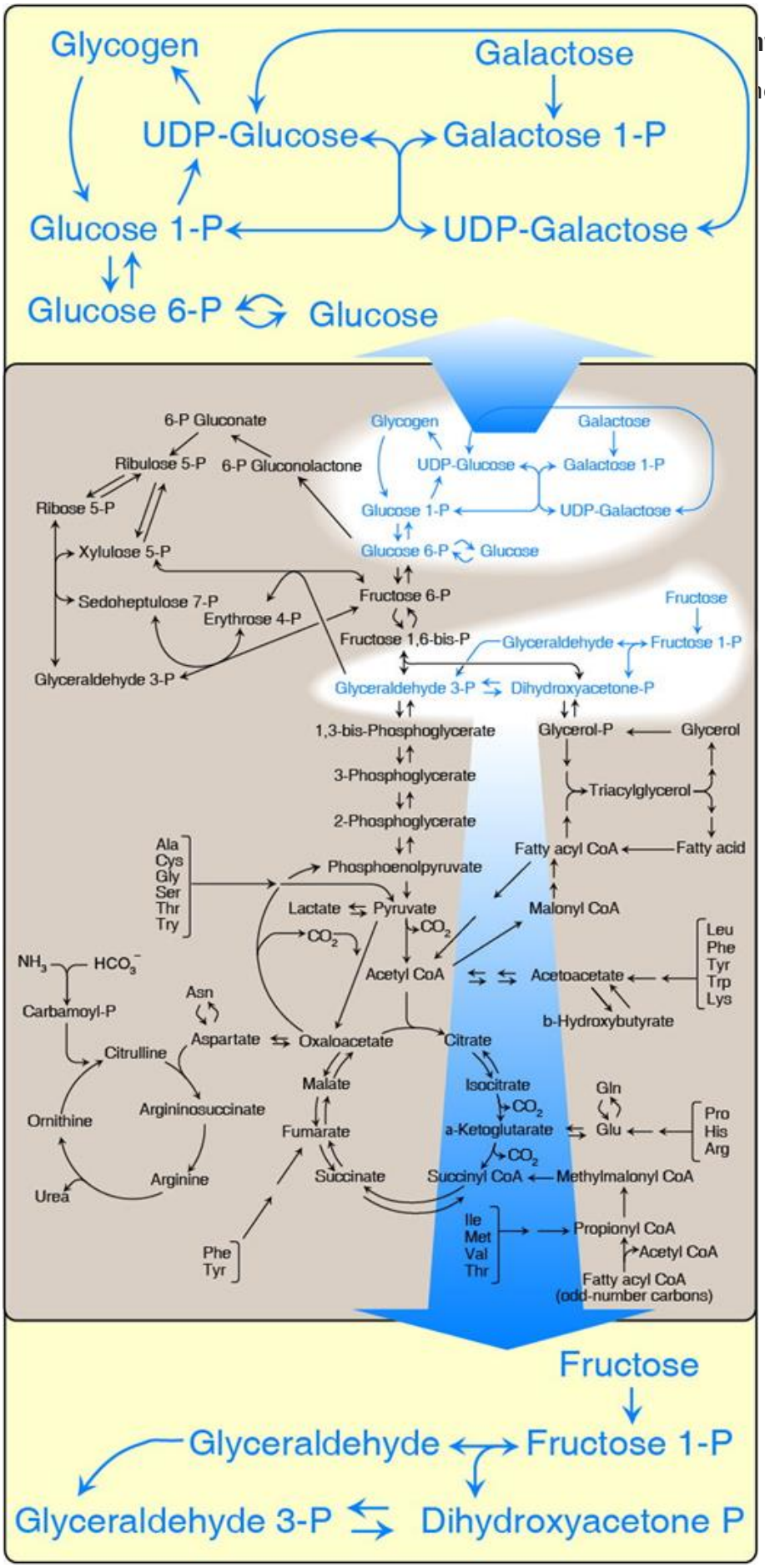
12: Monosaccharide and Disaccharide Metabolism

Overview

Listen

Glucose is the most common monosaccharide consumed by humans; its metabolism has already been discussed. Two other monosaccharides, fructose and galactose, also occur in significant amounts in the diet, primarily in disaccharides, and make important contributions to energy metabolism. In addition, galactose is an important component of glycosylated proteins. Figure 12.1 shows the metabolism of fructose and galactose as part of the essential pathways of energy metabolism.

FIGURE 12.1



ways of energy metabolism.

e diphosphate; P = phosphate.

Fructose Metabolism

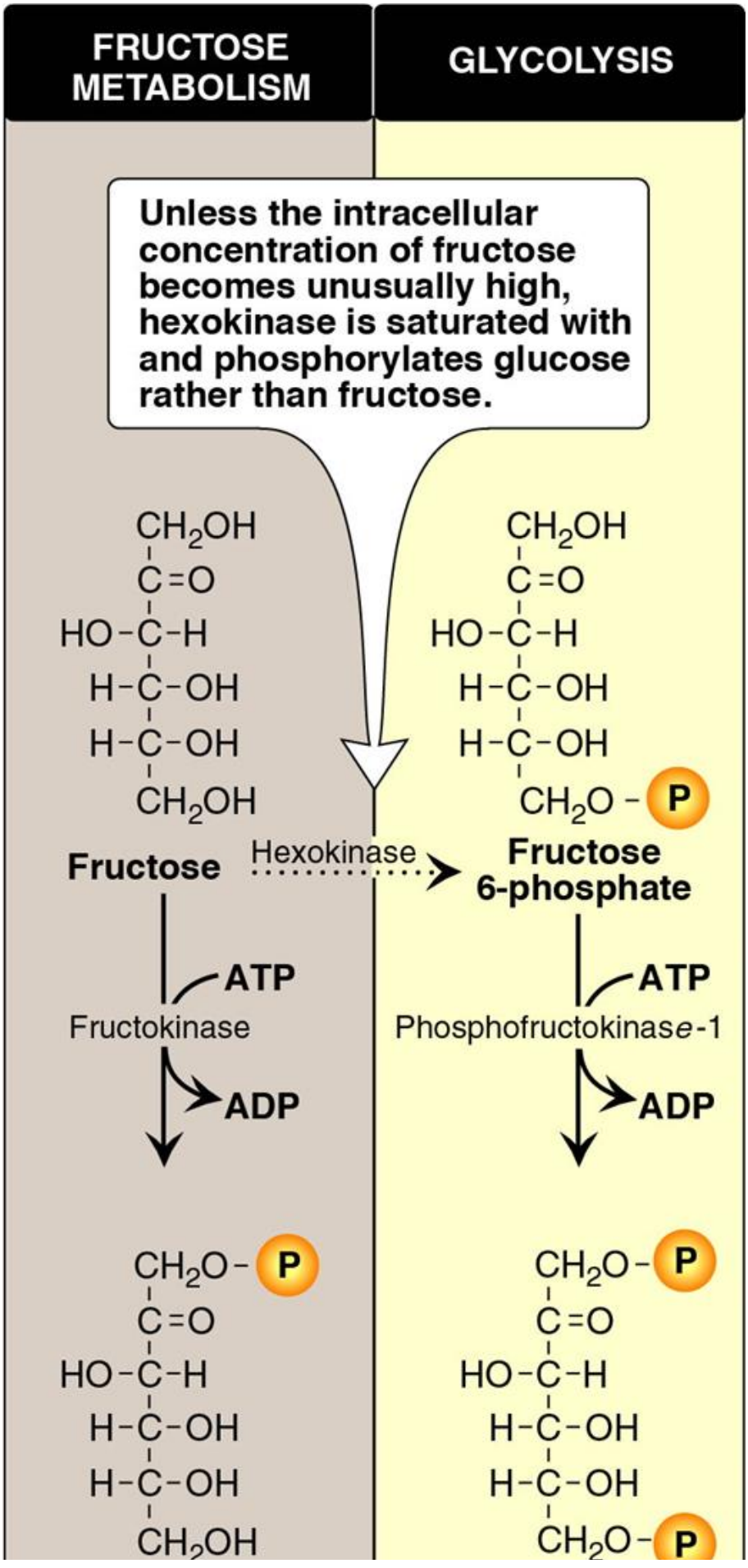
Listen

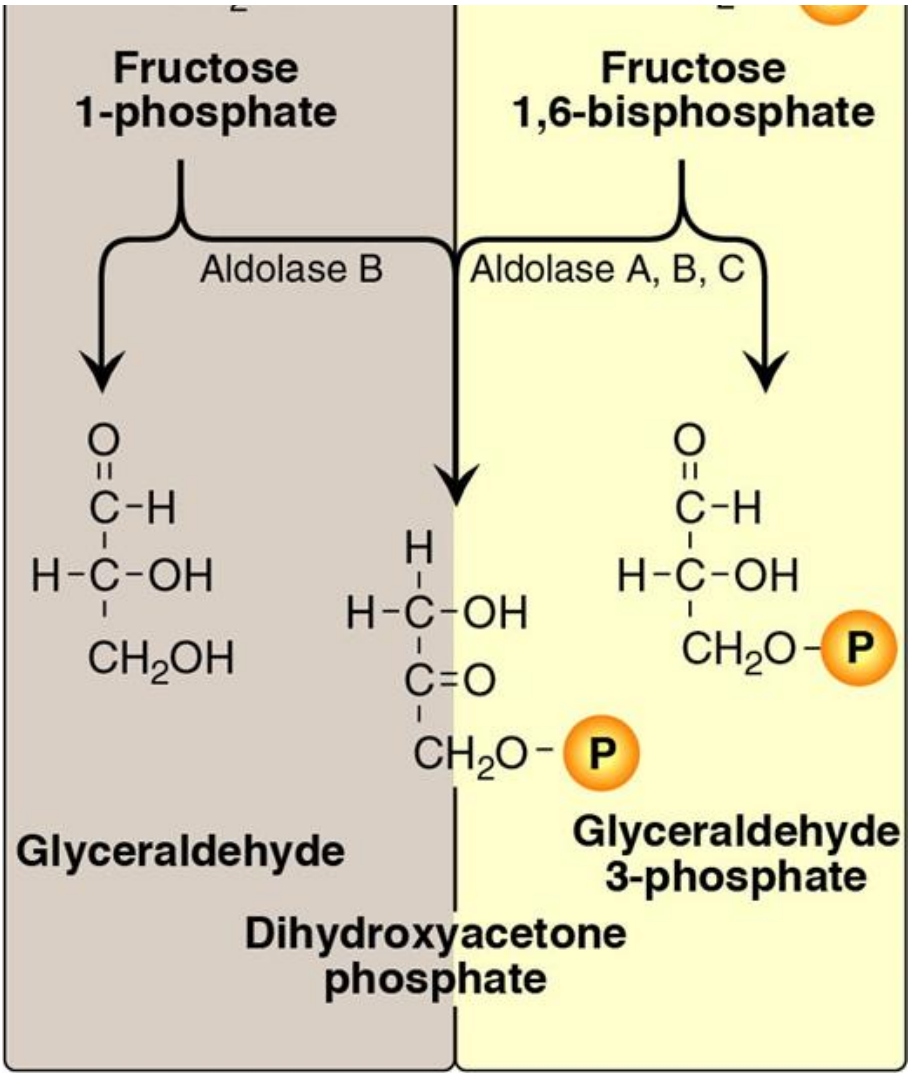
About 10% of the calories in the typical Western diet are supplied by fructose (~55 g/day). The major source of fructose is the disaccharide sucrose, which, when cleaved in the intestine, releases equimolar amounts of fructose and glucose. Fructose is also found as a free monosaccharide in many fruits, in honey, and in high-fructose corn syrup (typically, 55% fructose and 45% glucose), which is used to sweeten soft drinks and many foods. Fructose transport into cells is not insulin dependent (unlike that of glucose into certain tissues), and, in contrast to glucose, fructose does not promote the secretion of insulin.

Phosphorylation

For fructose to enter the pathways of intermediary metabolism, it must first be phosphorylated (Fig. 12.2). This can be accomplished by actions of either hexokinase or fructokinase. Hexokinase phosphorylates glucose in most cells of the body, and several additional hexoses can serve as substrates for this enzyme. However, it has a low affinity (a high K_m) for fructose.

FIGURE 12.2


FRUCTOSE METABOLISM
GLYCOLYSIS
Unless the intracellular concentration of fructose becomes unusually high, hexokinase is saturated with and phosphorylates glucose rather than fructose.
Fructose
Hexokinase
Fructose 6-phosphate
ATP
Fructokinase
ADP
ATP
Phosphofructokinase-1
ADP
P

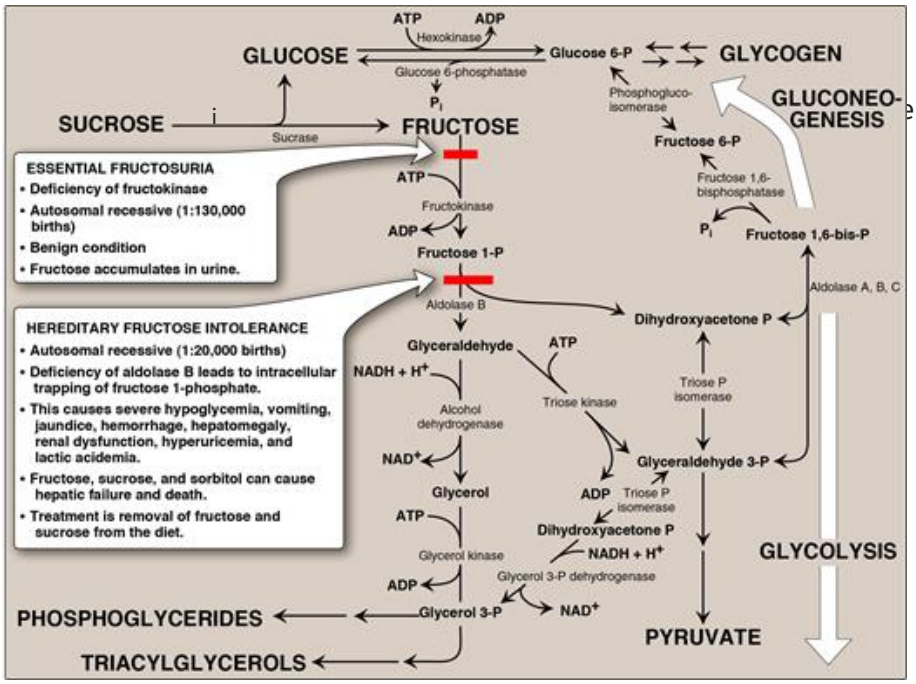


Therefore, unless the intracellular concentration of fructose becomes unusually high, the normal presence of saturating concentrations of glucose means that little fructose is phosphorylated by hexokinase. Fructokinase provides the primary mechanism for fructose phosphorylation (see Fig. 12.2). The enzyme has a low K_m for fructose and a high V_{max} (maximal velocity). It is found in the liver (which processes most of the dietary fructose), kidneys, and the small intestine and converts fructose to fructose 1-phosphate, using ATP as the phosphate donor. (Note: These three tissues also contain aldolase B, discussed in section B.)

Fructose 1-phosphate cleavage

Fructose 1-phosphate is not phosphorylated to fructose 1,6- bisphosphate as is fructose 6-phosphate (see p. 109) but is cleaved by aldolase B (also called fructose 1-phosphate aldolase) to two trioses, dihydroxyacetone phosphate (DHAP) and glyceraldehyde. (Note: Humans express three distinct aldolase isoenzymes, the products of three different genes: aldolase A in most tissues; aldolase B in the liver, kidneys, and small intestine; and aldolase C in the brain. All cleave fructose 1,6-bisphosphate produced during glycolysis to DHAP and glyceraldehyde 3-phosphate, but only aldolase B cleaves fructose 1-phosphate.) DHAP can be used in glycolysis or gluconeogenesis, whereas glyceraldehyde can be metabolized by a number of pathways, as illustrated in Figure 12.3.

FIGURE 12.3



e dinucleotide; ADP = adenosine

Kinetics

The rate of fructose metabolism is more rapid than that of glucose because triose production from fructose 1-phosphate bypasses phosphofructokinase-1, the major rate-limiting step in glycolysis.

Disorders

A deficiency of one of the key enzymes required for the entry of fructose into metabolic pathways can result in either a benign condition as a result of fructokinase deficiency (essential fructosuria) or a severe disturbance of liver and kidney metabolism as a result of aldolase B deficiency, or hereditary fructose intolerance (HFI), which occurs in ~1:20,000 live births (see Fig. 12.3).

The first symptoms of HFI appear when a baby is weaned from lactose-containing milk and begins ingesting food containing sucrose or fructose. Fructose 1-phosphate accumulates, resulting in a drop in the level of inorganic phosphate (P_i) and, therefore, of ATP production. As ATP falls, adenosine monophosphate (AMP) rises. The AMP is degraded, causing hyperuricemia and lactic acidemia. The decreased availability of hepatic ATP decreases gluconeogenesis (causing hypoglycemia with vomiting) and protein synthesis (causing a decrease in blood-clotting factors and other essential proteins). Renal reabsorption of P_i is also decreased. (Note: The drop in P_i also inhibits glycogenolysis.)

Diagnosis of HFI can be made on the basis of fructose in the urine, enzyme assay using liver cells, or by DNA-based testing (see Chapter 34). With HFI, sucrose, as well as fructose, must be removed from the diet to prevent liver failure and possible death. Note that individuals with HFI tend to display a life-long aversion to sweets.

Mannose conversion to fructose 6-phosphate

Mannose, the C-2 epimer of glucose, is an important component of glycoproteins. Hexokinase phosphorylates mannose, producing mannose 6-phosphate, which, in turn, is reversibly isomerized to fructose 6-phosphate by phosphomannose isomerase. (Note: Most intracellular mannose is synthesized from fructose or is pre-existing mannose produced by the degradation of glycoproteins and salvaged by hexokinase. Dietary carbohydrates contain little mannose.)

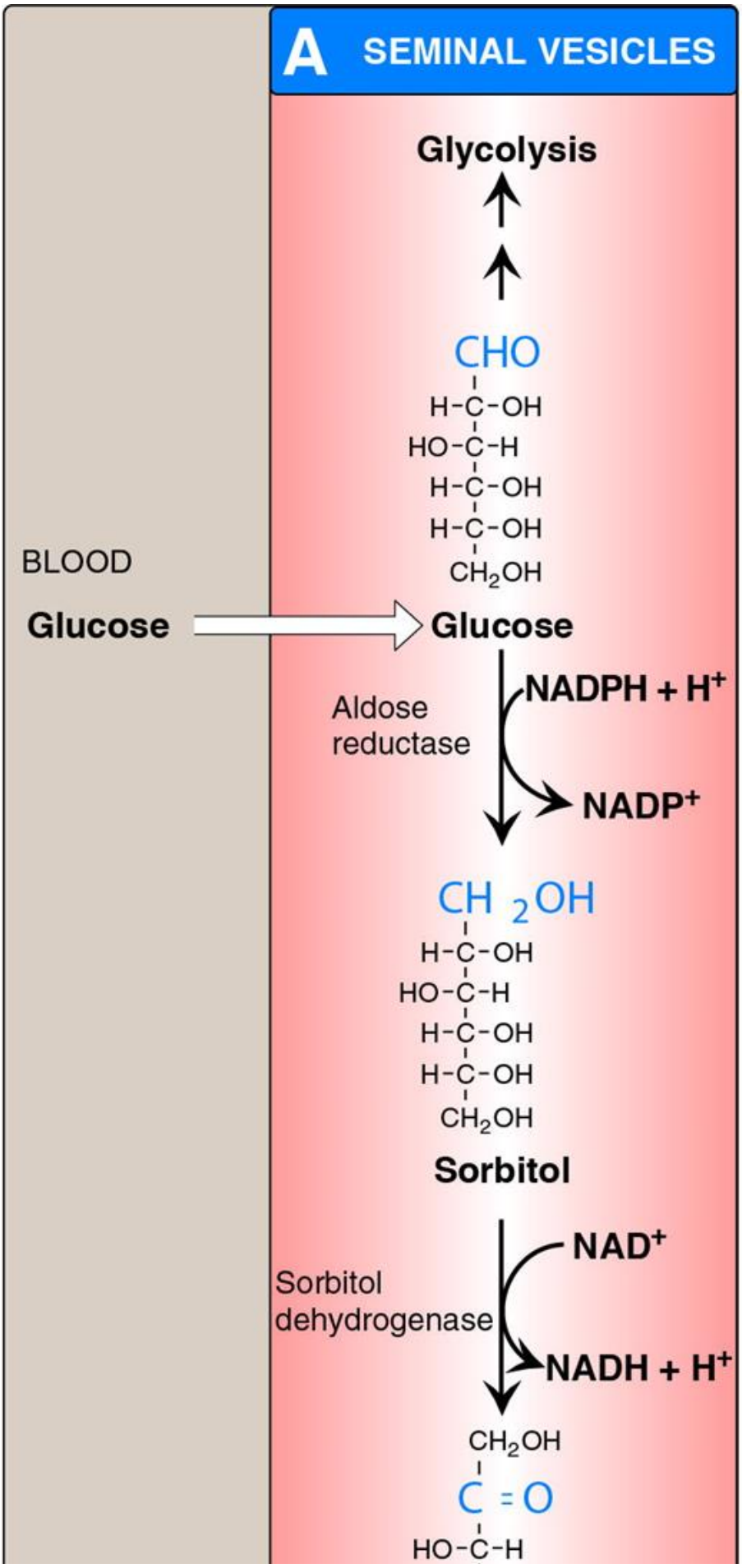
Glucose conversion to fructose via sorbitol

Most sugars are rapidly phosphorylated following their entry into cells. Therefore, they are trapped within the cells, because organic phosphates cannot freely cross membranes without specific transporters. An alternate mechanism for metabolizing a monosaccharide is to convert it to a polyol (sugar alcohol) by the reduction of an aldehyde group, thereby producing an additional hydroxyl group.

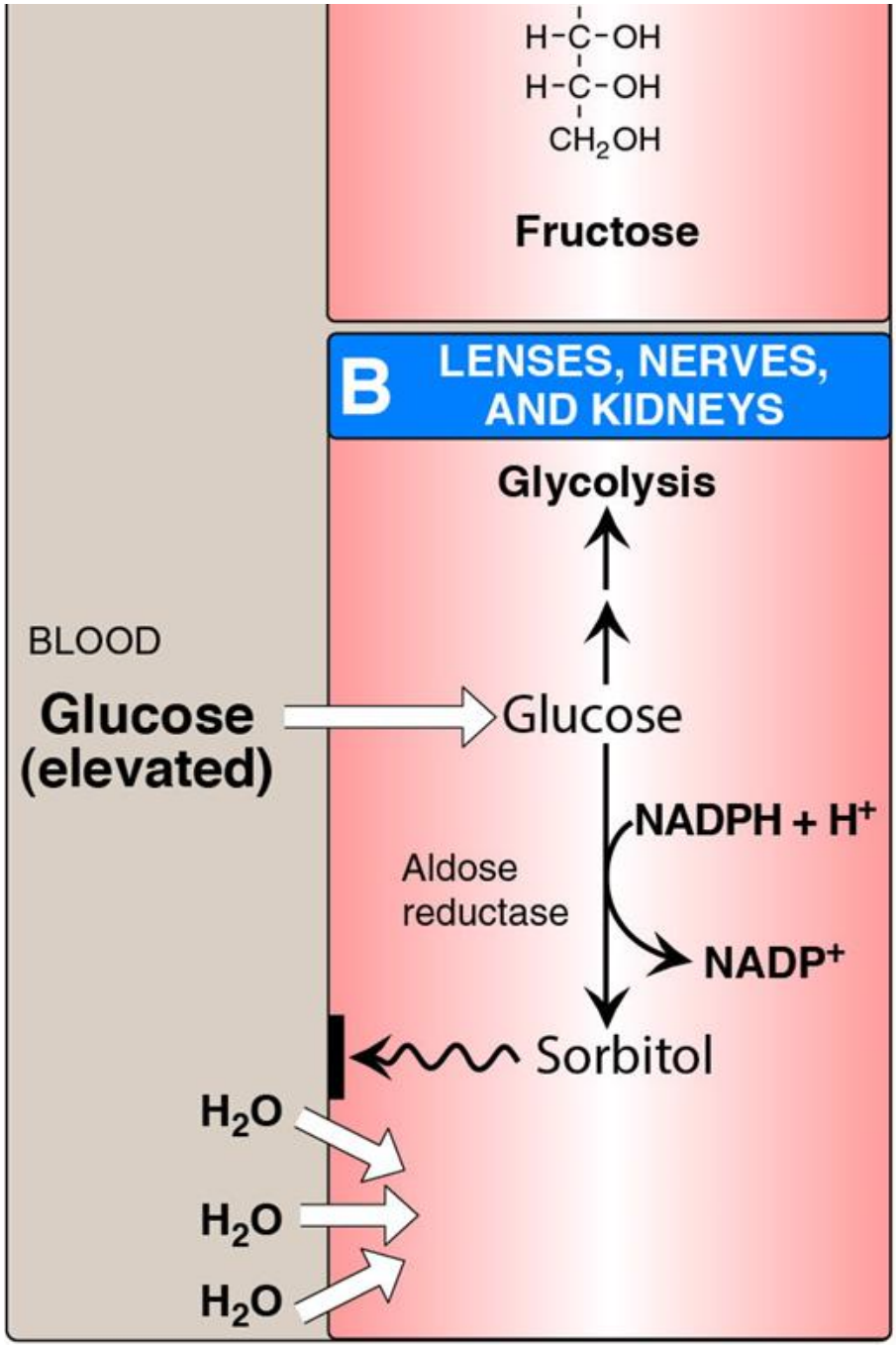
Sorbitol synthesis

Aldose reductase reduces glucose, producing sorbitol (or, glucitol; Fig. 12.4), but the K_m is high. This enzyme is found in many tissues, including the retina, lens, kidneys, peripheral nerves, ovaries, and seminal vesicles. A second enzyme, sorbitol dehydrogenase, can oxidize sorbitol to fructose in cells of the liver, ovaries, and seminal vesicles (see Fig. 12.4). The two-reaction pathway from glucose to fructose in the seminal vesicles benefits sperm cells, which use fructose as a major carbohydrate energy source. The pathway from sorbitol to fructose in the liver provides a mechanism by which any available sorbitol is converted into a substrate that can enter glycolysis.

FIGURE 12.4



denine dinucleotide phosphate.



Hyperglycemia and sorbitol metabolism

Because insulin is not required for the entry of glucose into cells of the retina, lens, kidneys, and peripheral nerves, large amounts of glucose may enter these cells during times of hyperglycemia (e.g., in poorly controlled diabetes mellitus). An elevated intracellular glucose concentration and an adequate supply of reduced nicotinamide adenine dinucleotide phosphate (NADPH) cause aldose reductase to produce a significant increase in sorbitol within the cell, which cannot pass efficiently through cell membranes and, therefore, remains trapped inside the cell (see Fig. 12.4). This is exacerbated when sorbitol dehydrogenase production is low or absent. As a result, sorbitol accumulates in these cells, causing strong osmotic effects and cell swelling due to water influx and retention.

Some of the pathologic alterations associated with diabetes mellitus can be partly attributed to this osmotic stress, including cataract formation, peripheral neuropathy, and microvascular problems leading to nephropathy and retinopathy. Use of NADPH in the aldose reductase reaction decreases the generation of reduced glutathione, an important antioxidant, and may also be related to complications of diabetes.

Galactose Metabolism

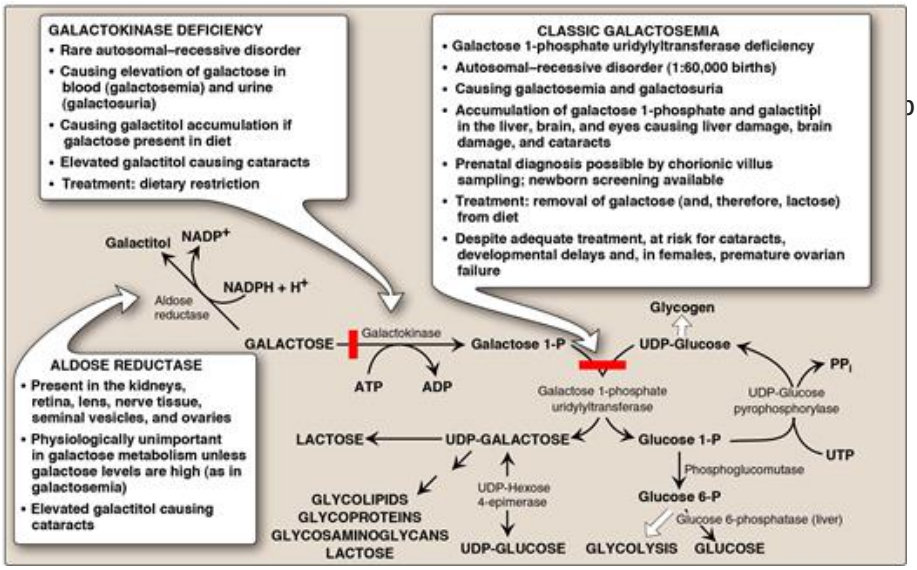
Listen

The major dietary source of galactose is lactose (galactosyl β-1,4-glucose) obtained from milk and milk products. (Note: The digestion of lactose by β-galactosidase, also called lactase, was discussed on p. 97.) Some galactose can also be obtained by lysosomal degradation of glycoproteins and glycolipids. Like fructose (and mannose), the transport of galactose into cells is not insulin dependent.

Phosphorylation

Like fructose, galactose must be phosphorylated before it can be further metabolized. Most tissues have a specific enzyme for this purpose, galactokinase, which produces galactose 1-phosphate (Fig. 12.5). As with other kinases, ATP is the phosphate donor.

FIGURE 12.5

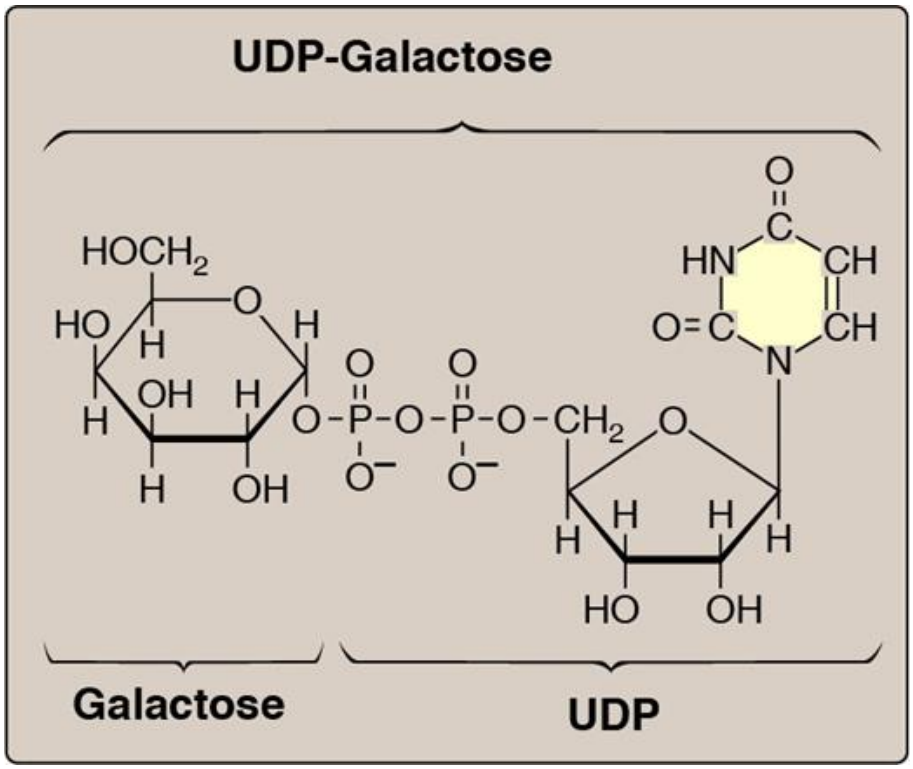


phosphate; NADP(H) = nicotinamide

Uridine diphosphate–galactose formation

Galactose 1-phosphate cannot enter the glycolytic pathway unless it is first converted to uridine diphosphate (UDP)-galactose (Fig. 12.6). This occurs in an exchange reaction, in which UDP-glucose reacts with galactose 1-phosphate, producing UDP-galactose and glucose 1-phosphate (see Fig. 12.5). The reaction is catalyzed by galactose 1-phosphate uridylyltransferase (GALT). (Note: The glucose 1-phosphate product can be isomerized to glucose 6-phosphate, which can enter glycolysis or be dephosphorylated.)

FIGURE 12.6



UDP-galactose conversion to UDP-glucose

For UDP-galactose to enter the mainstream of glucose metabolism, it must first be isomerized to its C-4 epimer, UDP-glucose, by UDP-hexose 4-epimerase. This “new” UDP-glucose (produced from the original UDP-galactose) can participate in biosynthetic reactions (e.g., glycogenesis) as well as in the GALT reaction. (Note: See Fig. 12.5 for a summary of the interconversions.)

UDP-galactose in biosynthetic reactions

UDP-galactose can serve as the donor of galactose units in a number of synthetic pathways, including synthesis of lactose (see IV. below), glycoproteins, glycolipids, and glycosaminoglycans. (Note: If galactose is not provided by the diet [e.g., when it cannot be released from lactose owing to a lack of β-galactosidase in people who are lactose intolerant], all tissue requirements for UDP-galactose can be met by the action of UDP-hexose 4-epimerase on UDP-glucose, which is efficiently produced from glucose 1-phosphate and uridine triphosphate [see Fig. 12.5].)

Disorders

GALT is severely deficient in individuals with classic galactosemia (see Fig. 12.5). In this disorder, galactose 1-phosphate and, therefore, galactose accumulate. Physiologic consequences are similar to those found in HFI, but a broader spectrum of tissues is affected. The accumulated galactose is shunted into side pathways such as that of galactitol production. This reaction is catalyzed by aldose reductase, the same enzyme that reduces glucose to sorbitol. GALT deficiency is part of the newborn screening panel. Treatment of galactosemia requires removal of galactose and lactose from the diet. Deficiencies in galactokinase and the epimerase result in less severe disorders of galactose metabolism, although cataracts are common (see Fig. 12.5).

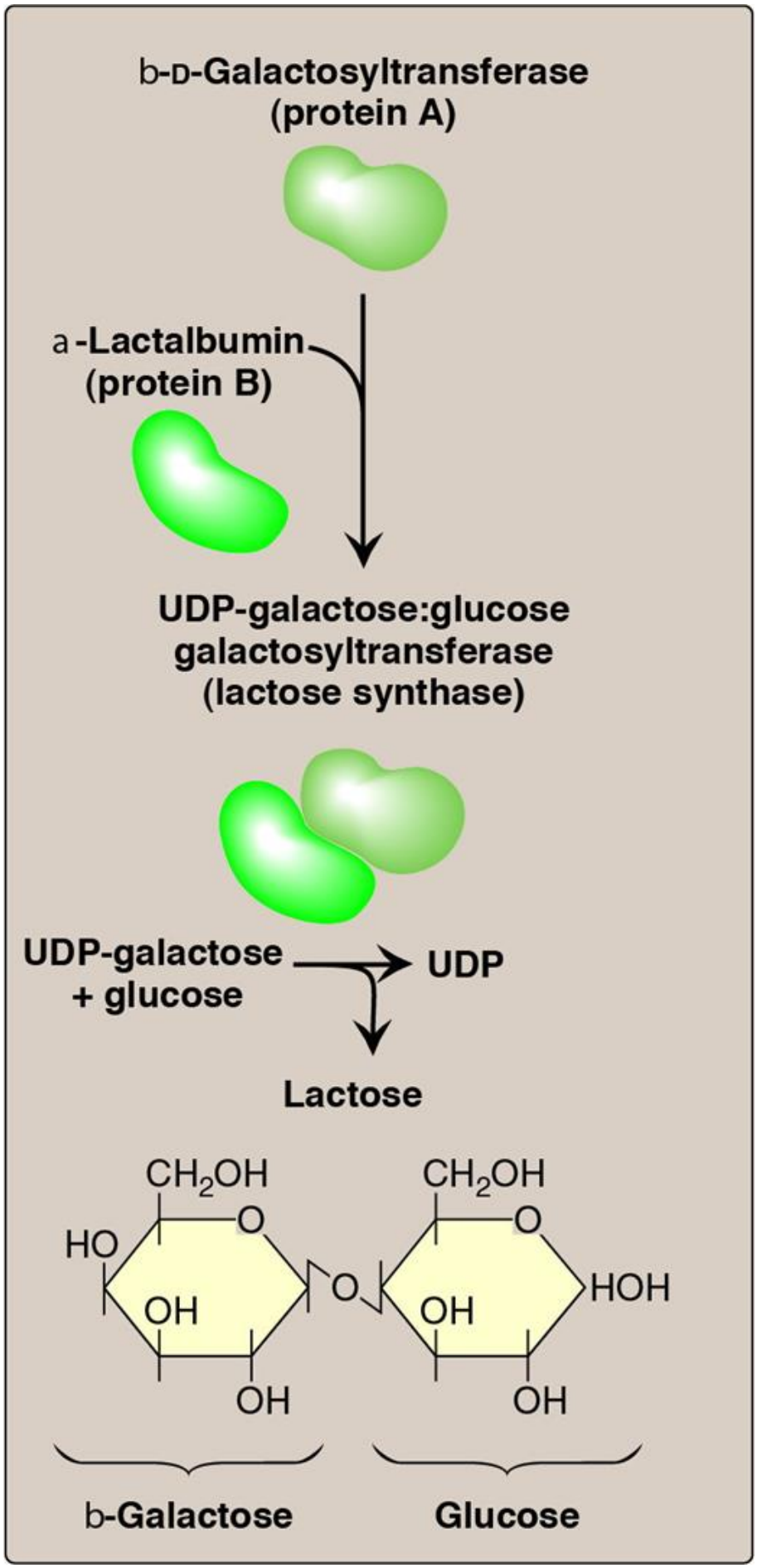
Lactose Synthesis

Listen

Lactose is a disaccharide that consists of a molecule of β-galactose attached by a β(1→4) linkage to glucose. Therefore, lactose is galactosyl β(1→4)-glucose. Because lactose, the sugar in milk, is made by lactating (milk-producing) mammary glands, milk and other dairy products are the dietary sources of lactose.

Lactose synthase (UDP-galactose:glucose galactosyltransferase) catalyzes lactose synthesis in the Golgi. This enzyme, composed of A and B proteins, transfers galactose from UDP-galactose to glucose, releasing UDP (Fig. 12.7). Protein A is a β-D-galactosyltransferase and is found in a number of body tissues. In tissues other than the lactating mammary gland, this enzyme transfers galactose from UDP-galactose to N-acetyl-D-glucosamine, forming the same β(1→4) linkage found in lactose, and producing N-acetyllactosamine, a component of the structurally important N-linked glycoproteins (see p. 185). In contrast, protein B is found only in lactating mammary glands. It is α-lactalbumin, and its synthesis is stimulated by the peptide hormone prolactin. Protein B forms a complex with the enzyme, protein A, changing the specificity of that transferase (by decreasing the K_m for glucose) so that lactose, rather than N-acetyllactosamine, is produced (see Fig. 12.7).

FIGURE 12.7


b-D-Galactosyltransferase
(protein A)
a-Lactalbumin
(protein B)
UDP-galactose:glucose
galactosyltransferase
(lactose synthase)
UDP-galactose
+ glucose
UDP
Lactose
CH2OH
O
HO
OH
OH
O
CH2OH
O
HOH
OH
OH
b-Galactose
Glucose

CLINICAL APPLICATION 12-1

Lactose Intolerance

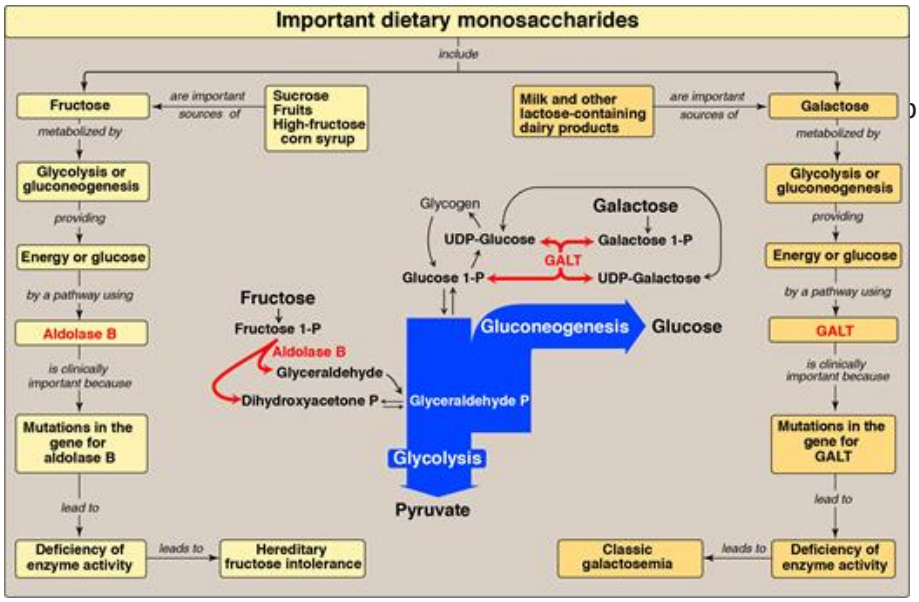
Lactose intolerance, also called lactose malabsorption, affects up to 60% of adults with ancestries other than Northern European. It results from deficiency of β-galactosidase or lactase in the small intestine. Recall (see p. 97 and Fig. 7.11) that with insufficient lactase there is an inability to fully digest dairy products. After consuming dairy, lactose intolerant individuals can experience cramping, diarrhea, and bloating. Lactase supplements and avoidance of dairy products can be effective in treating the condition.

Chapter Summary

Listen

- The major source of fructose is the disaccharide **sucrose**, which, when cleaved, releases equimolar amounts of **fructose** and **glucose** (Fig. 12.8).

FIGURE 12.8



- Transport of fructose into cells is **insulin independent**.
- Fructose is first phosphorylated to **fructose 1-phosphate** by **fructokinase** and then cleaved by **aldolase B** to **DHAP** and **glyceraldehyde**. These enzymes are found in the **liver**, **kidneys**, and **small intestine**.
- A deficiency of fructokinase causes a benign condition**, essential fructosuria**, whereas a deficiency of aldolase B causes **HFI**, in which **severe hypoglycemia** and **liver failure** lead to **death** if fructose (and sucrose) is not removed from the diet.
- **Mannose**, an important component of **glycoproteins**, is phosphorylated by **hexokinase** to **mannose 6-phosphate**, which is reversibly isomerized to **fructose 6-phosphate** by **phosphomannose isomerase**.
- Glucose can be reduced to **sorbitol** (**glucitol**) by **aldose reductase** in many tissues, including the **lens**, **retina**, **peripheral nerves**, **kidneys**, **ovaries**, and **seminal vesicles**. In the liver, ovaries, and seminal vesicles, a second enzyme, **sorbitol dehydrogenase**, can oxidize sorbitol to produce **fructose**.
- **Hyperglycemia** results in the accumulation of sorbitol in those cells lacking sorbitol dehydrogenase. The resulting **osmotic events** cause cell swelling and may contribute to the **cataract formation**, **peripheral neuropathy**, **nephropathy**, and **retinopathy** seen in **diabetes**.
- The major dietary source of **galactose** is **lactose**. The transport of galactose into cells is insulin independent. Galactose is first phosphorylated to galactose 1-phosphate by **galactokinase**, a deficiency of which results in cataracts.
- Galactose 1-phosphate is converted to **UDP-galactose** by **GALT**, with the nucleotide supplied by UDP-glucose. A deficiency of this enzyme causes **classic galactosemia**. Galactose 1-phosphate accumulates, and excess galactose is converted to **galactitol** by **aldose reductase**. This causes **liver damage**, **brain damage**, and **cataracts**. Treatment requires removal of galactose (and lactose) from the diet.

- For UDP-galactose to enter the mainstream of glucose metabolism, it must first be isomerized to UDP-glucose by **UDP-hexose 4-epimerase**. This enzyme can also be used to produce UDP-galactose from UDP-glucose when the former is required for glycoprotein and glycolipid synthesis.
- **Lactose** is a disaccharide of **galactose** and **glucose**. D**airy products** are the dietary sources of lactose. Lactose is synthesized by **lactose synthase** from **UDP-galactose** and **glucose** in the **lactating mammary gland**. The enzyme has two subunits, **protein A** (which is a **galactosyltransferase** found in most cells where it synthesizes **N-acetyllactosamine**) and **protein B** (**α-lactalbumin**, which is found only in lactating mammary glands, and whose synthesis is stimulated by the peptide hormone **prolactin**). When both subunits are present, the transferase produces lactose.

Study Questions

Listen

Choose the ONE best answer.

12.1. A female with classic galactosemia who is on a galactose-free diet delivers a full-term infant. She is able to produce lactose in her breast milk because:

A. galactose can be produced from fructose by isomerization.

B. galactose can be produced from a glucose metabolite by epimerization.

C. hexokinase can efficiently phosphorylate galactose to galactose 1-phosphate.

D. the enzyme affected in galactosemia is activated by a mammary gland hormone.

Correct answer = B. Uridine diphosphate (UDP)-glucose is converted to UDP-galactose by UDP-hexose 4-epimerase, thereby providing the appropriate form of galactose for lactose synthesis. Isomerization of fructose to galactose does not occur in the human body. Galactose is not converted to galactose 1-phosphate by hexokinase. A galactose-free diet provides no galactose. Galactosemia is the result of an enzyme (galactose 1-phosphate uridylyltransferase) deficiency.

12.2. A 6-month-old male child is brought to his pediatrician because of vomiting, night sweats, and tremors. History reveals that these symptoms began after fruit juices were introduced to his diet as he was being weaned off breast milk. The physical examination was remarkable for hepatomegaly. Tests on his urine were positive for reducing sugar but negative for glucose. The infant most likely has a deficiency of:

A. aldolase B.

B. fructokinase.

C. galactokinase.

D. β-galactosidase.

Correct answer = A. The symptoms suggest hereditary fructose intolerance, a deficiency in aldolase B. Deficiencies in fructokinase or galactokinase result in relatively benign conditions characterized by elevated levels of fructose or galactose in the blood and urine. Deficiency in β-galactosidase (lactase) results in a decreased ability to degrade lactose (milk sugar). Congenital lactase deficiency is quite rare and would have presented much earlier in this baby (and with different symptoms). Typical lactase deficiency (adult lactose intolerance) presents at a later age.

12.3. In lactose synthesis:

A. α-lactalbumin expression is decreased by the hormone prolactin.

B. galactosyltransferase catalyzes transfer of galactose from galactose 1-phosphate to glucose.

C. protein A is used exclusively.

D. α-lactalbumin decreases the affinity of protein A for glucose.

E. protein B expression is stimulated by prolactin.

Correct answer = D. α-Lactalbumin (protein B) expression is increased by the hormone prolactin. Uridine diphosphate–galactose is the form used by the galactosyltransferase (protein A). Protein A is also involved in the synthesis of the amino sugar N-acetyllactosamine. Protein B decreases the Michaelis constant (K_m) and, so, increases the affinity of protein A for glucose.

12.4. A 3-month-old child is evaluated for cloudiness of her eyes. Her physical examination reveals cataracts. Other than not having a social smile or being able to track objects visually, all other aspects of her examination are normal. Tests on her urine are positive for reducing sugar but negative for glucose. Which enzyme is most likely deficient in this child?

A. Aldolase B

B. Fructokinase

C. Galactokinase

D. Galactose 1-phosphate uridylyltransferase

Correct answer = C. The child is deficient in galactokinase and is unable to appropriately phosphorylate galactose. Galactose accumulates in the blood (and urine). In the lens of the eye, galactose is reduced by aldose reductase to galactitol, a sugar alcohol, which causes osmotic effects that result in cataract formation. Deficiency of galactose 1-phosphate uridylyltransferase also results in cataracts but is characterized by liver damage and neurologic effects. Fructokinase deficiency is a benign condition. Aldolase B deficiency is severe, with effects on several tissues but cataracts are not typically seen.

12.5. In a person with elevated blood glucose and an adequate supply of NADPH, which of the following will be produced in high concentration and then remain trapped in the cell?

A. fructose

B. galactose

C. lactose

D. sorbitol

E. sucrose

Correct answer = D. Sorbitol will be elevated in this situation. An elevated intracellular glucose concentration and an adequate supply of reduced NADPH cause aldose reductase to produce a significant increase in sorbitol, which cannot pass efficiently through cell membranes and, therefore, remains trapped inside the cell. Sorbitol trapped in the cells then contributes to complications of diabetes mellitus including cataract formation, peripheral neuropathy, and microvascular problems.