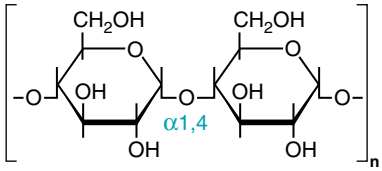
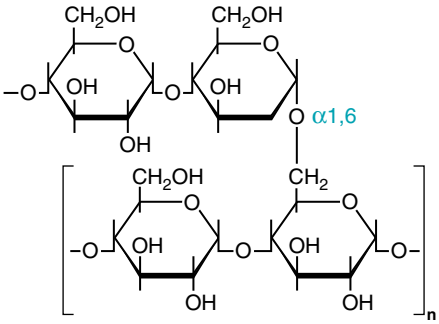
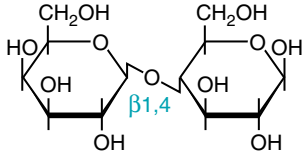
27 Digestion, Absorption, and Transport of Carbohydrates



Amylose

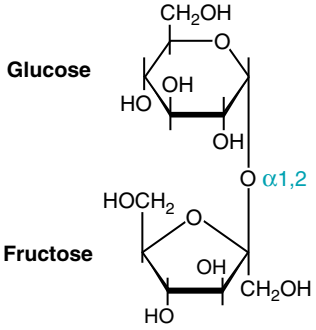


Amylopectin



Galactose Glucose

Lactose



Sucrose

Carbohydrates are the largest source of dietary calories for most of the world's population. The major carbohydrates in the American diet are starch, lactose, and sucrose. The ***starches amylose*** *and* ***amylopectin*** *are polysaccharides composed of hundreds to millions of glucosyl units linked together through α-1,4 and α-1,6 glycosidic bonds (Fig. 27.1).* ***Lactose*** *is a disaccharide composed of glucose and galactose, linked together through a β-1,4 glycosidic bond.* ***Sucrose*** *is a disaccharide composed of glucose and fructose, linked through an α-1,2 glycosidic bond. The digestive processes convert all of these dietary carbohydrates to their constituent monosaccharides by* ***hydrolyzing glycosidic bonds*** *between the sugars.*

The digestion of starch begins in the mouth (Fig. 27.2). The ***salivary*** *gland releases* ***α-amylase****, which converts starch to smaller polysaccharides called* ***α-dextrins.*** *Salivary α-amylase is inactivated by the acidity of the stomach (HCl).* ***Pancreatic α-amylase*** *and bicarbonate are secreted by the exocrine pancreas into the lumen of the small intestine, where bicarbonate neutralizes the gastric secretions. Pancreatic α-amylase continues the digestion of α-dextrins, converting them to disaccharides (****maltose****), trisaccharides (****maltotriose****), and oligosaccharides called* ***limit dextrins****. Limit dextrins usually contain four to nine glucosyl residues and an* ***isomaltose*** *branch (two glucosyl residues attached through an α-1,6 glycosidic bond).*

The digestion of the disaccharides lactose and sucrose, as well as further digestion of maltose, maltotriose and limit dextrins, occurs through ***disaccharidases*** *attached to the membrane surface of the* ***brush border (microvilli)*** *of intestinal epithelial cells.* ***Glucoamylase*** *hydrolyzes the α-1,4 bonds of dextrins. The* ***sucrase–isomaltase complex*** *hydrolyzes sucrose, most of maltose, and almost all of the isomaltose formed by glucoamylase from limit dextrins.* ***Lactase-glycosylceramidase*** *(β-glycosidase) hydrolyzes the β-glycosidic bonds in* ***lactose*** *and* ***glycolipids****. A fourth disaccharidase complex,* ***trehalase****, hydrolyzes the bond (an α-1,1 glycosidic bond) between two glucosyl units in the sugar trehalose. The monosaccharides produced by these hydrolases (glucose, fructose, and galactose) are then transported into the intestinal epithelial cells.*

Fig. 27.1. The structures of common dietary carbohydrates. For disaccharides and greater, the sugars are linked through glycosidic bonds between the anomeric carbon of one sugar and a hydroxyl group on another sugar. The glycosidic bond may be either α or β, depending on its position above or below the plane of the sugar containing the anomeric carbon. (see Chapter 5, Section II.A, to review terms used in the description of sugars). The starch amylose is a polysaccharide of glucose residues linked with α-1,4 glycosidic bonds. Amylopectin is amylase with the addition of α-1,6 glycosidic branchpoints. Dietary sugars may be monosaccharides (single sugar residues), disaccharides (two sugar residues), oligosaccharides (several sugar residues) or polysaccharides (hundreds of sugar residues).

A common malabsorption syndrome, **lactose intolerance,** is characterized by nausea, diarrhea, and flatulence after ingesting dairy products or other foods containing lactose. One of the causes of lactose intolerance is a low level of lactase, which decreases after infancy in most of the world's population **(nonpersistant lactase** or **adult hypolactasia).** However, lactase activity remains high in some populations (**persistent lactase),** including Northwestern Europeans and their descendants.

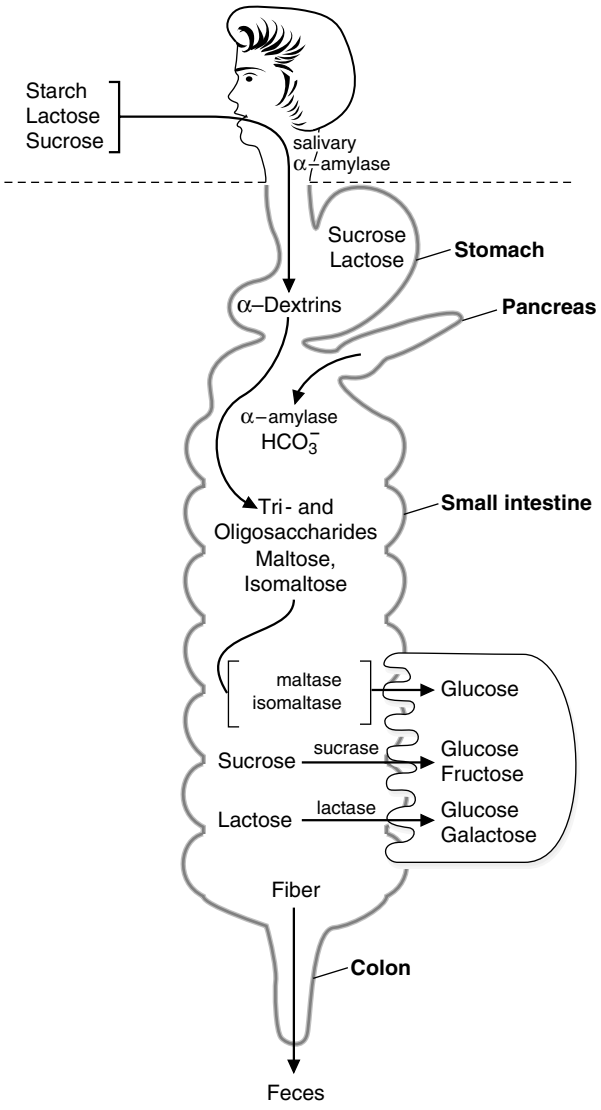


Fig. 27.2. Overview of carbohydrate digestion. **Digestion** of the carbohydrates occurs first, followed by **absorption** of monosaccharides. Subsequent **metabolic** reactions occur after the sugars are absorbed.

***Dietary fiber**, composed principally of polysaccharides, cannot be digested by human enzymes in the intestinal tract. In the colon, dietary fiber and other nondigested carbohydrates may be converted to gases (H_2, CO_2, and methane) and short-chain fatty acids (principally acetic acid, propionic acid, and butyric acid) by bacteria in the colon.*

***Glucose**, **galactose**, and **fructose** formed by the digestive enzymes are transported into the absorptive epithelial cells of the small intestine by protein-mediated **Na^+-dependent active transport** and **facilitative diffusion.** Monosaccharides are transported from these cells into the blood and circulate to the liver and peripheral tissues, where they are taken up by facilitative transporters. Facilitative transport of glucose across epithelial cells and other cell membranes is mediated by a family of **tissue-specific glucose transport proteins (GLUT I–V)**. The type of transporter found in each cell reflects the role of glucose metabolism in that cell.*

THE WAITING ROOM

Deria Voider is a 20-year-old exchange student from Nigeria who has noted gastrointestinal bloating, abdominal cramps, and intermittent diarrhea ever since arriving in the United States 6 months earlier. A careful history shows that these symptoms occur most commonly about 45 minutes to 1 hour after eating breakfast but may occur after other meals as well. Dairy products, not a part of Deria's diet in Nigeria, were identified as the probable offending agent because her gastrointestinal symptoms disappeared when milk and milk products were eliminated from her diet.

Ann Sulin's fasting and postprandial blood glucose levels are frequently above the normal range in spite of good compliance with insulin therapy. Her physician has referred her to a dietician skilled in training diabetic patients in the successful application of an appropriate American Diabetes Association diet. As part of the program, Ms. Sulin is asked to incorporate foods containing fiber into her diet, such as whole grains (e.g., wheat, oats, corn), legumes (e.g., peas, beans, lentils), tubers (e.g., potatoes, peanuts), and fruits.

Nona Melos (no sweets) is a 7-month-old baby girl, the second child born to unrelated parents. Her mother had a healthy, full-term pregnancy, and Nona's birth weight was normal. She did not respond well to breastfeeding and was changed entirely to a formula based on cow's milk at 4 weeks. Between 7 and 12 weeks of age, she was admitted to the hospital twice with a history of screaming after feeding but was discharged after observation without a specific diagnosis. Elimination of cow's milk from her diet did not relieve her symptoms; Nona's mother reported that the screaming bouts were worse after Nona drank juice and that Nona frequently had gas and a distended abdomen. At 7 months she was still thriving (weight above 97th percentile) with no abnormal findings on physical examination. A stool sample was taken.

The dietary sugar in fruit juice and other sweets is sucrose, a disaccharide composed of glucose and fructose joined through their anomeric carbons. **Nona Melos'** symptoms of pain and abdominal distension are caused by an inability to digest sucrose or absorb fructose, which are converted to gas by colonic bacteria. "Melos" is Latin for sweets, and her name means "no sweets." Nona Melos's stool sample had a pH of 5 and gave a positive test for sugar. The possibility of carbohydrate malabsorption was considered, and a hydrogen breath test was recommended.

I. DIETARY CARBOHYDRATES

Carbohydrates are the largest source of calories in the average American diet and usually constitute 40 to 45% of our caloric intake. The plant starches amylopectin and amylose, which are present in grains, tubers, and vegetables, constitute approximately 50 to 60% of the carbohydrate calories consumed. These starches are polysaccharides, containing 10,000 to 1 million glucosyl units. In amylose, the glucosyl residues form a straight chain linked via α-1,4 glycosidic bonds; in amylopectin, the α-1,4 chains contain branches connected via α-1,6 glycosidic bonds (see Fig. 27.1). The other major sugar found in fruits and vegetables is sucrose, a disaccharide of glucose and fructose (see Fig. 27.1). Sucrose and small amounts of the monosaccharides glucose and fructose are the major natural sweeteners found in fruit, honey, and vegetables. Dietary fiber, that portion of the diet that cannot be digested by human enzymes of the intestinal tract, is also composed principally of plant polysaccharides and a polymer called lignan.

Most foods derived from animals, such as meat or fish, contain very little carbohydrate except for small amounts of glycogen (which has a structure similar to amylopectin) and glycolipids. The major dietary carbohydrate of animal origin is lactose, a disaccharide composed of glucose and galactose found exclusively in milk and milk products (see Fig. 27.1).

Sweeteners, in the form of sucrose and high-fructose corn syrup (starch, partly hydrolyzed and isomerized to fructose), also appear in the diet as additives to processed foods. On average, a person in the United States consumes 65 lb added sucrose and 40 lb high-fructose corn syrup solids per year.

Starch blockers had been marketed many years ago as a means of losing weight without having to exercise or reduce your daily caloric intake. Starch blockers were based on a protein found in beans, which blocked the action of amylase. Thus, as the advertisements proclaimed, one could eat a large amount of starch during a meal, and as long as you took the starch blocker, the starch would pass through the digestive track without being metabolized. Unfortunately, this was too good to be true, and starch blockers were never shown to be effective in aiding weight loss. This was probably because of a combination of factors, such as inactivation of the inhibitor by the low pH in the stomach, and an excess of amylase activity as compared with the amount of starch blocker ingested. Recently this issue has been revisited, as a starch blocker from wheat has been developed that may work as advertised, although much more work is required to determine whether this amylase inhibitor will be safe and effective in humans.

Although all cells require glucose for metabolic functions, neither glucose nor other sugars are specifically required in the diet. Glucose can be synthesized from many amino acids found in dietary protein. Fructose, galactose, xylose, and all the other sugars required for metabolic processes in the human can be synthesized from glucose.

II. DIGESTION OF DIETARY CARBOHYDRATES

In the digestive tract, dietary polysaccharides and disaccharides are converted to monosaccharides by glycosidases, enzymes that hydrolyze the glycosidic bonds between the sugars. All of these enzymes exhibit some specificity for the sugar, the glycosidic bond (α or β), and the number of saccharide units in the chain. The monosaccharides formed by glycosidases are transported across the intestinal mucosal cells into the interstitial fluid and subsequently enter the bloodstream. Undigested carbohydrates enter the colon, where they may be fermented by bacteria.

A. Salivary and Pancreatic α-Amylase

The digestion of starch (amylopectin and amylose) begins in the mouth, where chewing mixes the food with saliva. The salivary glands secrete approximately 1 liter of liquid per day into the mouth, containing salivary α-amylase and other components. α-Amylase is an endoglucosidase, which means that it hydrolyzes internal α-1,4 bonds between glucosyl residues at random intervals in the polysaccharide chains (Fig. 27.3). The shortened polysaccharide chains that are formed are called α-dextrins. Salivary α-amylase may be largely inactivated by the acidity of the stomach contents, which contain HCl secreted by the peptic cells.

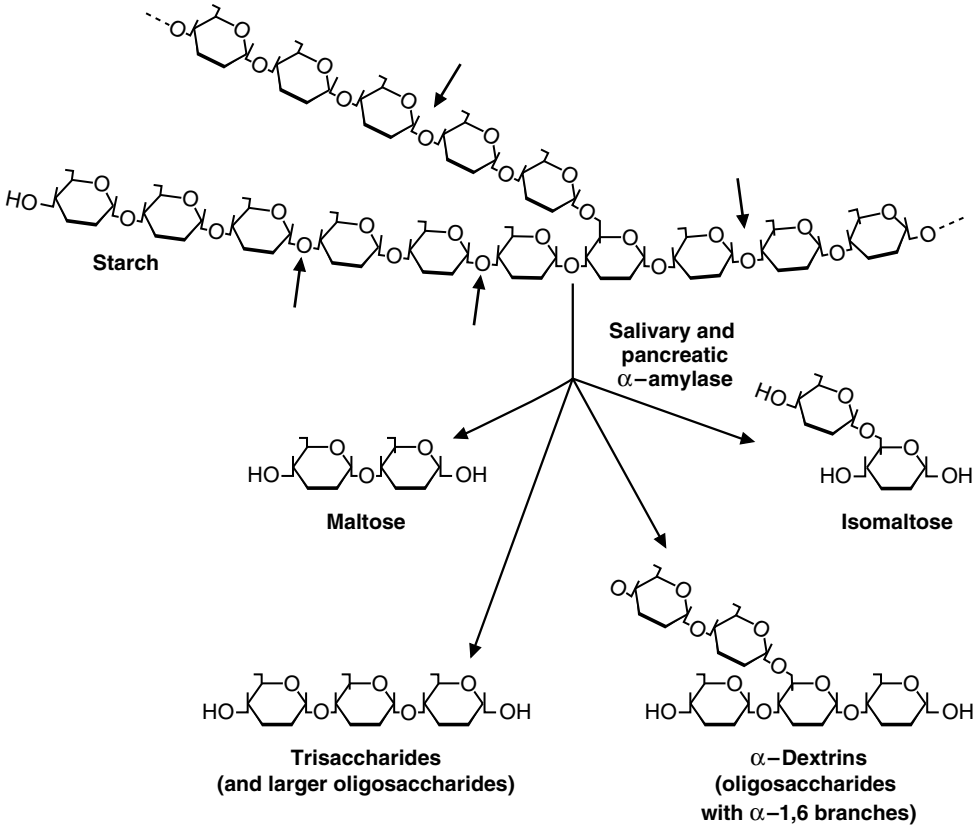


Fig. 27.3. Action of pancreatic and α-amylase.

The acidic gastric juice enters the duodenum, the upper part of the small intestine, where digestion continues. Secretions from the exocrine pancreas (approximately 1.5 liters/day) flow down the pancreatic duct and also enter the duodenum. These secretions contain bicarbonate (HCO_3^-), which neutralizes the acidic pH of stomach contents, and digestive enzymes, including pancreatic α-amylase.

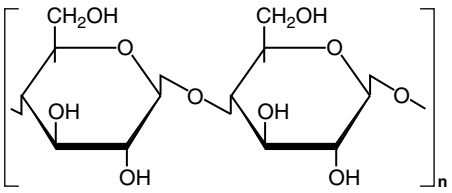
Pancreatic α-amylase continues to hydrolyze the starches and glycogen, forming the disaccharide maltose, the trisaccharide maltotriose, and oligosaccharides. These oligosaccharides, called limit dextrins, are usually four to nine glucosyl units long and contain one or more α-1,6 branches. The two glucosyl residues that contain the α-1,6 glycosidic bond will eventually become the disaccharide isomaltose, but α-amylase does not cleave these branched oligosaccharides all the way down to isomaltose.

α-Amylase has no activity toward sugar containing polymers other than glucose linked by α-1,4 bonds. α-Amylase displays no activity toward the α-1,6- bond at branchpoints and has little activity for the α-1,4 bond at the nonreducing end of a chain.

Amylase activity in the gut is abundant and is not normally rate limiting for the process of digestion. Alcohol-induced pancreatitis or surgical removal of part of the pancreas can decrease pancreatic secretion. Pancreatic exocrine secretion into the intestine also can be decreased through cystic fibrosis, in which mucus blocks the pancreatic duct, which eventually degenerates. However, pancreatic exocrine secretion can be decreased to 10% of normal and still not affect the rate of starch digestion, because amylases are secreted in the saliva and pancreatic fluid in excessive amounts. In contrast, protein and fat digestion is more strongly affected in cystic fibrosis.

B. Disaccharidases of the Intestinal Brush-Border Membrane

The dietary disaccharides lactose and sucrose, as well as the products of starch digestion, are converted to monosaccharides by glycosidases attached to the membrane in the brush-border of absorptive cells (Fig. 27.4). The different glycosidase activities are found in four glycoproteins: glucoamylase, the sucrase–maltase complex, the smaller glycoprotein trehalase, and lactase-glucosylceramidase (Table 27.1). These glycosidases are collectively called the small intestinal disaccharidases, although glucoamylase is really an oligosaccharidase.



Can the glycosidic bonds of the structure shown above be hydrolyzed by α-amylose?

1. GLUCOAMYLASE

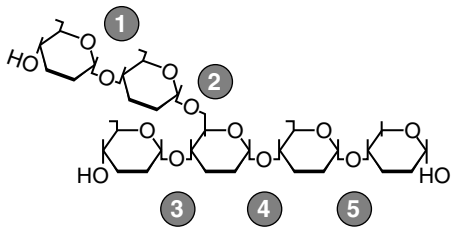
Glucoamylase and the sucrase–isomaltase complex have similar structures and exhibit a great deal of sequence homogeneity (Fig. 27.5). A membrane-spanning domain near the N-terminal attaches the protein to the luminal membrane. The long polypeptide chain forms two globular domains, each with a catalytic site. In glucoamylase, the two catalytic sites have similar activities, with only small differences in substrate specificity. The protein is heavily glycosylated with oligosaccharides that protect it from digestive proteases.

Glucoamylase is an exoglucosidase that is specific for the α–1,4 bonds between glucosyl residues (Fig. 27.6). It begins at the nonreducing end of a polysaccharide or limit dextrin, and sequentially hydrolyzes the bonds to release glucose monosaccharides. It will digest a limit dextrin down to isomaltose, the glucosyl disaccharide with an α–1,6-branch, that is subsequently hydrolyzed principally by the isomaltase activity in the sucrase–isomaltase complex.

Individuals with genetic deficiencies of the sucrase-isomaltase complex show symptoms of sucrose intolerance but are able to digest normal amounts of starch in a meal, without problems. The maltase activity in the glucoamylase complex, and residual activity in the sucrase-isomaltase complex (which is normally present in excess of need) is apparently sufficient to digest normal amounts of dietary starch.

2. SUCRASE–ISOMALTASE COMPLEX

The structure of the sucrase–isomaltase complex is very similar to that of glucoamylase, and these two proteins have a high degree of sequence homology. However, after the single polypeptide chain of sucrase–isomaltase is inserted through the membrane and the protein protrudes into the intestinal lumen, an intestinal protease clips it into two separate subunits that remain attached to each other. Each subunit has a catalytic site that differs in substrate specificity from the other through noncovalent interactions. The sucrase–maltase site accounts for approximately 100% of the intestine's ability to hydrolyze sucrose in addition to maltase activity; the isomaltase–maltase site accounts for almost all of the intestine's ability to hydrolyze α-1,6-bonds (Fig. 27.7), in addition to maltase activity. Together, these sites account for approximately 80% of the maltase activity of the small intestine. The remainder of the maltase activity is found in the glucoamylase complex.



Which of the bonds in the structure above are hydrolyzed by the sucrase–isomaltase complex? Which by glucoamylase?

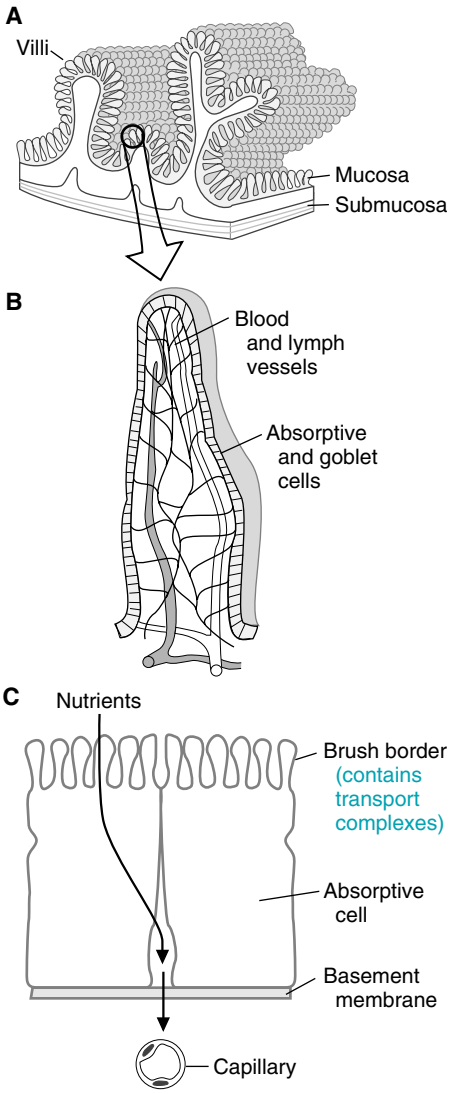


Fig. 27.4. Location of disaccharide complexes in intestinal villi.

Table 27.1. The Different Forms of the Brush Border Glycosidases

Complex	Catalytic Sites	Principal Activities
β-Glucoamylase	α-Glucosidase	Split α-1,4 glycosidic bonds between glucosyl units, beginning sequentially with the residue at the tail end (nonreducing end) of the chain. This is an exoglycosidase. Substrates include amylase, amylopectin, glycogen and maltose.
	α-Glucosidase	Same as above, but with slightly different specificity and affinities for the substrates
Sucrase–Isomaltase	Sucrase–maltase	Splits sucrose, maltose, and maltotriose
	Isomaltase–maltase	Splits α-1, 6 bonds in a number of limit dextrins, as well as the α-1,4 bonds in maltose and maltotriose.
β-Glycosidase	Glucosyl–ceramidase (Phlorizin hydrolase)	Splits β-glycosidic bonds between glucose or galactose and hydrophobic residues, such as the glycolipids glucosylceramide and galactosylceramide
	Lactase	Splits the β-1,4 bond between glucose and galactose. To a lesser extent also splits the β-1,4 bond between some cellulose disaccharides.
Trehalase	Trehalase	Splits bond in trehalose, which is 2 glucosyl units linked α-1,1 through their anomeric carbons.

3. TREHALASE

Trehalase is only half as long as the other disaccharidases and has only one catalytic site. It hydrolyzes the glycosidic bond in trehalose, a disaccharide composed of two glucosyl units linked by an α-bond between their anomeric carbons (Fig. 27.8). Trehalose, which is found in insects, algae, mushrooms, and other fungi, is not currently a major dietary component in the United States. However, unwitting consumption of trehalose can cause nausea, vomiting, and other symptoms of severe gastrointestinal distress if consumed by an individual deficient in the enzyme. Trehalase deficiency was discovered when a woman became very sick after eating mushrooms and was initially thought to have α-amanitin poisoning.

4. β-GLYCOSIDASE COMPLEX (LACTASE-GLUCOSYLCERAMIDASE)

The β-glycosidase complex is another large glycoprotein found in the brush border that has two catalytic sites extending in the lumen of the intestine. However, its primary structure is very different from the other enzymes, and it is attached to the membrane through its carboxyl end by a phosphatidylglycan anchor (see Fig.10.7). The lactase catalytic site hydrolyzes the β-bond connecting glucose and galactose in lactose (a β-galactosidase activity; Fig. 27.9). The major activity of the other catalytic site in humans is the β-bond between glucose or galactose and ceramide in glycolipids (this catalytic site is sometimes called phlorizin hydrolase, named for its ability to hydrolyze an artificial substrate).

5. LOCATION WITHIN THE INTESTINE

The production of maltose, maltotriose, and limit dextrins by pancreatic α-amylase occurs in the duodenum, the most proximal portion of the small intestine. Sucrase–isomaltase activity is highest in the jejunum, where the enzymes can hydrolyze sucrose and the products of starch digestion. β-Glycosidase activity is also highest in the jejenum. Glucoamylase activity progressively increases along the length of the small intestine, and its activity is highest in the ileum. Thus, it

A: No. This polysaccharide is cellulose, which contains β-1,4 glycosidic bonds. Pancreatic and salivary α-amylase cleave only α-1,4 bonds between glucosyl units.

A: Bonds (1) and (3) would first be hydrolyzed by glucoamylase. Bond (2) would require isomaltase. Bonds (4) and (5) could then be hydrolyzed by the sucrase–isomaltase complex, or by the glucoamylase complex, all of which can convert maltotriose and maltose to glucose.

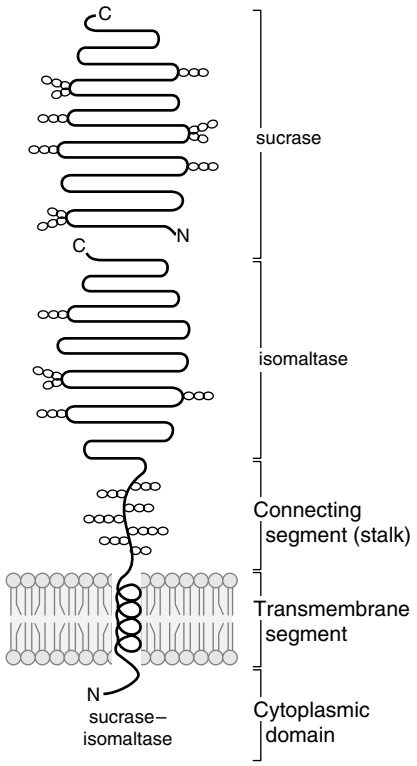


Fig. 27.5. The major portion of the sucrase-isomaltase complex, containing the catalytic sites, protrudes from the absorptive cells into the lumen of the intestine. Other domains of the protein form a connecting segment (stalk), and an anchoring segment that extends through the membrane into the cell. The complex is synthesized as a single polypeptide chain that is split into its two enzyme subunits extracellularly. Each subunit is a domain with a catalytic site (sucrase-maltase) and isomaltase-maltase sites. In spite of their maltase activity, these catalytic sites are often called just sucrase and isomaltase.

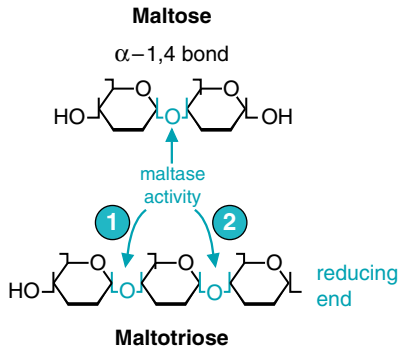


Fig. 27.6. Glucoamylase activity. Glucoamylase is an α-1,4 exoglycosidase, which initiates cleavage at the nonreducing end of the sugar. Thus, for malotriose, the bond labeled 1 will be hydrolyzed first, which frees up the bond at position 2 to be the next one hydrolyzed.

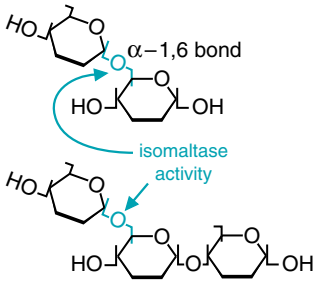


Fig. 27.7. Isomaltase activity. Arrows indicate the α-1,6 bonds that are cleaved.

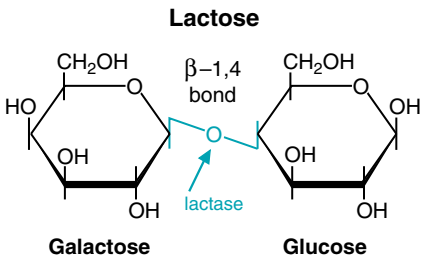


Fig. 27.9. Lactase activity. Lactase is a β-galactosidase. It cleaves the β-galactoside lactose, the major sugar in milk, forming galactose and glucose.

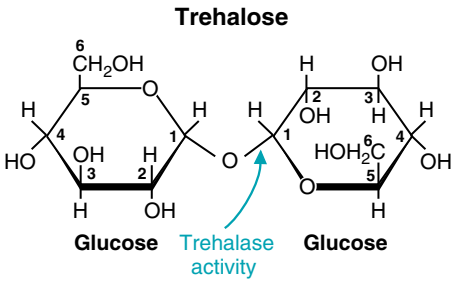


Fig. 27.8. Trehalose. This disaccharide contains two glucose moieties linked by an unusual bond that joins their anomeric carbons. It is cleaved by trehalase.

presents a final opportunity for digestion of starch oligomers that have escaped amylase and disaccharidase activities at the more proximal regions of the intestine.

C. Metabolism of Sugars by Colonic Bacteria

Not all of the starch ingested as part of foods is normally digested in the small intestine (Fig. 27.10). Starches high in amylose, or less well hydrated (e.g., starch in dried beans), are resistant to digestion and enter the colon. Dietary fiber and undigested sugars also enter the colon. Here colonic bacteria rapidly metabolize the saccharides, forming gases, short-chain fatty acids, and lactate. The major short-chain fatty acids formed are acetic acid (two carbon), propionic acid (three carbon), and butyric acid (four carbon). The short-chain fatty acids are absorbed by the colonic mucosal cells and can provide a substantial source of energy for these cells. The major gases formed are hydrogen gas (H_2), carbon dioxide (CO_2), and methane (CH_4). These gases are released through the colon, resulting in flatulence, or in the breath. Incomplete products of digestion in the intestines increase the retention of water in the colon, resulting in diarrhea.

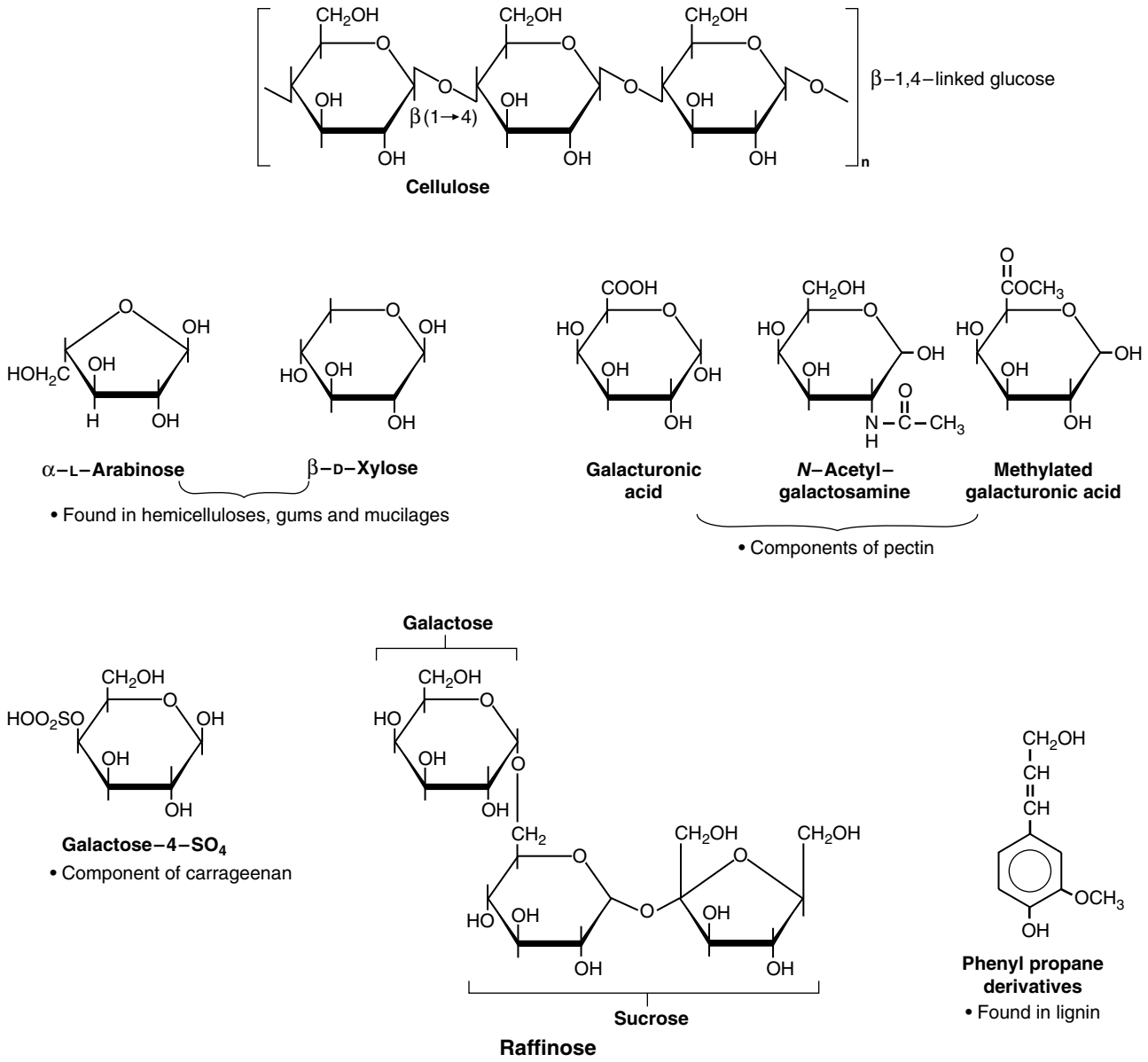


Fig. 27.10. Some indigestible carbohydrates. These compounds are components of dietary fiber.

Nona Melos was given a hydrogen breath test, a test measuring the amount of hydrogen gas released after consuming a test dose of sugar. The association of **Nona Melos's** symptoms with her ingestion of fruit juices suggests that she might have a problem resulting from a low sucrase activity or an inability to absorb fructose. Her ability to thrive and her adequate weight gain suggest that any deficiencies of the sucrase–isomaltase complex must be partial and do not result in a functionally important reduction in maltase activity (maltase activity is also present in the glucoamylase complex). Her urine tested negative for sugar, suggesting the problem is in digestion or absorption, because only sugars that are absorbed and enter the blood can be found in urine. The basis of the hydrogen breath test is that if a sugar is not absorbed, it is metabolized in the intestinal lumen by bacteria that produce various gases, including hydrogen. The test is often accompanied by measurements of the amount of sugar appearing in the blood or feces, and acidity of the feces.

Q: Beans, peas, soybeans, and other leguminous plants contain oligosaccharides with (1,6)-linked galactose residues that cannot be hydrolyzed for absorption, including sucrose with 1, 2, or 3 galactose residues attached (see Fig. 27.10). What is the fate of these polysaccharides in the intestine?

D. Lactose Intolerance

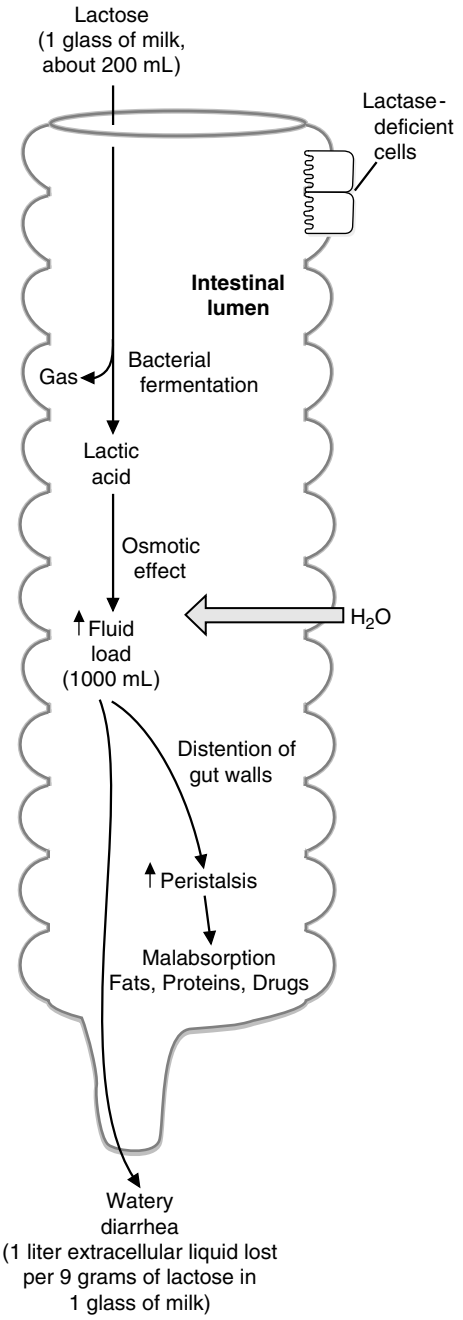
Lactose intolerance refers to a condition of pain, nausea, and flatulence after the ingestion of foods containing lactose, most notably dairy products. Although it is often caused by low levels of lactase, it also can be caused by intestinal injury (defined below).

1. NONPERSISTENT AND PERSISTANT LACTASE

Lactase activity increases in the human from about 6 to 8 weeks of gestation, and it rises during the late gestational period (27–32 weeks) through full term. It remains high for about 1 month after birth and then begins to decline. For most of the world's population, lactase activity decreases to adult levels at approximately 5 to 7 years of age. Adult levels are less than 10% of that present in infants. These populations have adult hypolactasia (formerly called adult lactase deficiency) and exhibit the lactase nonpersistence phenotype. In people who are derived mainly from western Northern Europeans, and milk-dependent Nomadic tribes of Saharan Africa, the levels of lactase remain at, or only slightly below, infant levels throughout adulthood (lactase persistence phenotype). Thus, adult hypolactasia is the normal condition for most of the world's population. (Table 27.2).

2. INTESTINAL INJURY

Intestinal diseases that injure the absorptive cells of the intestinal villi diminish lactase activity along the intestine, producing a condition known as secondary lactase deficiency. Kwashiorkor (protein malnutrition), colitis, gastroenteritis, tropical and



Lactose intolerance can either be the result of a primary deficiency of lactase production in the small bowel (as is the case for **Deria Voider**) or it can be secondary to an injury to the intestinal mucosa, where lactase is normally produced. The lactose that is not absorbed is converted by colonic bacteria to lactic acid, methane gas (CH_4), and H_2 gas (see figure on left). The osmotic effect of the lactose and lactic acid in the bowel lumen is responsible for the diarrhea often seen as part of this syndrome. Similar symptoms can result from sensitivity to milk proteins (milk intolerance) or from the malabsorption of other dietary sugars.

In adults suspected of having a lactase deficiency, the diagnosis is usually made inferentially when avoidance of all dairy products results in relief of symptoms and a rechallenge with these foods reproduces the characteristic syndrome. If the results of these measures are equivocal, however, the malabsorption of lactose can be more specifically determined by measuring the H_2 content of the patient's breath after a test dose of lactose has been consumed.

Deria Voider's symptoms did not appear if she took tablets containing lactase when she ate dairy products.

A: These sugars are not digested well by the human intestine but form good sources of energy for the bacteria of the gut. These bacteria convert the sugars to H_2, lactic acid and short-chain fatty acids. The amount of gas released after a meal containing beans is especially notorious.

Table 27.2. Prevalence of Late-Onset Lactase Deficiency

Group	Prevalence (%)
U.S. population	
Asians	100
American Indians (Oklahoma)	95
Black Americans	81
Mexican Americans	56
White Americans	24
Other Populations	
Ibo, Yoruba (Nigeria)	89
Italians	71
Aborigines (Australia)	67
Greeks	53
Danes	3
Dutch	0

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nontropical sprue, and excessive alcohol consumption fall into this category. These diseases also affect other disaccharidases, but sucrase, maltase, isomaltase, and glucoamylase activities are usually present at such excessive levels that there are no pathologic effects. Lactase is usually the first activity lost and the last to recover.

III. DIETARY FIBER

Dietary fiber is the portion of the diet resistant to digestion by human digestive enzymes. It consists principally of plant materials that are polysaccharide derivatives and lignan (see Fig.27.10). The components of fiber are often divided into the categories of soluble and insoluble fiber, according to their ability to dissolve in water. Insoluble fiber consists of three major categories; cellulose, hemicellulose, and lignins. Soluble fiber categories include pectins, mucilages, and gums (Table 27.3). Although human enzymes cannot digest fiber, the bacterial flora in the normal human gut may metabolize the more soluble dietary fibers to gases and short-chain fatty acids, much as they do undigested starch and sugars. Some of these

Table 27.3 Types of Fiber in the Diet

Classical Nomenclature	Classes of compounds	Dietary Sources
Insoluble Fiber		
Cellulose	Polysaccharide composed of glucosyl residues linked β-1,4.	Whole wheat flour, unprocessed bran, cabbage, peas, green beans, wax beans, broccoli, brussel sprouts, cucumber with skin, green peppers, apples, carrots
Hemicelluloses	Polymers of arabinoxylans or galactomannans	Bran cereals, whole grains, brussel sprouts, mustard beans, beet root
Lignin	Noncarbohydrate, polymeric derivatives of phenylpropane	Bran cereals, unprocessed bran, strawberries, eggplant, peas, green beans, radishes
Water Soluble Fiber (or dispersable)		
Pectic Substances	Galactouranans, arabinoglactans, β-glucans, arabinoxylans	Squash, apples, citrus fruits
Gums	Galactomannans, arabinogalactans	Oatmeal, dried beans, cauliflower, green beans, cabbage, carrots, dried peas, potatoes, strawberries
Mucilages	Wide range of branched and substituted galactans	Flax seed, psyllium, mustard seed

fatty acids may be absorbed and used by the colonic epithelial cells of the gut, and some may travel to the liver through the hepatic portal vein. We may obtain as much as 10% of our total calories from compounds produced by bacterial digestion of substances in our digestive tract.

In 2002, the Committee on Dietary Reference Intakes issued new guidelines for fiber ingestion; anywhere from 19 to 38 g/day, depending on age and sex of the individual. No distinction was made between soluble and insoluble fibers. Adult males between the ages of 14 and 50 years require 38 grams of fiber per day. Females from ages 4 to 8 years require 25 g/day; from ages 9 to 16 years, 26 g/day; and from ages 19 to 30, 25 g/day. These numbers are increased during pregnancy and lactation. One beneficial effect of fiber is seen in diverticular disease, in which sacs or pouches may develop in the colon because of a weakening of the muscle and submucosal structures. Fiber is thought to "soften" the stool, thereby reducing pressure on the colonic wall and enhancing expulsion of feces.

Certain types of soluble fiber have been associated with disease prevention. For example, pectins may lower blood cholesterol levels by binding bile acids. β-glucan (obtained from oats) has also been shown, in some studies, to reduce cholesterol levels through a reduction in bile acid resorption in the intestine (see Chapter 34). Pectins also may have a beneficial effect in the diet of individuals with diabetes mellitus by slowing the rate of absorption of simple sugars and preventing high blood glucose levels after meals. However, each of the beneficial effects which have been related to "fiber" are relatively specific for the type of fiber, and the physical form of food which contains the fiber. This factor, along with many others, has made it difficult to obtain conclusive results from studies of the effects of fiber on human health.

Pectins are found in fruits, such as apples. Could this be the basis for the saying "An apple a day keeps the doctor away"?

Carrageenan is a type of fiber derived from seaweed. It is composed of sulfated galactose and galacturonic acid derivatives (see Fig. 27.10). The negatively charged sulfate groups form hydrogen bonds with water and convert the polysaccharide into a gel-like substance. It is added to many foods, such as ice cream and McDonald's McLean burger.

IV. ABSORPTION OF SUGARS

Once the carbohydrates have been split into monosaccharides, the sugars are transported across the intestinal epithelial cells and into the blood for distribution to all tissues. Not all complex carbohydrates are digested at the same rate within the intestine, and some carbohydrate sources lead to a near-immediate rise in blood glucose levels after ingestion, whereas others slowly raise blood glucose levels over an extended period after ingestion. The glycemic index of a food is an indication of how rapidly blood glucose levels rise after consumption. Glucose and maltose have the highest glycemic indices (142, with white bread defined as an index of 100). Table 27.4 indicates the glycemic index for a variety of food types. Although there is no need to memorize this table, note that cornflakes and potatoes have high glycemic indices, whereas yogurt and skim milk have particularly low glycemic indices.

The glycemic response to ingested foods depends not only on the glycemic index of the foods, but also on the fiber and fat content of the food, as well as its method of preparation. Highly glycemic carbohydrates can be consumed before and after exercise, as their metabolism results in a rapid entry of glucose into the blood, where it is then immediately available for muscle use. Low glycemic carbohydrates enter the circulation slowly and can be used to best advantage if consumed before exercise, such that as exercise progresses glucose is slowly being absorbed from the intestine into the circulation, where it can be used to maintain blood glucose levels during the exercise period.

A. Absorption by the Intestinal Epithelium

Glucose is transported through the absorptive cells of the intestine by facilitated diffusion and by Na^+-dependent facilitated transport. (See Chapter 10 for a description of transport mechanisms.) Glucose, therefore, enters the absorptive cells by binding

The dietician explained to **Ann Sulin** the rationale for a person with diabetes to watch their diet. It is important for Ann to add a variety of fibers to her diet. The gel-forming, water-retaining pectins and gums delay gastric emptying and retard the rate of absorption of disaccharides and monosaccharides, thus reducing the rate at which blood glucose levels rise. The glycemic index of foods also needs to be considered for appropriate maintenance of blood glucose levels in diabetic patients. Consumption of a low glycemic index diet results in a lower rise in blood glucose levels after eating, which can be more easily controlled by exogenous insulin. For example, Ms. Sulin is advised to eat pasta and rice (glycemic index of 67 and 65, respectively) instead of potatoes (glycemic index of 80–120, depending on the method of preparation), and to incorporate breakfast cereals composed of wheat bran, barley, and oats into her morning routine.

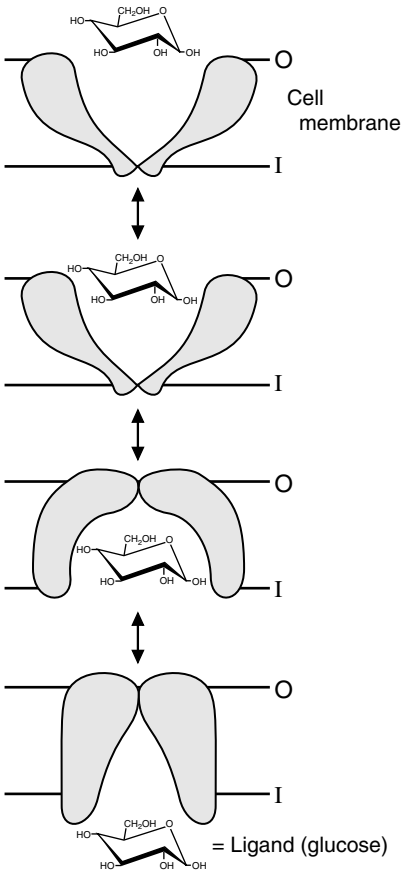

Fig. 27.11. Facilitative transport. Transport of glucose occurs without rotation of the glucose molecule. Multiple groups on the protein bind the hydroxyl groups of glucose and close behind it as it is released into the cell (i.e., the transporter acts like a "gated pore"). O = outside; I = inside.

The glucose molecule is extremely polar and cannot diffuse through the hydrophobic phospholipid bilayer of the cell membrane. Each hydroxyl group of the glucose molecule forms at least two hydrogen bonds with water molecules, and random movement would require energy to dislodge the polar hydroxyl groups from their hydrogen bonds and to disrupt the Van der Waals' forces between the hydrocarbon tails of the fatty acids in the membrane phospholipid.

The epithelial cells of the kidney, which reabsorb glucose into the blood, have Na^+-dependent glucose transporters similar to those of intestinal epithelial cells. They are thus also able to transport glucose against its concentration gradient. Other types of cells use mainly facilitative glucose transporters that carry glucose down its concentration gradient.

Table 27.4 Glycemic Index of Selected Foods, with Values Adjusted to White Bread of 100

Breads		Legumes	
Whole wheat	100	Baked beans (canned)	70
Pumpernickel (whole grain rye)	88	Butter beans	46
Pasta		Garden peas (frozen)	85
Spaghetti, white, boiled	67		
		Kidney beans (dried)	43
Cereal grains		Kidney beans (canned)	74
Barley (pearled)	36	Peanuts	15
Rice (instant, boiled 1 min)	65	Fruit	
Rice, polished (boiled 10–25 min)	81	Apple	52
Sweet corn	80	Apple juice	45
Breakfast cereals		Orange	59
All bran	74	Raisins	93
Cornflakes	121	Sugars	
Muesli	96	Fructose	27
Cookies		Glucose	142
Oatmeal	78	Lactose	57
Plain water crackers	100	Sucrose	83
Root vegetables		Dairy Products	
Potatoes (instant)	120	Ice cream	69
Potato (new,white, boiled)	80	Whole milk	44
Potato chips	77	Skim milk	46
Yam	74	Yogurt	52

to transport proteins, membrane-spanning proteins that bind the glucose molecule on one side of the membrane and release it on the opposite side (Fig. 27.11). Two types of glucose transport proteins are present in the intestinal absorptive cells: the Na^+-dependent glucose transporters and the facilitative glucose transporters (Fig. 27.12).

1. NA^+-DEPENDENT TRANSPORTERS

Na^+-dependent glucose transporters, which are located on the luminal side of the absorptive cells, enable these cells to concentrate glucose from the intestinal lumen. A low intracellular Na^+ concentration is maintained by a Na^+,K^+-ATPase on the serosal (blood) side of the cell that uses the energy from ATP cleavage to pump Na^+ out of the cell into the blood. Thus, the transport of glucose from a low concentration in the lumen to a high concentration in the cell is promoted by the cotransport of Na^+ from a high concentration in the lumen to a low concentration in the cell (secondary active transport).

2. FACILITATIVE GLUCOSE TRANSPORTERS

Facilitative glucose transporters, which do not bind Na^+, are located on the serosal side of the cells. Glucose moves via the facilitative transporters from the high concentration inside the cell to the lower concentration in the blood without the expenditure of energy. In addition to the Na^+-dependent glucose transporters, facilitative transporters for glucose also exist on the luminal side of the absorptive cells. The various types of facilitative glucose transporters found in the plasma membranes of cells (referred to as GLUT 1 to GLUT 5), are described in Table 27.5. One common structural theme to these proteins is that they all contain 12 membrane-spanning domains. Note that the sodium-linked transporter on the luminal side of the intestinal epithelial cell is not a member of the GLUT family.

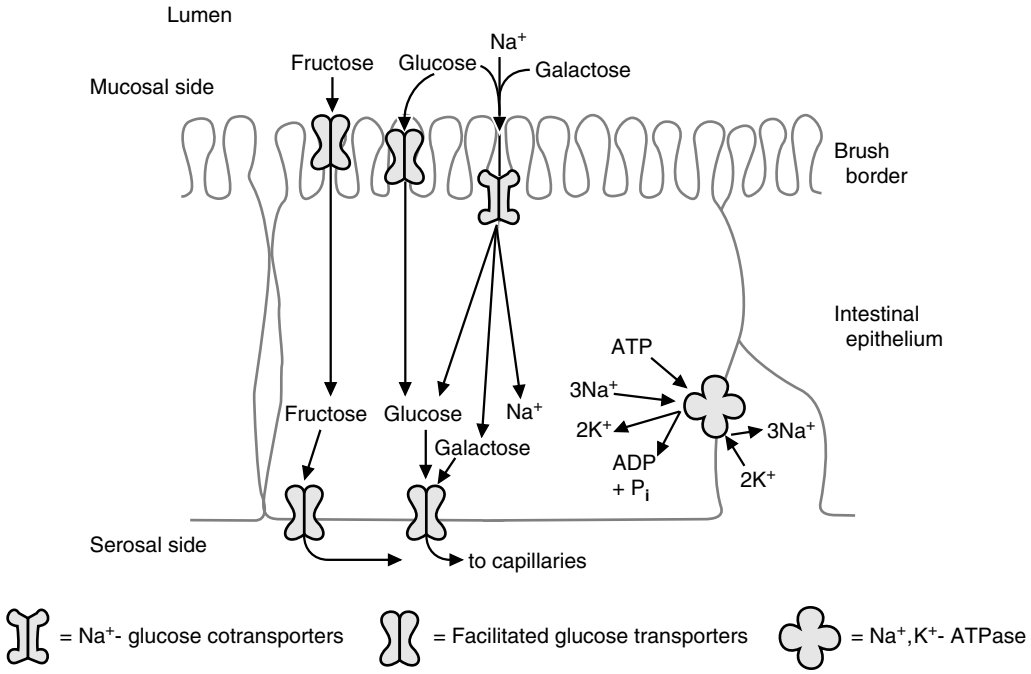

Fig. 27.12. Na^+-dependent and facilitative transporters in the intestinal epithelial cells. Both glucose and fructose are transported by the facilitated glucose transporters on the luminal and serosal sides of the absorptive cells. Glucose and galactose are transported by the Na^+-glucose cotransporters on the luminal (mucosal) side of the absorptive cells.

Table 27.5. Properties of the GLUT 1-GLUT 5 Isoforms of the Glucose Transport Proteins

Transporter	Tissue Distribution	Comments
GLUT 1	Human erythrocyte Blood-brain barrier Blood-retinal barrier Blood-placental barrier Blood-testis barrier	Expressed in cell types with barrier functions; a high-affinity glucose transport system
GLUT 2	Liver Kidney Pancreatic β-cell Serosal surface of Intestinal mucosa cells	A high capacity, low affinity transporter. May be used as the glucose sensor in the pancreas.
GLUT 3	Brain (neurons)	Major transporter in the central nervous system. A high-affinity system.
GLUT 4	Adipose tissue Skeletal muscle Heart muscle	Insulin-sensitive transporter. In the presence of insulin the number of GLUT 4 transporters increases on the cell surface. A high-affinity system
GLUT 5	Intestinal epithelium Spermatozoa	This is actually a fructose transporter.

Genetic techniques have identified additional GLUT transporters (GLUT 7-12), but the role of these transporters has not yet been fully described.

3. GALACTOSE AND FRUCTOSE ABSORPTION THROUGH GLUCOSE TRANSPORTERS

Galactose is absorbed through the same mechanisms as glucose. It enters the absorptive cells on the luminal side via the Na^+-dependent glucose transporters and facilitative glucose transporters and is transported through the serosal side on the facilitative glucose transporters.

Fructose both enters and leaves absorptive epithelial cells by facilitated diffusion, apparently via transport proteins that are part of the GLUT family. The transporter on the luminal side has been identified as GLUT 5. Although this transporter can transport glucose, it has a much higher activity with fructose (see Fig. 27.12). Other fructose transport proteins also may be present. For reasons as yet unknown, fructose is absorbed at a much more rapid rate when it is ingested as sucrose than when it is ingested as a monosaccharide.

B. Transport of Monosaccharides into Tissues

The properties of the GLUT transport proteins differ between tissues, reflecting the function of glucose metabolism in each tissue. In most cell types, the rate of glucose transport across the cell membrane is not rate-limiting for glucose metabolism. This is because the isoform of transporter present in these cell types has a relatively low K_m for glucose (that is, a low concentration of glucose will result in half the maximal rate of glucose transport) or is present in relatively high concentration in the cell membrane so that the intracellular glucose concentration reflects that in the blood. Because the hexokinase isozyme present in these cells has an even lower K_m for glucose (0.05–0.10 mM), variations in blood glucose levels do not affect the intracellular rate of glucose phosphorylation. However, in several tissues, the rate of transport becomes rate limiting when the serum level of glucose is low or when low levels of insulin signal the absence of dietary glucose.

In the liver, the K_m for the glucose transporter (GLUT 2) is relatively high compared with that of other tissues, probably 15 mM or above. This is in keeping with the liver's role as the organ that maintains blood glucose levels. As such, the liver will only convert glucose into other energy storage molecules when the blood glucose levels are high, such as the time immediately after ingestion of a meal. In muscle and adipose tissue, the transport of glucose is greatly stimulated by insulin. The mechanism involves the recruitment of glucose transporters (specifically, GLUT 4) from intracellular vesicles into the plasma membrane (Fig. 27.13). In adipose tissue, the stimulation of glucose transport across the plasma membrane by insulin increases its availability for the synthesis of fatty acids and glycerol from the glycolytic pathway. In skeletal muscle, the stimulation of glucose transport by insulin increases its availability for glycolysis and glycogen synthesis.

The erythrocyte (red blood cell) is an example of a tissue in which glucose transport is not rate-limiting. Although the glucose transporter (GLUT 1) has a K_m of 1 to 7 mM, it is present in extremely high concentrations, constituting approximately 5% of all membrane proteins. Consequently, as the blood glucose levels fall from a postprandial level of 140 mg/dL (7.5 mM) to the normal fasting level of 80 mg/dL (4.5 mM), or even the hypoglycemic level of 40 mg/dL (2.2 mM), the supply of glucose is still adequate for the rates at which glycolysis and the pentose phosphate pathway operate.

V. GLUCOSE TRANSPORT THROUGH THE BLOOD-BRAIN BARRIER AND INTO NEURONS

A hypoglycemic response is elicited by a decrease of blood glucose concentration to some point between 18 and 54 mg/dL (1 and 3 mM). The hypoglycemic response is a result of a decreased supply of glucose to the brain and starts with light-headedness and dizziness and may progress to coma. The slow rate of transport of glucose through the blood-brain barrier (from the blood into the cerebrospinal fluid) at low levels of glucose is thought to be responsible for this neuroglycopenic response. Glucose transport from the cerebrospinal fluid across the plasma membranes of neurons is rapid and is not rate limiting for ATP generation from glycolysis.

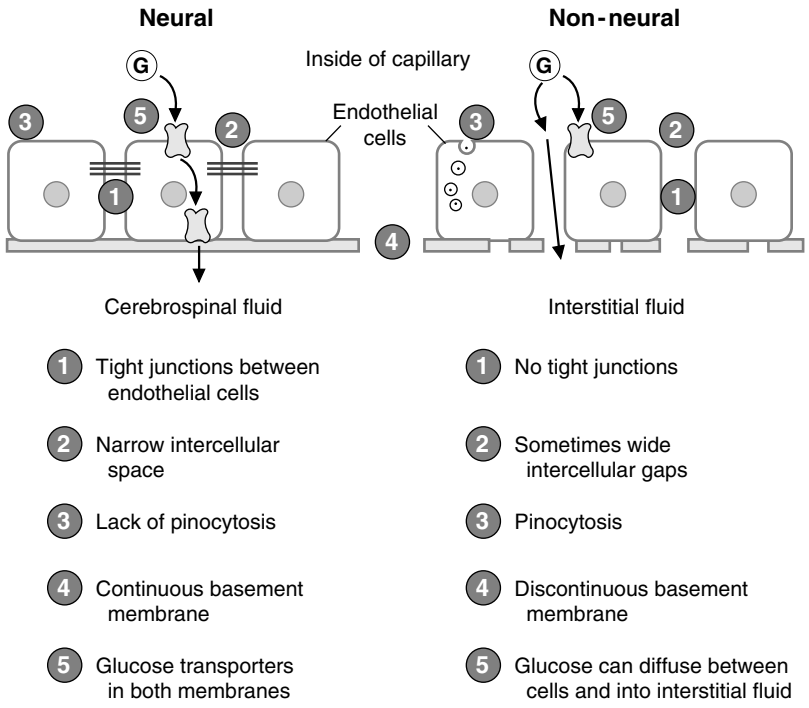

Fig. 27.14. Glucose transport through the capillary endothelium in neural and nonneural tissues. Characteristics of transport in each type of tissue are listed by numbers that refer to the numbers in the drawing. G = glucose.

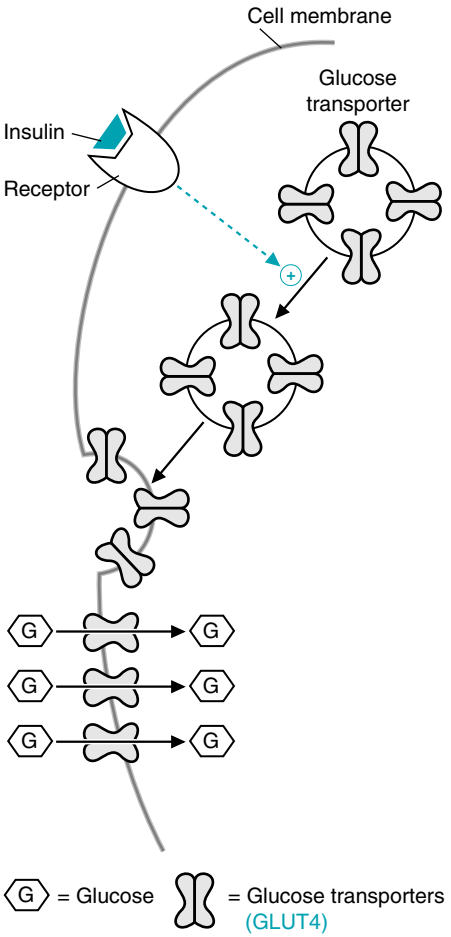

Fig. 27.13. Stimulation by insulin of glucose transport into muscle and adipose cells. Binding of insulin to its cell membrane receptor causes vesicles containing glucose transport proteins to move from inside the cell to the cell membrane.

In the brain, the endothelial cells of the capillaries have extremely tight junctions, and glucose must pass from the blood into the extracellular cerebrospinal fluid by GLUT 1 transporters in the endothelial cell membranes (Fig. 27.14), and then through the basement membrane. Measurements of the overall process of glucose transport from the blood into the brain (mediated by GLUT 3 on neural cells) show a $K_{m,app}$ of 7 to 11 mM, and a maximal velocity not much greater than the rate of glucose utilization by the brain. Thus, decreases of blood glucose below the fasting level of 80 to 90 mg/dL (approximately 5 mM) are likely to significantly affect the rate of glucose metabolism in the brain, because of reduced glucose transport into the brain.

CLINICAL COMMENTS

One of five Americans experiences some form of gastrointestinal discomfort from 30 minutes to 12 hours after ingesting lactose-rich foods. Most become symptomatic when they consume more than 25 g lactose at one time (e.g., 1 pint of milk or its equivalent). **Deria Voider's** symptoms were caused by her "new" diet in this country, which included a glass of milk in addition to the milk she used on her cereal with breakfast each morning.

Management of lactose intolerance includes a reduction or avoidance of lactose-containing foods depending on the severity of the deficiency of intestinal lactase. Hard cheeses (cheddar, Swiss, Jarlsberg) are low in lactose and may be tolerated by patients with only moderate lactase deficiency. Yogurt with "live and active cultures" printed on the package contain bacteria that release free lactases when the bacteria are lysed by gastric acid and proteolytic enzymes. The free lactases then digest the

lactose. Commercially available milk products that have been hydrolyzed with a lactase enzyme provide a 70% reduction in total lactose content, which may be adequate to prevent digestive symptoms in mildly affected patients. Tablets and capsules containing lactase are also available and should be taken one-half hour before meals.

Many adults who have a lactase deficiency develop the ability to ingest small amounts of lactose in dairy products without experiencing symptoms. This adaptation probably involves an increase in the population of colonic bacteria that can cleave lactose and not a recovery or induction of human lactase synthesis. For many individuals, dairy products are the major dietary source of calcium, and their complete elimination from the diet can lead to osteoporosis.

Lactose, however, is used as a "filler" or carrying agent in more than 1,000 prescription and over-the-counter drugs in this country. People with lactose intolerance often unwittingly ingest lactose with their medications.

Poorly controlled diabetic patients such as **Ann Sulin** frequently have elevations in serum glucose levels (hyperglycemia). This is often attributable to a lack of circulating, active insulin, which will stimulate glucose uptake (through the recruitment of GLUT 4 transporters from the endoplasmic reticulum to the plasma membrane) by the peripheral tissues (heart, muscle, and adipose tissue). Without uptake by these tissues, glucose tends to accumulate within the bloodstream, leading to hyperglycemia.

The large amount of H_2 produced on fructose ingestion suggested that **Nona Melos's** problem was one of a deficiency in fructose transport into the absorptive cells of the intestinal villi. If fructose were being absorbed properly, the fructose would not have traveled to the colonic bacteria, which metabolized the fructose to generate the hydrogen gas. To confirm the diagnosis, a jejunal biopsy was taken; lactase, sucrase, maltase, and trehalase activities were normal in the jejunal cells. The tissue was also tested for the enzymes of fructose metabolism; these were in the normal range as well. Although Nona had no sugar in her urine, malabsorption of disaccharides can result in their appearance in the urine if damage to the intestinal mucosal cells allows their passage into the interstitial fluid. When Nona was placed on a diet free of fruit juices and other foods containing fructose, she did well and could tolerate small amounts of pure sucrose.

More than 50% of the adult population are estimated to be unable to absorb fructose in high doses (50 g), and more than 10% cannot completely absorb 25 g fructose. These individuals, like those with other disorders of fructose metabolism, must avoid fruits and other foods containing high concentrations of fructose.

BIOCHEMICAL COMMENTS

Cholera is an acute watery diarrheal disorder caused by the water-borne, Gram-negative bacterium *Vibrio cholerae*. It is a disease of antiquity; descriptions of epidemics of the disease date to before 500 BC. During epidemics, the infection is spread by large numbers of vibrio that enter water sources from the voluminous liquid stools and contaminate the environment, particularly in areas of extreme poverty where plumbing and modern waste-disposal systems are primitive or nonexistent.

After being ingested, the *V. cholerae* organisms attach to the brush border of the intestinal epithelium and secrete an exotoxin that binds irreversibly to a specific chemical receptor (G_{M1} ganglioside) on the cell surface. This exotoxin catalyzes an ADP-ribosylation reaction that increases adenylate cyclase activity and thus cAMP levels in the enterocyte. As a result, the normal absorption of sodium, anions, and water from the gut lumen into the intestinal cell is markedly diminished. The exotoxin also stimulates the crypt cells to secrete chloride, accompanied by cations

and water, from the bloodstream into the lumen of the gut. The resulting loss of solute-rich diarrheal fluid may, in severe cases, exceed 1 liter/hour, leading to rapid dehydration and even death.

The therapeutic approach to cholera takes advantage of the fact that the Na^+-dependent transporters for glucose and amino acids are not affected by the cholera exotoxin. As a result, coadministration of glucose and Na^+ by mouth results in the uptake of glucose and Na^+, accompanied by chloride and water, thereby partially correcting the ion deficits and fluid loss. Amino acids and small peptides are also adsorbed by Na^+-dependent cotransport involving transport proteins distinct from the Na^+-dependent glucose transporters. Therefore, addition of protein to the glucose–sodium replacement solution enhances its effectiveness and markedly decreases the severity of the diarrhea. Adjunctive antibiotic therapy also shortens the diarrheal phase of cholera but does not decrease the need for the oral replacement therapy outlined earlier.

Suggested Readings

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REVIEW QUESTIONS—CHAPTER 27

1. The facilitative transporter most responsible for transporting fructose from the blood into cells is which of the following?

   (A) GLUT 1
   (B) GLUT 2
   (C) GLUT 3
   (D) GLUT 4
   (E) GLUT 5

2. An alcoholic patient developed a pancreatitis that affected his exocrine pancreatic function. He exhibited discomfort after eating a high-carbohydrate meal. The patient most likely had a reduced ability to digest which of the following?

   (A) Starch
   (B) Lactose
   (C) Fiber
   (D) Sucrose
   (E) Maltose

3. A type I diabetic neglects to take his insulin injections while on a weekend vacation. Cells of which tissue would be most greatly affected by this mistake?

   (A) Brain
   (B) Liver
   (C) Muscle
   (D) Red blood cells
   (E) Pancreas

4. After digestion of a piece of cake that contains flour, milk, and sucrose as its primary ingredients, the major carbohydrate products entering the blood are which of the following?

   (A) Glucose
   (B) Fructose and galactose
   (C) Galactose and glucose
   (D) Fructose and glucose
   (E) Glucose, galactose and fructose

5. A patient has a genetic defect that causes intestinal epithelial cells to produce disaccharidases of much lower activity than normal. Compared with a normal person, after eating a bowl of milk and oatmeal sweetened with table sugar, this patient will exhibit higher levels of which of the following?

   (A) Maltose, sucrose, and lactose in the stool
   (B) Starch in the stool
   (C) Galactose and fructose in the blood
   (D) Glycogen in the muscles
   (E) Insulin in the blood