7: Introduction to Carbohydrates

Overview

Carbohydrates are the most abundant organic molecules in nature. They have a wide range of functions, including providing a significant fraction of the dietary calories for most organisms, acting as a storage form of energy in the body, and serving as cell membrane components that mediate some forms of intercellular communication. Carbohydrates also serve as a structural component of many organisms, including the cell walls of bacteria, the exoskeleton of insects, and the fibrous cellulose of plants. The empiric formula for many of the simpler carbohydrates is $(CH_2O)_n$, where $n \geq 3$, hence the name “hydrate of carbon.”

Classification and Structure

Monosaccharides or simple sugars can be classified according to the number of carbon atoms they contain. Examples of some monosaccharides commonly found in humans are listed in Figure 7.1. They can also be classified by the type of carbonyl group they contain. Carbohydrates with an aldehyde as their carbonyl group are called aldoses, whereas those with a keto as their carbonyl group are called ketoses (Fig. 7.2). For example, glyceraldehyde is an aldose, whereas dihydroxyacetone is a ketose. Carbohydrates that have a free carbonyl group have the suffix -ose. (Note: Ketoses have an additional “ul” in their suffix such as xylulose. There are exceptions, such as fructose, to this rule.) Monosaccharides can be linked by glycosidic bonds to create larger structures (Fig. 7.3). Disaccharides contain two monosaccharide units, oligosaccharides contain 3 to 10 monosaccharide units, and polysaccharides contain more than 10 monosaccharide units and can be hundreds of sugar units in length.

FIGURE 7.1

rding to the number of carbons

GENERIC NAMES	EXAMPLES
3 Carbons: trioses	Glyceraldehyde
4 Carbons: tetroses	Erythrose
5 Carbons: pentoses	Ribose
6 Carbons: hexoses	Glucose
7 Carbons: heptoses	Sedoheptulose
9 Carbons: nonoses	Neuraminic acid

FIGURE 7.2

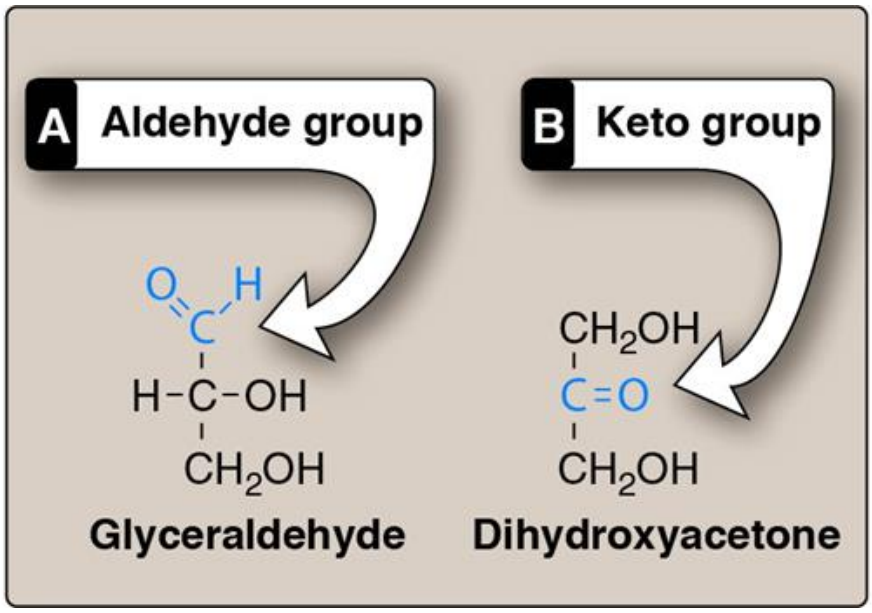
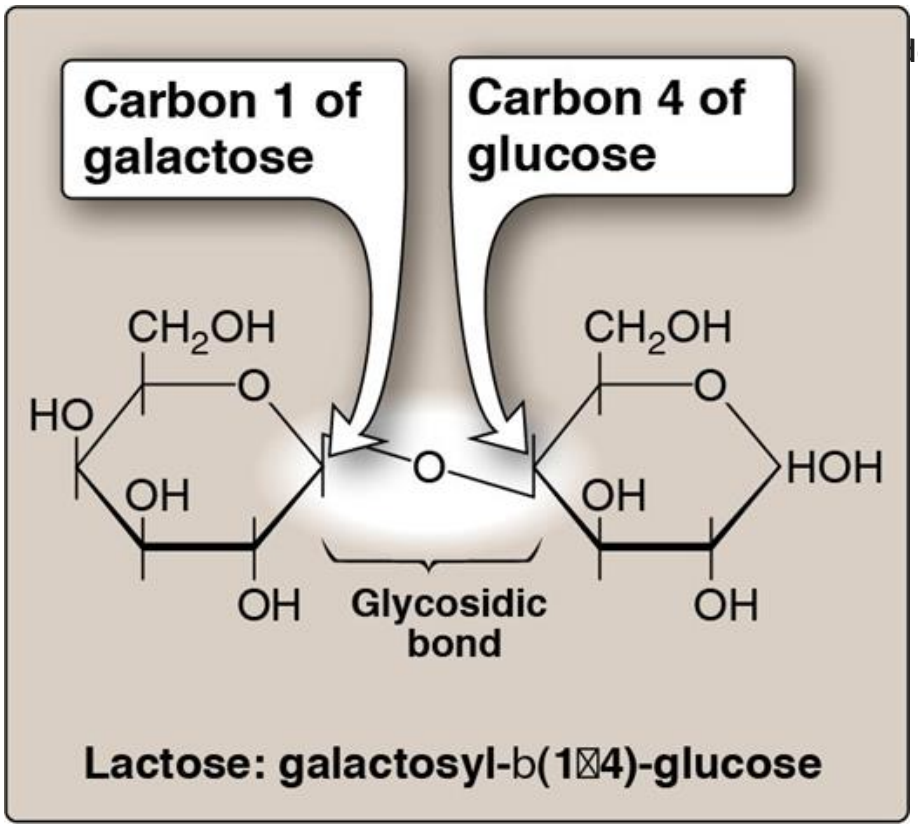


FIGURE 7.3



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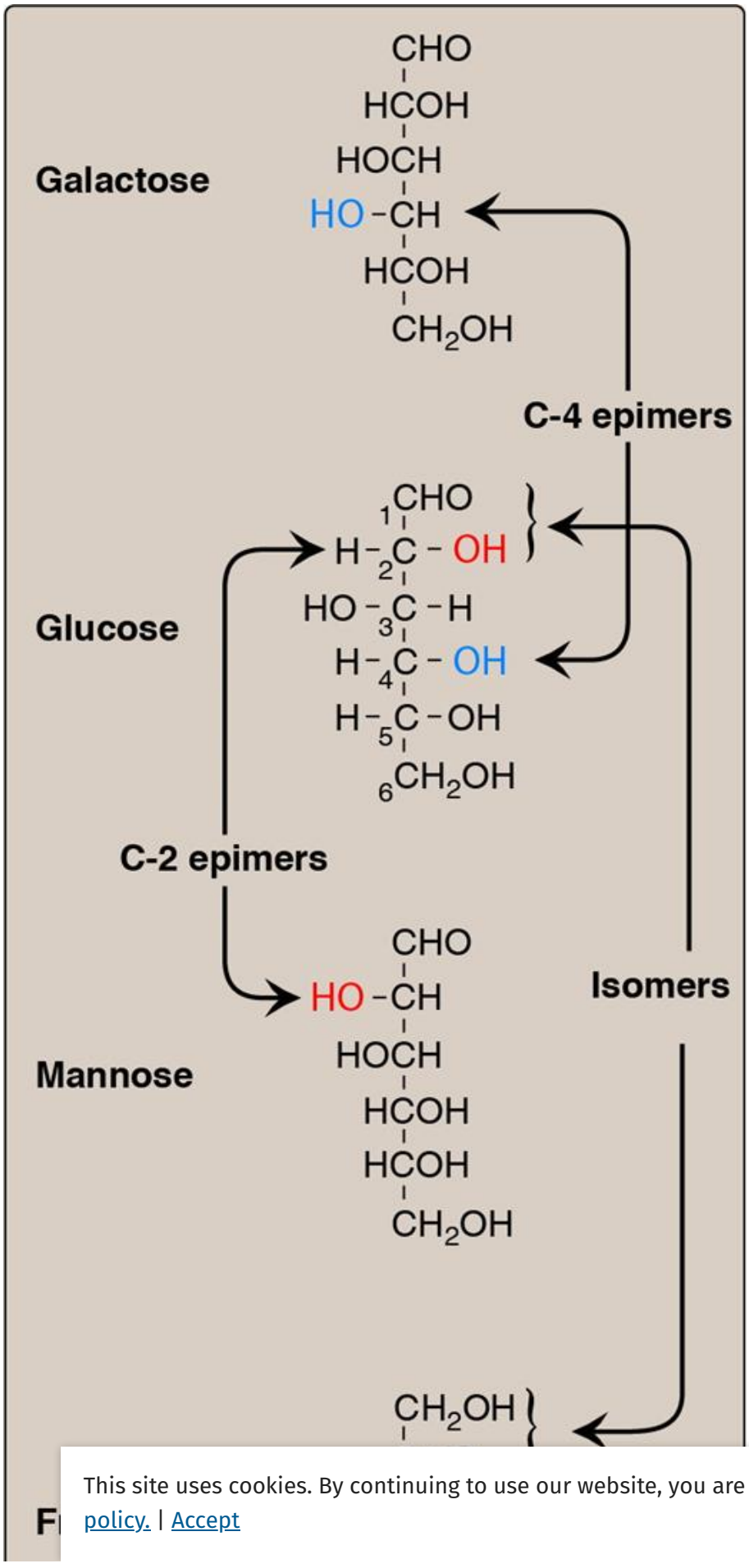
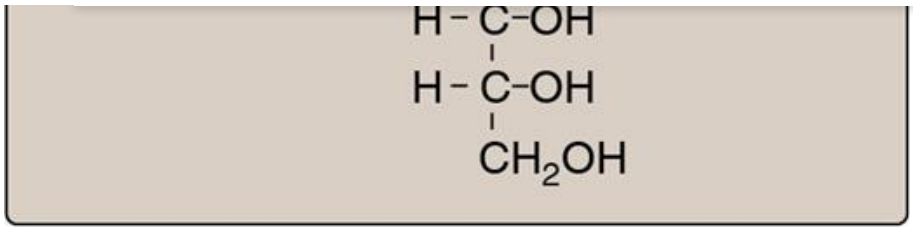
Isomers and epimers

Compounds that have the same chemical formula but different structures are isomers of each other. For example, fructose, glucose, mannose, and galactose all have the same chemical formula, $C_6H_{12}O_6$, with different structures. Carbohydrate isomers that differ in configuration around only one specific carbon atom (with the exception of the carbonyl carbon, see C. 1. below) are defined as epimers of each other. For example, glucose and galactose are C-4 epimers because their structures differ only in the position of the –OH (hydroxyl) group at carbon 4. (Note: The carbons in sugars are numbered beginning at the end that contains the carbonyl carbon [i.e., the aldehyde or keto group], as shown in Fig. 7.4.) Glucose and mannose are C-2 epimers. However, because galactose and mannose differ in the position of –OH groups at two carbons (carbons 2 and 4), they are isomers rather than epimers (see Fig. 7.4).

FIGURE 7.4

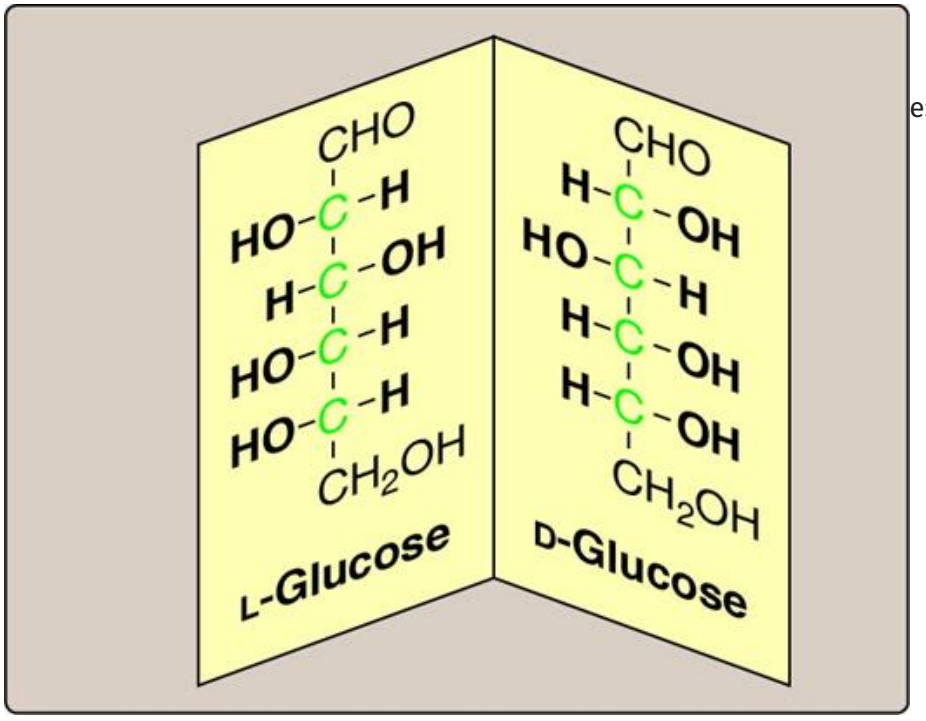




Enantiomers

A special type of isomerism is found in the pairs of structures that are mirror images of each other. These mirror images are called enantiomers, and the two members of the pair are designated as a D- and an L-sugar (Fig. 7.5). The vast majority of the sugars in humans are D-isomers. In the D-isomeric form, the –OH group on the asymmetric carbon (a carbon linked to four different atoms or groups) farthest from the carbonyl carbon is on the right, whereas in the L-isomer, it is on the left. Most enzymes are specific for either the D or the L form, but enzymes known as isomerases are able to interconvert D- and L-isomers.

FIGURE 7.5



e: The asymmetric carbons are shown

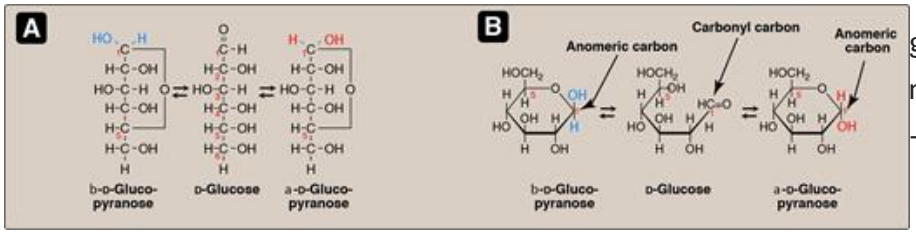
Monosaccharide cyclization

Less than 1% of each of the monosaccharides with five or more carbons exists in the open-chain (acyclic) form in solution. Rather, they are predominantly found in a ring or cyclic form, in which the aldehyde (or keto) group has reacted with a hydroxyl group on the same sugar, making the carbonyl carbon (carbon 1 for an aldose, carbon 2 for a ketose) asymmetric. This asymmetric carbon is referred to as the anomeric carbon.

Anomers

Creation of an anomeric carbon (the former carbonyl carbon) generates a new pair of isomers, the α and β configurations of the sugar (e.g., α-D-glucopyranose and β-D-glucopyranose), as shown in Figure 7.6, that are anomers of each other. (Note: In the α configuration, the –OH group on the anomeric carbon projects to the same side as the ring in a modified Fischer projection formula [see Fig. 7.6A] and is trans to the CH_2OH group in a Haworth projection formula [see Fig. 7.6B]. The α and β forms are not mirror images, and they are referred to as diastereomers.) Enzymes are able to distinguish between these two structures and use one or the other preferentially. For example, glycogen is synthesized from α-D-glucopyranose, whereas cellulose is synthesized from β-D-glucopyranose. The cyclic α and β anomers of a sugar in solution spontaneously (but slowly) form an equilibrium mixture, a process known as mutarotation (see Fig. 7.6). (Note: For glucose, the α form makes up 36% of the mixture.)

FIGURE 7.6



glucose shown as modified Fischer n formulas. (Note: A sugar with a six- -membered ring [4 C + 1 O] is a

Reducing sugars

If the hydroxyl group on the anomeric carbon of a cyclized sugar is not linked to another compound by a glycosidic bond (see E. below), the ring can open. The sugar can act as a reducing agent and is termed a reducing sugar. Such sugars can react with chromogenic agents (e.g., the Benedict reagent) causing the reagent to be reduced and colored as the aldehyde group of the acyclic sugar is oxidized to a carboxyl group. All monosaccharides, but not all disaccharides, are reducing sugars. (Note: Fructose, a ketose, is a reducing sugar because it can be isomerized to an aldose.)

A colorimetric test can detect a reducing sugar in urine. A positive result is indicative of an underlying pathology (because sugars are not normally present in urine) and can be followed up by more specific tests to identify the reducing sugar.

Monosaccharide joining

Monosaccharides can be joined to form disaccharides, oligosaccharides, and polysaccharides. Important disaccharides include lactose (galactose + glucose), sucrose (glucose + fructose), and maltose (glucose + glucose). Important polysaccharides include branched glycogen (from animal sources) and starch (plant sources) and unbranched cellulose (plant sources). Each is a polymer of glucose.

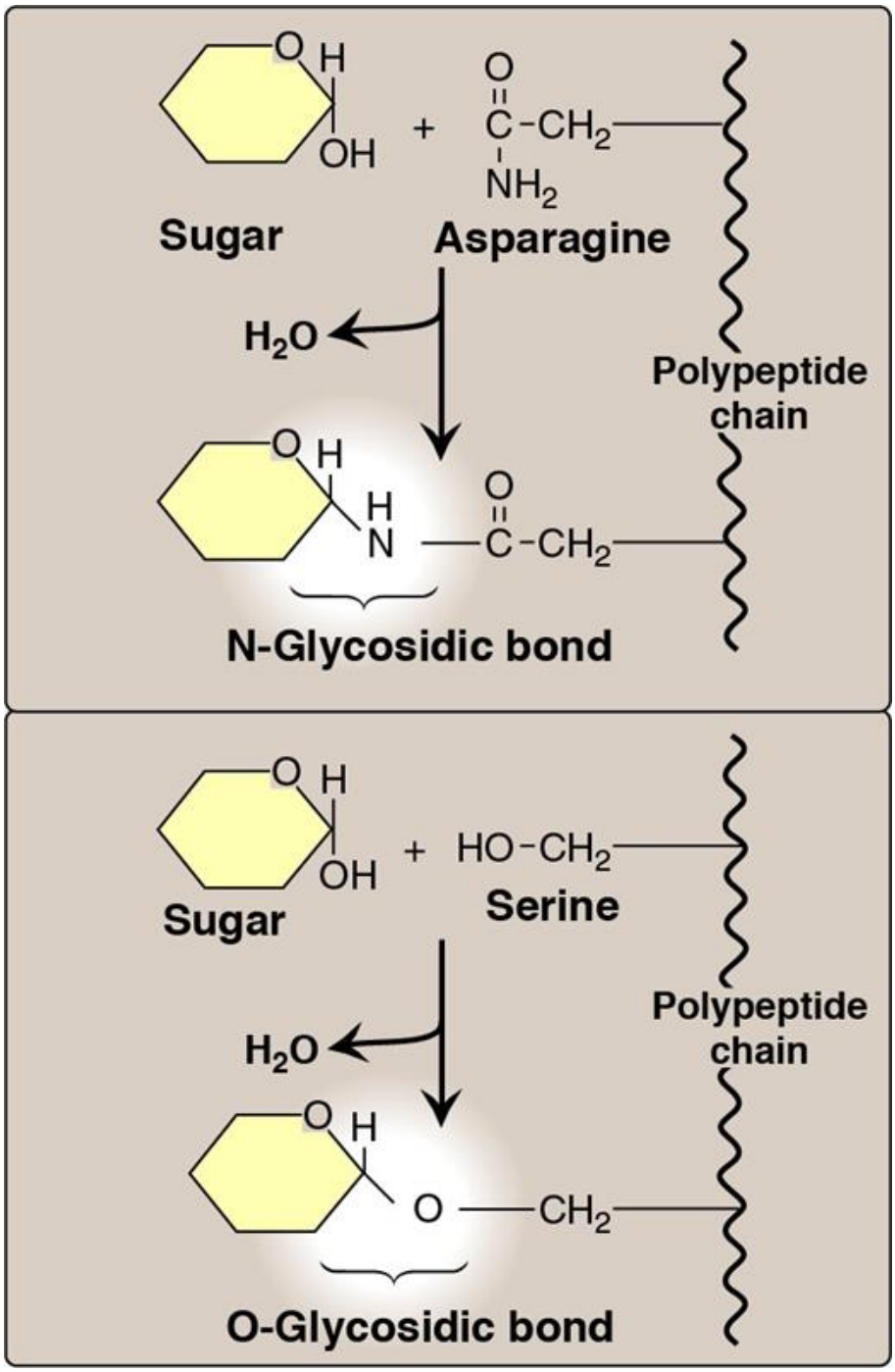
Glycosidic bonds

The bonds that link sugars are called glycosidic bonds. They are formed by enzymes known as glycosyltransferases that use nucleotide sugars (activated sugars) such as uridine diphosphate glucose as substrates. Glycosidic bonds between sugars are named according to the numbers of the connected carbons and with regard to the position of the anomeric hydroxyl group of the first sugar involved in the bond. If this anomeric hydroxyl is in the α configuration, then the linkage is an α-bond. If it is in the β configuration, then the linkage is a β-bond. Lactose, for example, is synthesized by forming a glycosidic bond between carbon 1 of β-galactose and carbon 4 of glucose. Therefore, the linkage is a β(1→4) glycosidic bond (see Fig. 7.3). (Note: Because the anomeric end of the glucose residue is not involved in the glycosidic linkage, it [and, therefore, lactose] remains a reducing sugar.)

Carbohydrate linkage to noncarbohydrates

Carbohydrates can be attached by glycosidic bonds to noncarbohydrate structures, including purine and pyrimidine bases in nucleic acids, aromatic rings such as those found in steroids, proteins, and lipids. If the group on the noncarbohydrate molecule to which the sugar is attached is an $-NH_2$ group, then the bond is called an N-glycosidic link. If the group is an –OH, then the bond is an O-glycosidic link (Fig. 7.7). (Note: All sugar-sugar glycosidic bonds are O-type linkages.)

FIGURE 7.7



Dietary Carbohydrate Digestion

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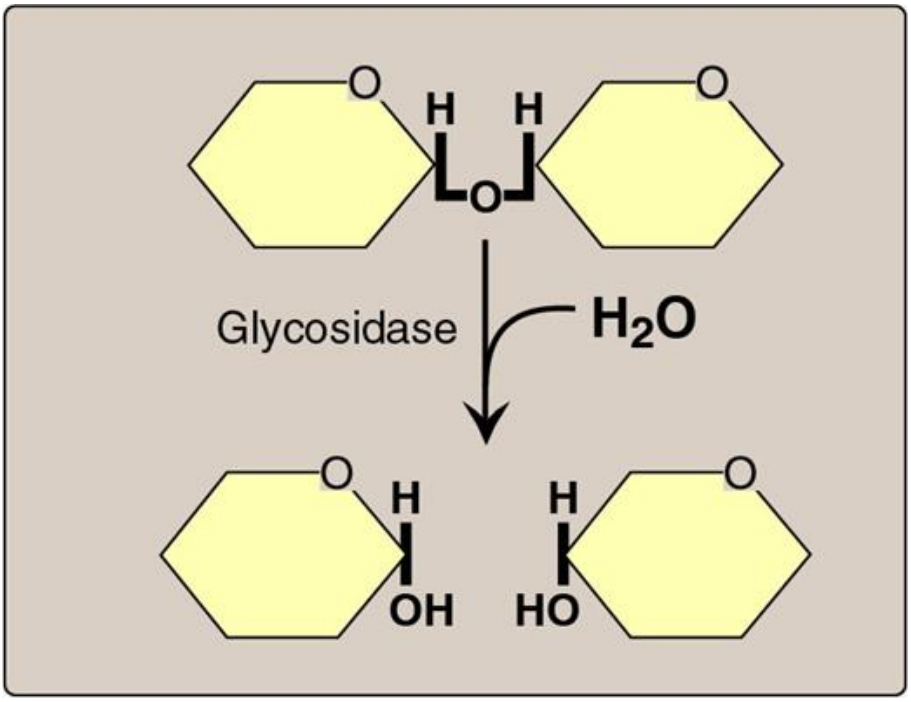
The principal sites of dietary carbohydrate digestion are the mouth and intestinal lumen. This digestion is rapid and is catalyzed by enzymes known as glycoside hydrolases (glycosidases) that hydrolyze glycosidic bonds (Fig. 7.8). Because little monosaccharide is present in diets of mixed animal and plant origin, the enzymes are primarily endoglycosidases that hydrolyze polysaccharides and oligosaccharides and disaccharidases that hydrolyze tri- and disaccharides into their reducing sugar components. Glycosidases are usually specific for the structure and configuration of the glycosyl residue to be removed as well as for the type of bond to be broken. The final products of carbohydrate digestion are the monosaccharides glucose, galactose, and fructose that are absorbed by cells (enterocytes) of the small intestine.

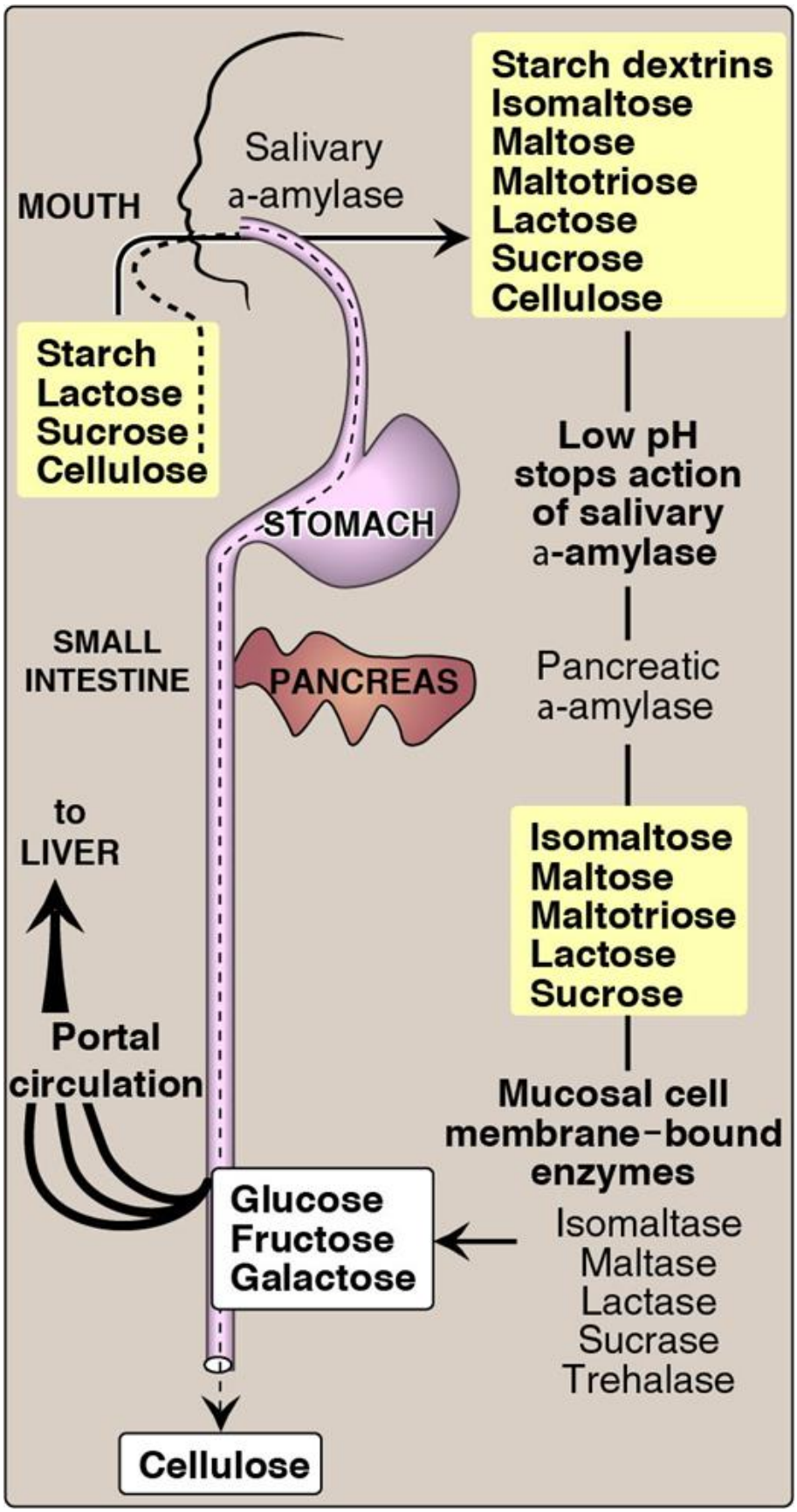
FIGURE 7.8



Salivary α-amylase

The major dietary polysaccharides consumed by humans are of plant (starch, composed of amylose and amylopectin) and animal (glycogen) origin. During mastication or chewing, salivary α-amylase acts briefly on dietary starch and glycogen, hydrolyzing random α(1→4) bonds. (Note: There are both α[1→4]- and β[1→4]-endoglucosidases in nature, but humans do not produce the latter. Therefore, we are unable to digest cellulose, a carbohydrate of plant origin containing β[1→4] glycosidic bonds between glucose residues.) Because branched amylopectin and glycogen also contain α(1→6) bonds, which α-amylase cannot hydrolyze, the digest resulting from its action contains a mixture of short, branched and unbranched oligosaccharides known as dextrins (Fig. 7.9). (Note: Disaccharides are also present as they, too, are resistant to amylase.) Carbohydrate digestion halts temporarily in the stomach, because the high acidity inactivates salivary α-amylase.

FIGURE 7.9



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When the acidic stomach contents reach the small intestine, they are neutralized by bicarbonate secreted by the pancreas, and pancreatic α-amylase continues the process of starch digestion.

Intestinal disaccharidases

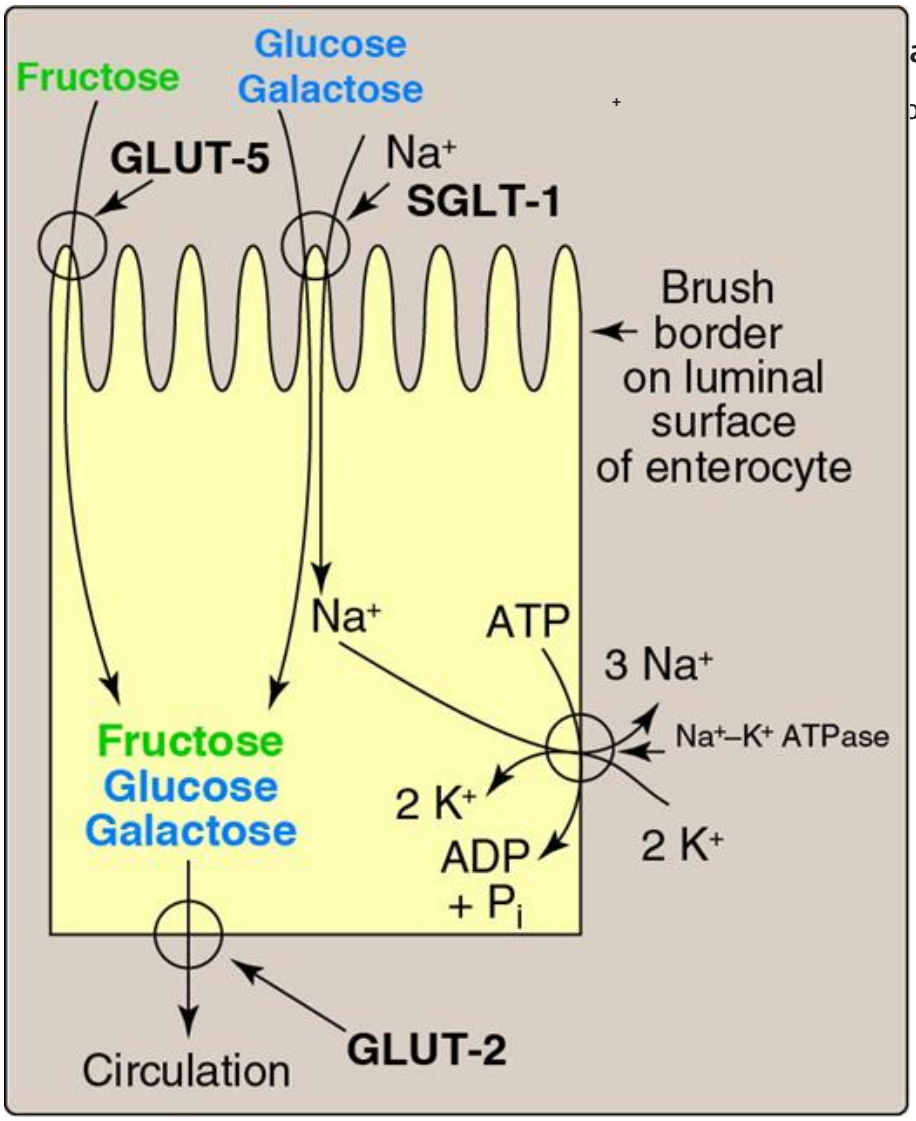
The final digestive processes occur primarily at the mucosal lining of the duodenum and upper jejunum and include the action of several disaccharidases (see Fig. 7.9). For example, isomaltase cleaves the α(1→6) bond in isomaltose, and maltase cleaves the α(1→4) bond in maltose and maltotriose, each producing glucose. Sucrase cleaves the α(1→2) bond in sucrose, producing glucose and fructose, and lactase (β-galactosidase) cleaves the β(1→4) bond in lactose, producing galactose and glucose. (Note: The substrates for isomaltase are broader than its name suggests, and it hydrolyzes the majority of maltose.) Trehalose, an α(1→1) disaccharide of glucose found in mushrooms and other fungi, is cleaved by trehalase. These enzymes are transmembrane proteins of the brush border on the luminal (apical) surface of the enterocytes.

Sucrase and isomaltase are enzymatic activities of a single protein cleaved into two functional subunits that remain associated in the cell membrane and form the sucrase–isomaltase (SI) complex. In contrast, maltase is one of two enzymic activities of the single membrane protein maltase—glucoamylase (MGA) that does not get cleaved. Its second enzymic activity, glucoamylase, cleaves α(1→4) glycosidic bonds in dextrins.

Intestinal absorption of monosaccharides

The upper jejunum absorbs the bulk of the monosaccharide products of digestion. However, different sugars have different mechanisms of absorption (Fig. 7.10). For example, galactose and glucose are taken into enterocytes by secondary active transport that requires a concurrent uptake (symport) of sodium (Na^+) ions. The transport protein is the sodium-dependent glucose cotransporter 1 (SGLT-1). (Note: Sugar transport is driven by the Na^+ gradient created by the Na^+-potassium [K^+] ATPase that moves Na^+ out of the enterocyte and K^+ in [see Fig. 7.10].) Fructose absorption utilizes an energy- and Na^+-independent monosaccharide transporter (GLUT-5). All three monosaccharides are transported from the enterocytes into the portal circulation by yet another transporter, GLUT-2. (Note: See pp. 106 and 107 for a discussion of these transporters.)

FIGURE 7.10



arbohydrate digestion.

otransporter. K^+ = potassium.

Abnormal degradation of disaccharides

The overall process of carbohydrate digestion and absorption is so efficient in healthy individuals that ordinarily all digestible dietary carbohydrate is absorbed by the time the ingested material reaches the lower jejunum. However, because only monosaccharides are absorbed, any deficiency (genetic or acquired) in a specific disaccharidase activity of the intestinal mucosa causes the passage of undigested carbohydrate into the large intestine. As a consequence of the presence of this osmotically active material, water is drawn from the mucosa into the large intestine, causing osmotic diarrhea. This is reinforced by the bacterial fermentation of the remaining carbohydrate to two- and three-carbon compounds (which are also osmotically active) plus large volumes of carbon dioxide and hydrogen gas (H_2), causing abdominal cramps, diarrhea, and flatulence.

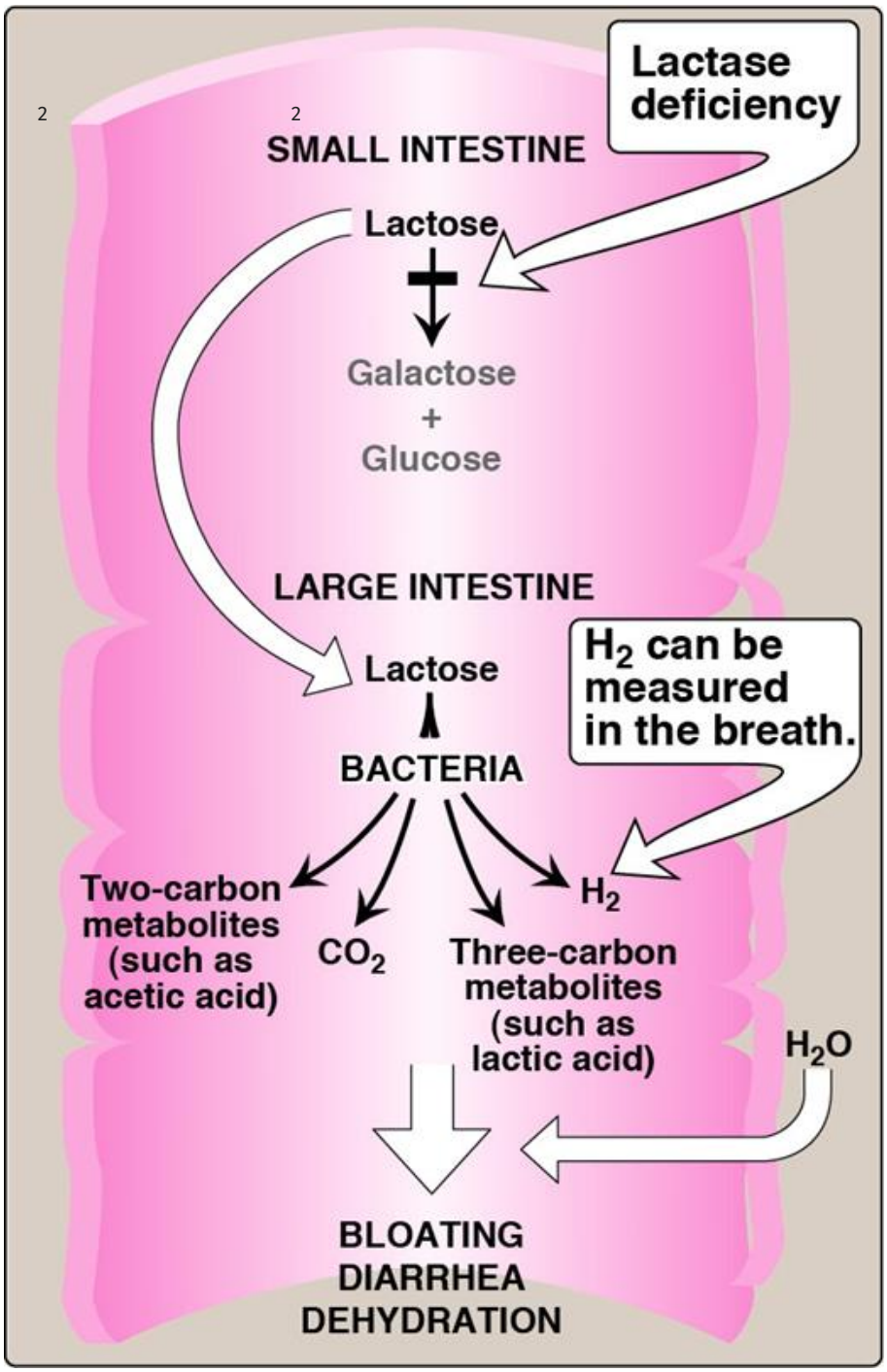
Digestive enzyme deficiencies

Genetic deficiencies of the individual disaccharidases result in disaccharide intolerance. Alterations in disaccharide degradation can also be caused by a variety of intestinal diseases, malnutrition, and drugs that injure the mucosa of the small intestine. For example, brush border enzymes are rapidly lost in normal individuals with severe diarrhea, causing a temporary, acquired enzyme deficiency. Therefore, patients suffering or recovering from such a disorder cannot drink or eat significant amounts of dairy products or sucrose without exacerbating the diarrhea.

Lactose intolerance

Over 60% of the world's adults experience lactose malabsorption because they lack the enzyme lactase (Fig. 7.11). Individuals of Northern European heritage are most likely to maintain the ability to digest lactose into adulthood. Up to 90% of adults of African or Asian descent are lactase deficient. Consequently, they are less able to metabolize lactose than are individuals of Northern European origin. The age-dependent loss of lactase activity starting at approximately age 2 years represents a reduction in the amount of enzyme produced. It is thought to be caused by small variations in the DNA sequence of a region on chromosome 2 that controls expression of the gene for lactase, also on chromosome 2. Treatment for this disorder is to reduce consumption of milk; eat yogurt and some cheeses (bacterial action and aging process decrease lactose content) as well as green vegetables, such as broccoli, to ensure adequate calcium intake; use lactase-treated products; or take lactase in pill form prior to eating. Rare cases of congenital lactase deficiency are known.

FIGURE 7.11



Sucrase–isomaltase deficiency

SI deficiency results in intolerance of ingested sucrose. This condition was considered quite rare, more common in the Inuit people of Alaska and Greenland; now, up to 9% of Americans of European descent are estimated to be affected by a form of SI deficiency.

Initially considered to be exclusively an autosomal-recessive disorder, those with one mutation (carriers) sometimes express disease manifestations. Now, 25 different mutations in the human sucrose gene are known. Individuals homozygous for mutations express congenital SI deficiency and experience osmotic diarrhea, mild steatorrhea, irritability, and vomiting after consuming sucrose. Heterozygous carriers often have symptoms including chronic diarrhea, abdominal pain, and bloating. Treatment includes the dietary restriction of sucrose and enzyme replacement therapy.

Diagnosis of enzyme deficiencies

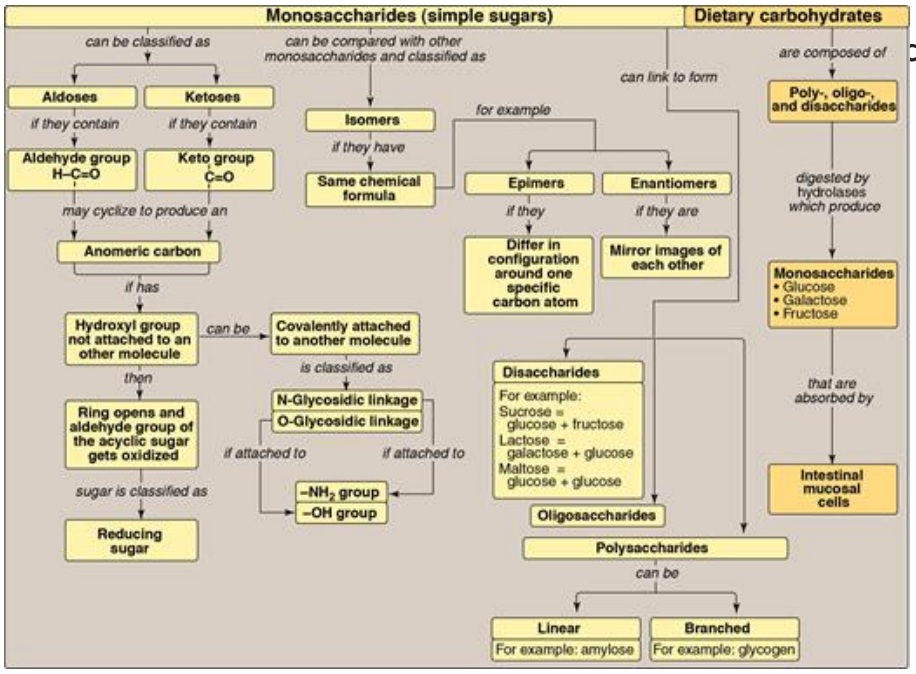
Identification of a specific enzyme deficiency can be obtained by performing oral tolerance tests with the individual disaccharides. Measurement of H_2 in the breath is a reliable test for determining the amount of ingested carbohydrate not absorbed by the body, but which is metabolized instead by the intestinal flora (see Fig. 7.11).

Chapter Summary

Listen

- **Monosaccharides** (Fig. 7.12) containing an aldehyde group are called **aldoses**, and those with a keto group are called **ketoses**.

FIGURE 7.12



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- **Disaccharides**, **oligosaccharides**, and **polysaccharides** consist of monosaccharides linked by **glycosidic bonds**.
- Compounds with the same chemical formula but different structures are called **isomers**.
- Two monosaccharide isomers differing in configuration around one specific carbon atom (not the carbonyl carbon) are defined as **epimers**.
- In **enantiomers** (mirror images), the members of the sugar pair are designated as **d-** and **l-isomers**. When the aldehyde group on an acyclic sugar is oxidized as a chromogenic agent is reduced, that sugar is a **reducing sugar**.
- When a sugar cyclizes, an **anomeric carbon** is created from the carbonyl carbon of the aldehyde or keto group. The sugar can have two configurations, forming **α** or **β anomers**.
- A sugar can have its anomeric carbon linked to an $–NH_2$ or an –OH group on another structure through **N-** and **O-glycosidic bonds**, respectively.
- **Salivary α-amylase** initiates digestion of **dietary polysaccharides** (e.g., starch or glycogen), producing oligosaccharides. **Pancreatic α-amylase** continues the process. The final digestive processes occur at the **mucosal lining** of the **small intestine**.
- Several disaccharidases (e.g., **lactase** [**β-galactosidase**], **sucrase**, **isomaltase**, and **maltase**) produce monosaccharides (glucose, galactose, and fructose). These enzymes are **transmembrane proteins** of the lum

- Absorption of the monosaccharides requires specific **transporters**. If carbohydrate degradation is deficient (as a result of heredity, disease, or drugs that injure the intestinal mucosa), undigested carbohydrate will pass into the large intestine, where it can cause **osmotic diarrhea**.
- Bacterial fermentation of the material produces large volumes of carbon dioxide and hydrogen gas, causing abdominal cramps, diarrhea, and flatulence. **Lactose intolerance**, primarily caused by the age-dependent loss of **lactase** (**adult-type hypolactasia**), is by far the most common of these deficiencies.

Study Questions

Listen

Choose the ONE best answer.

7.1. Glucose is

A. a C-4 epimer of galactose.

B. a ketose and usually exists as a furanose ring in solution.

C. produced from dietary starch by the action of α-amylase.

D. utilized in biologic systems only in the L-isomeric form.

Correct answer = A. Because glucose and galactose differ only in configuration around carbon 4, they are C-4 epimers that are interconvertible by the action of an epimerase. Glucose is an aldose sugar that typically exists as a pyranose ring in solution. Fructose, however, is a ketose with a furanose ring. α-Amylase does not produce monosaccharides. The D-isomeric form of carbohydrates is the form typically found in biologic systems, in contrast to amino acids that typically are found in the L-isomeric form.

7.2. A 28-year-old male presents in the office with a chief complaint of recurrent bloating and diarrhea. His eyes are sunken, and the physician notes additional signs of dehydration. The patient's temperature is normal. He explains that the most recent episode occurred last night soon after he had ice cream for dessert. This clinical picture is most likely caused by a deficiency in the activity of:

A. isomaltase.

B. lactase.

C. pancreatic α-amylase.

D. salivary α-amylase.

E. sucrase.

Correct answer = B. The physical symptoms suggest a deficiency in an enzyme responsible for carbohydrate degradation. The symptoms observed following the ingestion of dairy products suggest that the patient is deficient in lactase as a result of the age-dependent reduction in expression of the enzyme.

7.3. Routine examination of the urine of an asymptomatic pediatric patient showed a positive reaction with Clinitest (a copper reduction method of detecting reducing sugars) but a negative reaction with the glucose oxidase test for detecting glucose. Using these data, show on the chart below which of the sugars could (YES) or could not (NO) be present in the urine of this individual.

Sugar	Yes	No
Fructose		
Galactose		
Glucose		
Lactose		
Sucrose		
Xylulose		

Each of the listed sugars, except for sucrose and glucose, could be present in the urine of this individual. Clinitest is a nonspecific test that produces a change in color if urine is positive for reducing substances such as reducing sugars (fructose, galactose, glucose, lactose, xylulose). Because sucrose is not a reducing sugar, it is not detected by Clinitest. The glucose oxidase test will detect only glucose, and it cannot detect other sugars. The negative glucose oxidase test coupled with a positive reducing sugar test means that glucose cannot be the reducing sugar in the patient's urine.

7.4. Explain why α-glucosidase inhibitors such as acarbose and miglitol, which are taken with meals, can be used in the treatment of some patients with diabetes mellitus. What effect should these drugs have on the digestion of lactose?

α-Glucosidase inhibitors slow the production of glucose from dietary carbohydrates, thereby reducing the postprandial rise in blood glucose and facilitating better blood glucose control in diabetic patients. These drugs have no effect on lactose digestion because the disaccharide lactose contains a β-glycosidic bond, not an α-glycosidic bond.