucleotide base pairs that bind ChREBP to DNA (**Figure 3.26**). This transcription protein is normally abundant in the cytosol in fasting conditions and is apparently unable to enter the cell nucleus due to the degree of phosphorylation. However, when glucose in the cytosol increases, a series of reactions occurs to partially dephosphorylate ChREBP, which allows it to translocate to the nucleus and bind to the promoters of the genes encoding these enzymes. Interestingly, it is not glucose itself, but rather a metabolite, xylulose-5-phosphate, that initiates the steps in dephosphorylating ChREBP. After up-regulation of the target genes has occurred, ChREBP is phosphorylated by either cAMP or AMP-dependent kinases, which causes the ChREBP to disassociate from the gene promoters and exit the nucleus.

BEFORE YOU GO ON . . .

1. What are the impacts of insulin and glucagon on phosphofructosekinase 2 (PFK2) activity, and how is this activity mediated?
2. What is the role of uridine diphosphate glucose (UDP-glucose) in the synthesis of glycogen?
3. How do increased cAMP levels resulting from increased glucagon play a role in glycogen breakdown?
4. What are the two ways in which an increased ratio of ADP to ATP enhances activity in the Krebs cycle?
5. How is phosphoenolpyruvate in glycolysis made from pyruvate to generate more glucose in gluconeogenesis?

Summary

1. Carbohydrates are a class of nutrients that include sugars, starches, fibers, and related molecules such as glycosaminoglycans, amino sugars, and more. Carbohydrates provide energy for all cells and play structural and functional roles in cells and tissue.

2. Fibers are special carbohydrates and related molecules that are not broken down by digestive enzymes. However, based on their metabolism by gut microflora and conversion to absorbable energy molecules, they can provide a small amount of energy.
3. Carbohydrate contributes roughly 50% of the calories in the typical adult diet. Although some monosaccharides are available in the diet via fruits, most are derived from disaccharides and polysaccharides. Cereal grains such as rice and wheat, as well as potatoes, make a significant contribution to carbohydrate intake, as do fruits and dairy foods.
4. The Acceptable Macronutrient Distribution Range (AMDR) for carbohydrate intake in the United States and Canada is 45% to 65% of total energy. The broad range of AMDR is meant to provide individual guidance based on glucose tolerance and activity level. Meanwhile, it is recommended that the intake of added sugar not exceed 25% of calories, providing guidance for people to derive more than 75% of their carbohydrates from foods such as dairy products, grains, legumes, and fruits and vegetables.
5. Circulating glucose and stored glycogen are principal energy sources for most cells and tissues and are mandatory for others, such as red blood cells and the brain. Red blood cells can only use glucose for fuel, and in the process generate lactate.
6. Monosaccharides gain access to cells via glucose transport proteins, which vary based on their presence in different tissue and their K_m. GLUT4 is the glucose transporter in muscle and adipose tissue responsible for reducing much of circulating blood glucose after a meal.
7. Carbohydrate metabolism is regulated by hormones such as insulin, epinephrine, glucagon, and cortisol. In general, insulin is anabolic with regard to carbohydrate, whereas epinephrine is catabolic, leading to glycogen breakdown in the liver and muscle. Cortisol supports glycogen storage and gluconeogenesis simultaneously in the liver.
8. Insulin is primarily anabolic, directing the uptake of glucose into muscle and adipose tissue cells during hyperglycemic states. This happens via stimulation of the translocation of GLUT4 from storage sites within those cells.
9. Glucagon, cortisol, and epinephrine work to raise blood glucose levels by supporting gluconeogenesis in hepatocytes. Glucagon strongly promotes glycogen breakdown in the liver, whereas epinephrine promotes glycogen breakdown in both the liver and skeletal muscle.
10. Glycogen is found in a variety of tissues but is most concentrated in the liver and muscle. Liver glycogen serves as a resource to preserve blood glucose levels during early fasting, whereas muscle glycogen serves as an immediate energy resource during intense physical activity, including strenuous exercise. Lactate derived from muscle glycogen metabolism can circulate to the liver and be converted to glucose, which, in turn, can enter the blood and serve as energy for muscle and other tissue.

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