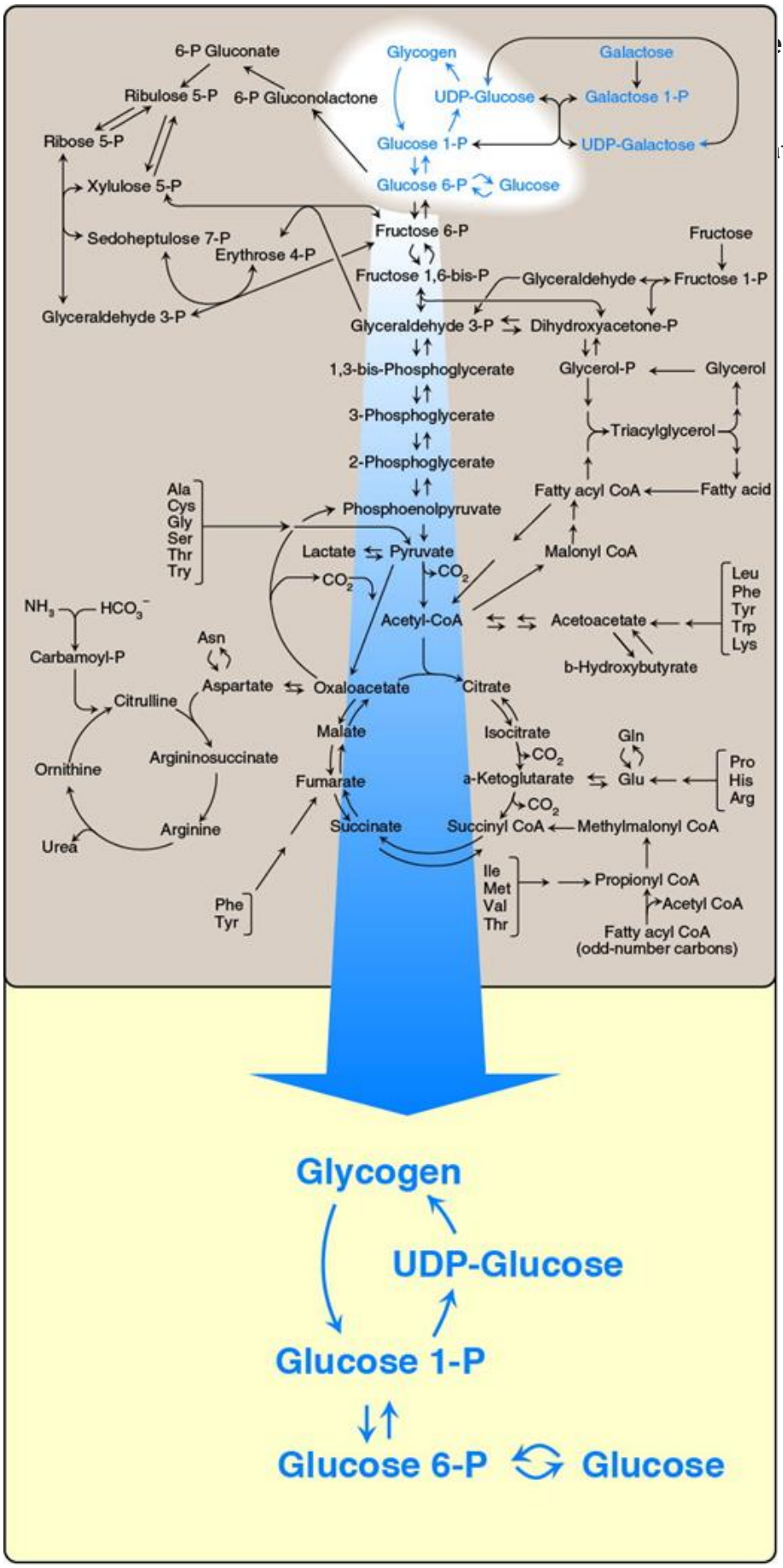
11: Glycogen Metabolism

Overview

A constant source of blood glucose is an absolute requirement for human life. Glucose is the greatly preferred energy source for the brain and the required energy source for cells with few or no mitochondria such as mature red blood cells. Glucose is also essential as an energy source for exercising muscle, where it is the substrate for anaerobic glycolysis. Blood glucose can be obtained from three primary sources: the diet, glycogen degradation, and gluconeogenesis. Dietary intake of glucose and glucose precursors, such as starch (a polysaccharide), disaccharides, and monosaccharides, is sporadic and, depending on the diet, is not always a reliable source of blood glucose. In contrast, gluconeogenesis can provide sustained synthesis of glucose, but it is somewhat slow in responding to a falling blood glucose level. Therefore, the body has developed mechanisms for storing a supply of glucose in a rapidly mobilized form, namely, glycogen. In the absence of a dietary source of glucose, this sugar is rapidly released into the blood from liver glycogen. Similarly, muscle glycogen is extensively degraded in exercising muscle to provide that tissue with an important energy source. When glycogen stores are depleted, specific tissues synthesize glucose *de novo*, using glycerol, lactate, pyruvate, and amino acids as carbon sources for gluconeogenesis (see Chapter 10). Figure 11.1 shows the reactions of glycogen synthesis and degradation as part of the essential pathways of energy metabolism.

FIGURE 11.1



ntial pathways of energy

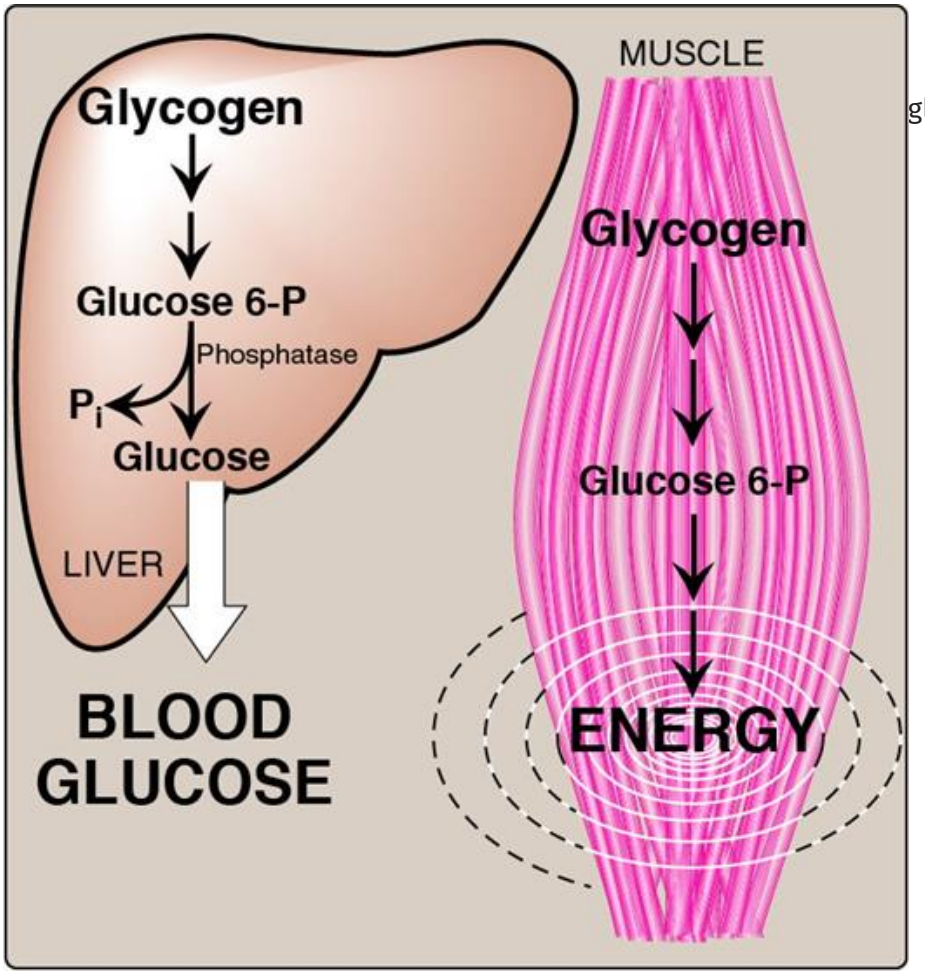
te; UDP = uridine diphosphate.

Structure and Function

Listen

The main stores of glycogen are found in skeletal muscle and liver, although most other cells store small amounts of glycogen for their own use. The function of muscle glycogen is to serve as a fuel reserve for the synthesis of ATP during muscle contraction, while the purpose of liver glycogen is to maintain the blood glucose concentration, particularly during the early stages of a fast (Fig. 11.2). (Note: Liver glycogen can maintain blood glucose for <24 hours.)

FIGURE 11.2



glucose into blood.) P = phosphate; P_i =

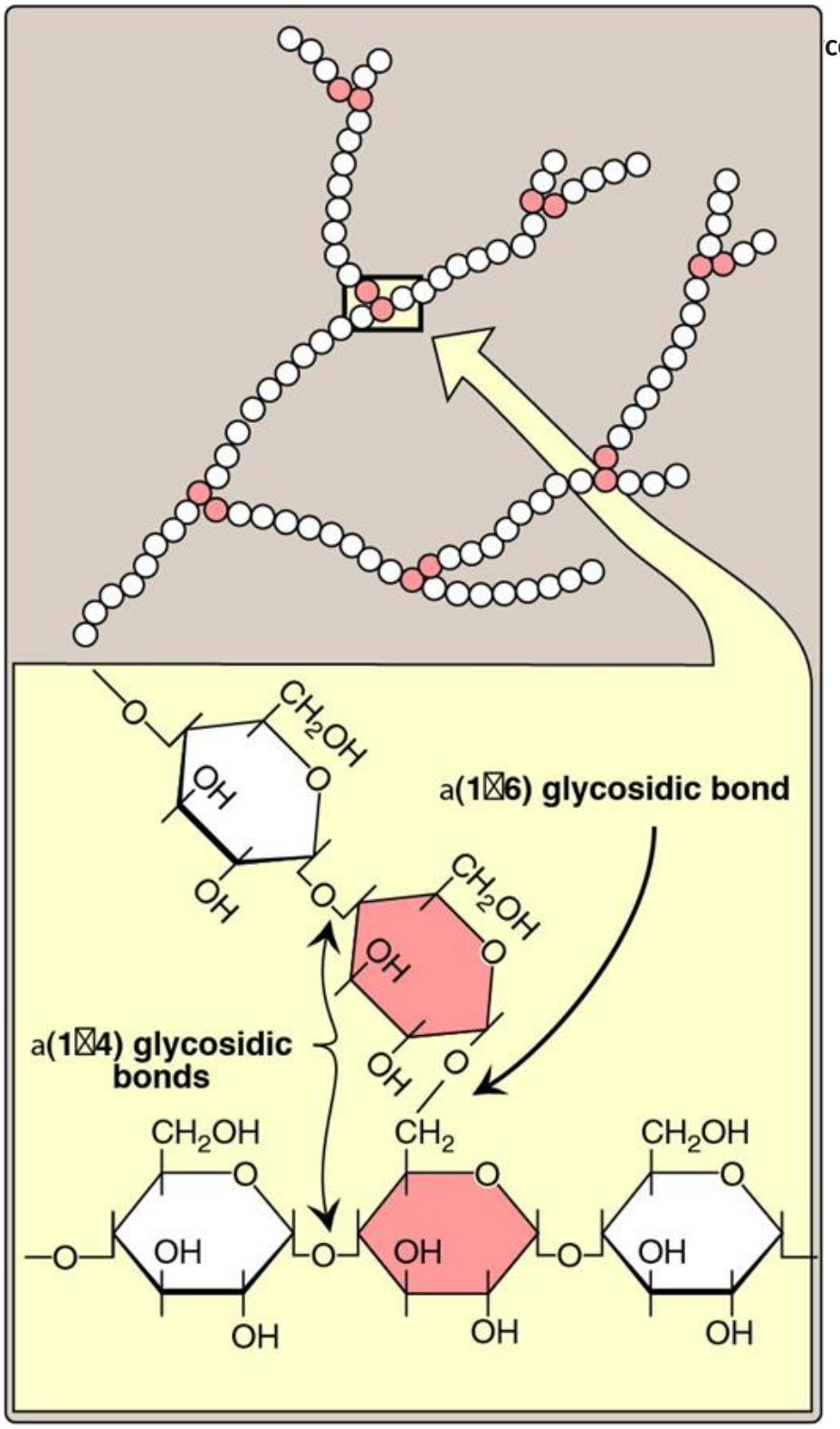
Amounts in liver and muscle

Approximately 400 g of glycogen make up 1% to 2% of the fresh weight of resting muscle, and ~100 g of glycogen make up to 10% of the fresh weight of a well-fed adult liver. What limits the production of glycogen at these levels is not clear. However, in some glycogen storage diseases (GSDs) (see Fig. 11.8), the amount of glycogen in the liver and/or muscle can be significantly higher. (Note: In the body, muscle mass is greater than liver mass. Consequently, most of the body's glycogen is found in skeletal muscle.)

Structure

Glycogen is a branched-chain polysaccharide made exclusively from α-D-glucose. The primary glycosidic bond is an α(1→4) linkage. After an average of 8 to 14 glucosyl residues, there is a branch containing an α(1→6) linkage (Fig. 11.3). A single glycogen molecule can contain up to 55,000 glucosyl residues. These polymers of glucose exist as large, spherical, cytoplasmic granules (particles) that also contain most of the enzymes necessary for glycogen synthesis and degradation.

FIGURE 11.3



cosidic bonds.

Glycogen store fluctuation

Liver glycogen stores increase during the well-fed state and are depleted during a fast. Muscle glycogen is not affected by short periods of fasting (a few days) and is only moderately decreased in prolonged fasting (weeks). Muscle glycogen is synthesized to replenish muscle stores after they have been depleted following strenuous exercise. (Note: Glycogen synthesis and degradation go on continuously. The difference between the rates of these two processes determines the levels of stored glycogen during specific physiologic states.)

Synthesis (Glycogenesis)

Listen

Glycogen is synthesized from molecules of α-D-glucose. The process occurs in the cytosol and requires energy supplied by ATP (for the phosphorylation of glucose) and uridine triphosphate (UTP).

Uridine diphosphate glucose synthesis

α-D-Glucose attached to uridine diphosphate (UDP) is the source of all the glucosyl residues that are added to the growing glycogen molecule. UDP-glucose (Fig. 11.4) is synthesized from glucose 1-phosphate and UTP by UDP–glucose pyrophosphorylase (Fig. 11.5). Pyrophosphate (PP_i), the second product of the reaction, is hydrolyzed to two inorganic phosphates (P_i) by pyrophosphatase. The hydrolysis is exergonic, which ensures that the UDP–glucose pyrophosphorylase reaction proceeds in the direction of UDP-glucose production. (Note: Glucose 1-phosphate is generated from glucose 6-phosphate by phosphoglucomutase. Glucose 1,6-bisphosphate is an obligatory intermediate in this reversible reaction [Fig. 11.6].)

FIGURE 11.4

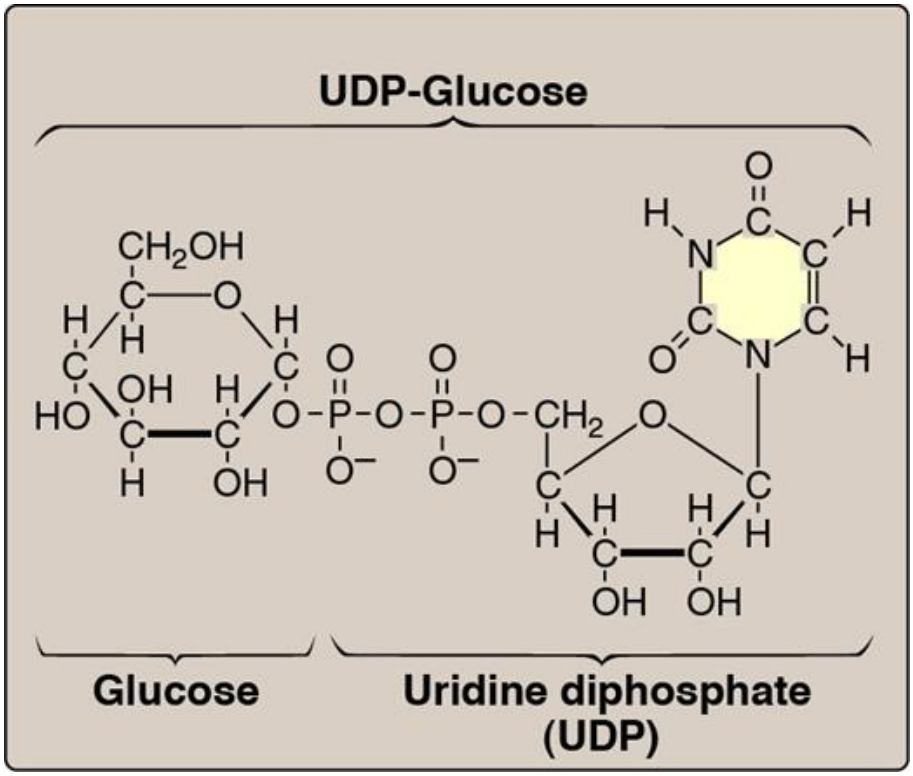
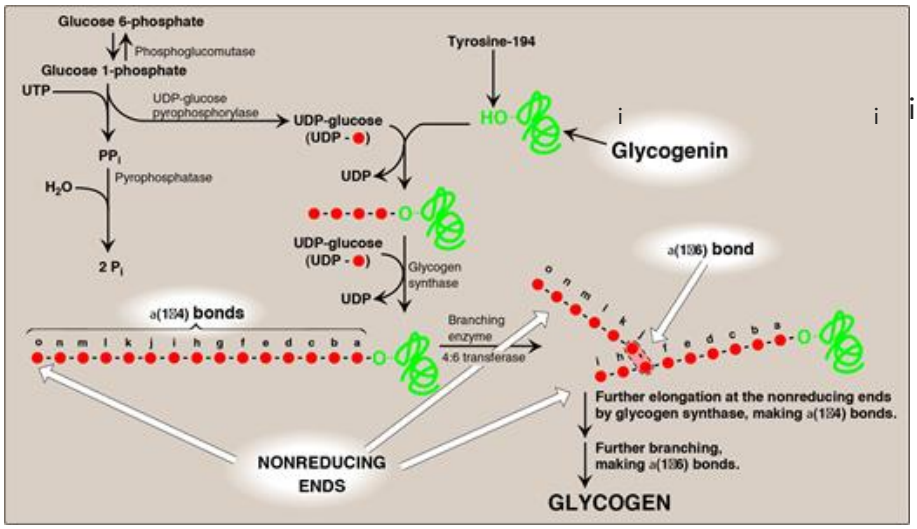
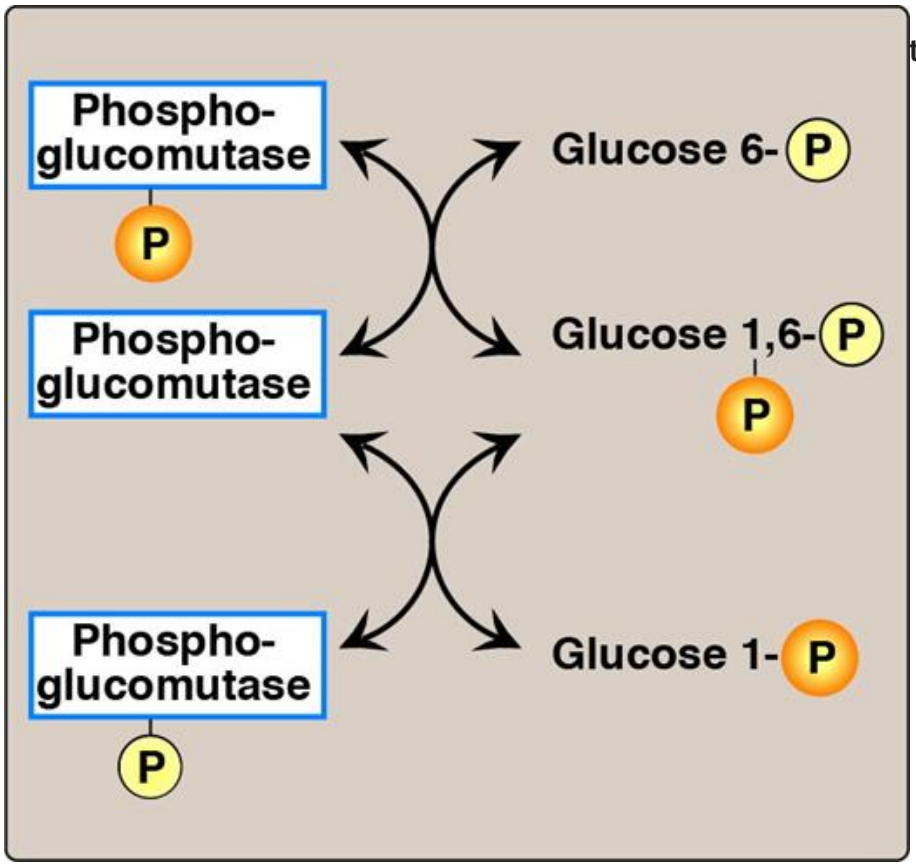


FIGURE 11.5



i i inorganic phosphate.

FIGURE 11.6



te by phosphoglucomutase.

Primer requirement and synthesis

Glycogen synthase catalyzes the α(1→4) linkages in glycogen. This enzyme cannot initiate chain synthesis using free glucose as an acceptor of a molecule of glucose from UDP-glucose. Instead, it can only elongate already existing chains of glucose and, therefore, requires a primer. A fragment of glycogen can serve as a primer. In the absence of a fragment, the homodimeric protein glycogenin can serve as an acceptor of glucose from UDP-glucose (see Fig. 11.5). The side-chain hydroxyl group of tyrosine-194 in the protein is the site at which the initial glucosyl unit is attached. Because the reaction is catalyzed by glycogenin itself via autoglucosylation, glycogenin is an enzyme. Glycogenin then catalyzes the transfer of at least four molecules of glucose from UDP-glucose, producing a short, α(1→4)-linked glucosyl chain. This short chain serves as a primer that is able to be elongated by glycogen synthase, which is recruited by glycogenin, as described in C. below. (Note: Glycogenin stays associated with and forms the core of a glycogen granule.)

Elongation by glycogen synthase

Elongation of a glycogen chain involves the transfer of glucose from UDP-glucose to the nonreducing end of the growing chain, forming a new glycosidic bond between the anomeric hydroxyl group of carbon 1 of the activated glucose and carbon 4 of the accepting glucosyl residue (see Fig. 11.5). (Note: The nonreducing end of a carbohydrate chain is one in which the anomeric carbon of the terminal sugar is linked by a glycosidic bond to another molecule, making the terminal sugar nonreducing.) The enzyme responsible for making the α(1→4) linkages in glycogen is glycogen synthase. (Note: The UDP released when the new α[1→4] glycosidic bond is made can be phosphorylated to UTP by nucleoside diphosphate kinase [UDP + ATP UTP + ADP].)

Branch formation

If no other synthetic enzyme acted on the chain, the resulting structure would be a linear (unbranched) chain of glucosyl residues attached by α(1→4) linkages. Such a compound is found in plant tissues and is called amylose. In contrast, glycogen has branches located, on average, eight glucosyl residues apart, resulting in a highly branched, tree-like structure (see Fig. 11.3) that is far more soluble than the unbranched amylose. Branching also increases the number of nonreducing ends to which new glucosyl residues can be added (and also, as described in IV. below, from which these residues can be removed), thereby greatly accelerating the rate at which glycogen synthesis can occur and dramatically increasing the size of the glycogen molecule.

Branch synthesis

Branches are made by the action of the branching enzyme, amylo-α(1→4)→α(1→6)-transglycosylase. This enzyme removes a set of six to eight glucosyl residues from the nonreducing end of the glycogen chain, breaking an α(1→4) bond to another residue on the chain, and attaches it to a nonterminal glucosyl residue by an α(1→6) linkage, thus functioning as a 4:6 transferase. The resulting new, nonreducing end (see “i” in Fig. 11.5), as well as the old nonreducing end from which the six to eight residues were removed (see “o” in Fig. 11.5), can now be further elongated by glycogen synthase.

Additional branch synthesis

After elongation of these two ends has been accomplished, their terminal six to eight glucosyl residues can be removed and used to make additional branches.

Degradation (Glycogenolysis)

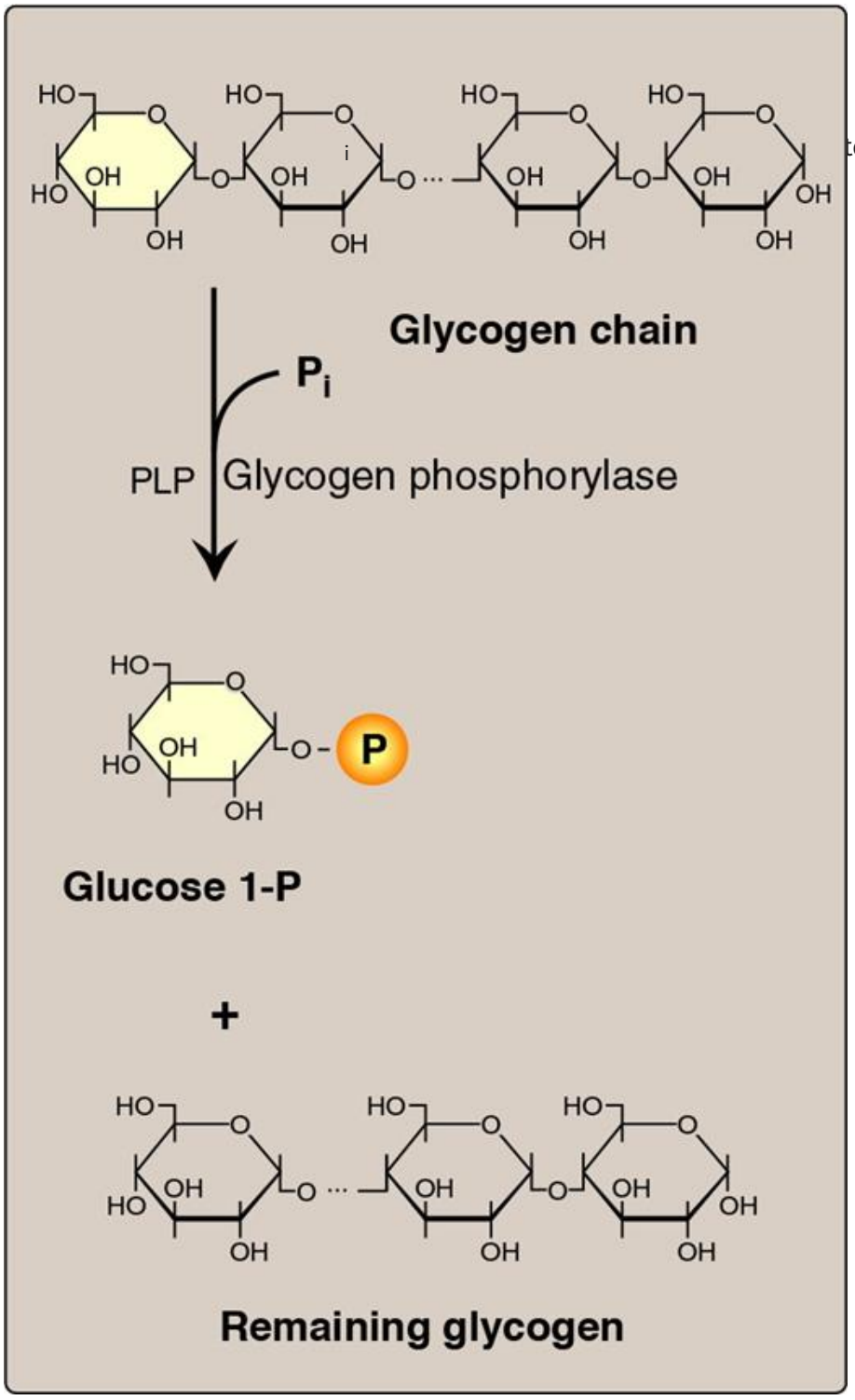
Listen

The degradative pathway that mobilizes stored glycogen in liver and skeletal muscle is not a reversal of the synthetic reactions. Instead, a separate set of cytosolic enzymes is required. When glycogen is degraded, the primary product is glucose 1-phosphate, obtained by breaking α(1→4) glycosidic bonds. In addition, free glucose is released from each α(1→6)–linked glucosyl residue (branch point).

Chain shortening

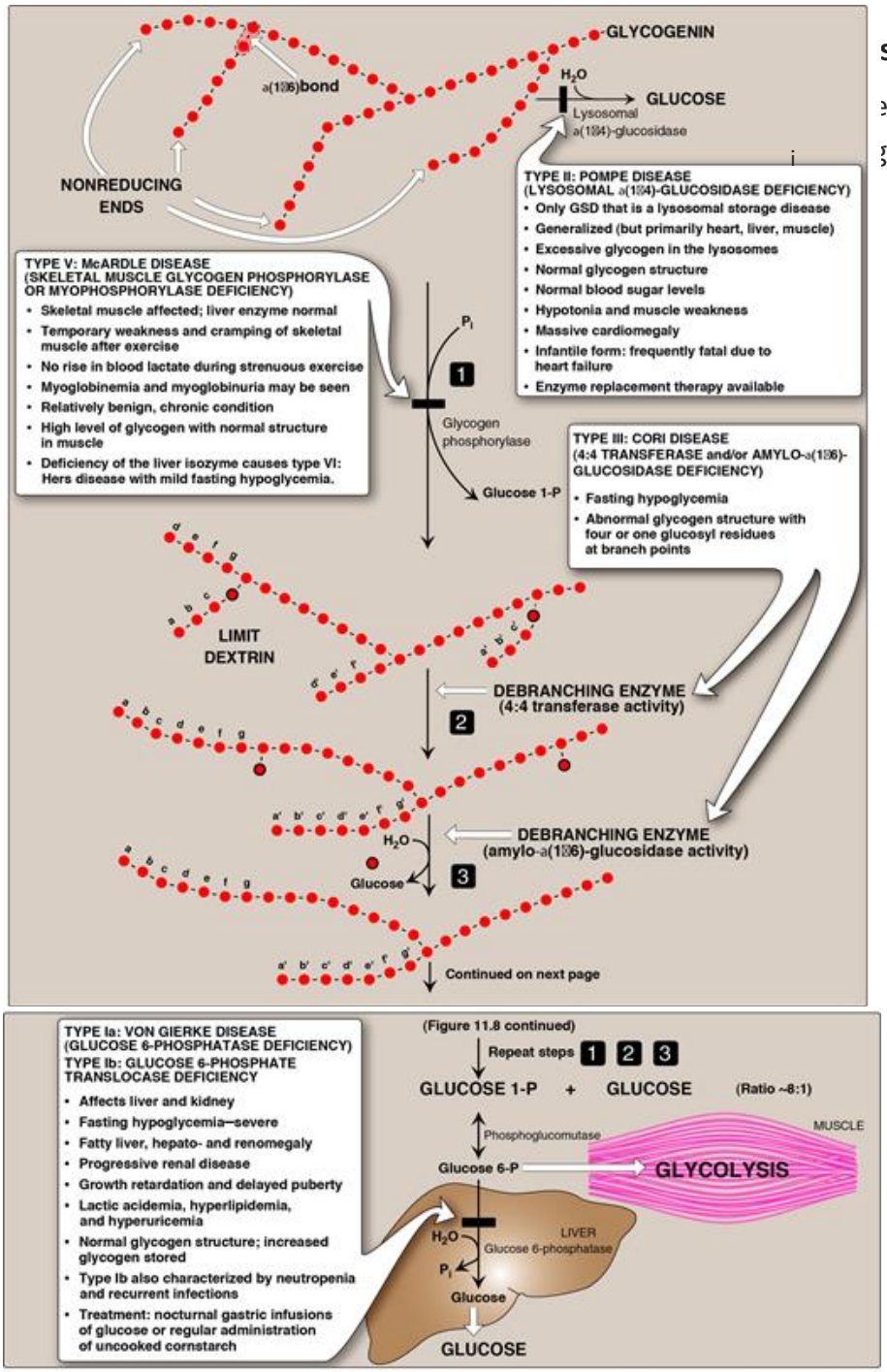
Glycogen phosphorylase sequentially cleaves the α(1→4) glycosidic bonds between the glucosyl residues at the nonreducing ends of the glycogen chains by simple phosphorolysis (producing glucose 1-phosphate) until four glucosyl units remain on each chain at a branch point (Fig. 11.7). The resulting structure is called a limit dextrin, and phosphorylase cannot degrade it any further (Fig. 11.8). (Note: Phosphorylase requires pyridoxal phosphate [a derivative of vitamin B_6] as a coenzyme.)

FIGURE 11.7



te.

FIGURE 11.8



seases (GSD).

enzyme, an enzyme of synthesis, ganic phosphate; P = phosphate.

Branch removal

Branches are removed by the two enzymic activities of a single bifunctional protein, the debranching enzyme (see Fig. 11.8). First, oligo-α(1→4)→α(1→4)-glucantransferase activity removes the outer three of the four glucosyl residues remaining at a branch. It next transfers them to the nonreducing end of another chain, lengthening it accordingly. Thus, an α(1→4) bond is broken and an α(1→4) bond is made, and the enzyme functions as a 4:4 transferase. Next, the remaining glucose residue attached in an α(1→6) linkage is removed hydrolytically by amylo-α(1→6)-glucosidase activity, releasing free (nonphosphorylated) glucose. The glucosyl chain is now available again for degradation by glycogen phosphorylase until four glucosyl units in the next branch are reached.

Glucose 1-phosphate isomerization to glucose 6-phosphate

Glucose 1-phosphate, produced by glycogen phosphorylase, is isomerized in the cytosol to glucose 6-phosphate by phosphoglucomutase (see Fig. 11.6). In the liver, glucose 6-phosphate is transported into the endoplasmic reticulum (ER) by glucose 6-phosphate translocase. There, it is dephosphorylated to glucose by glucose 6-phosphatase (the same enzyme used in the last step of gluconeogenesis; see p. 131). The glucose is then transported from the ER to the cytosol. Hepatocytes release glycogen-derived glucose into the blood to help maintain blood glucose levels until the gluconeogenic pathway is actively producing glucose. (Note: Muscle lacks glucose 6-phosphatase. Consequently, glucose 6-phosphate cannot be dephosphorylated and sent into the blood. Instead, it enters glycolysis, providing energy needed for muscle contraction.)

Lysosomal degradation

A small amount (1% to 3%) of glycogen is degraded by the lysosomal enzyme, acid α(1→4)-glucosidase (acid maltase). The purpose of this autophagic pathway is unknown. However, a deficiency of this enzyme causes accumulation of glycogen in vacuoles in the lysosomes, resulting in the serious GSD type II: Pompe disease (see Table 11.1 and Fig. 11.8). (Note: Pompe disease, caused by acid maltase deficiency, is the only GSD that is a lysosomal storage disease.)

TABLE 11.1

Descriptions of Glycogen Storage Diseases

Type[a]	Deficient Enzyme	Main Signs/Symptoms
I – Von Gierke disease	Glucose-6-phosphatase	Lactic acidosis, hypoglycemia, hyperuricemia, Impaired growth, bone thinning
II – Pompe disease[a]	Acid α-glucosidase (acid maltase)	Excess glycogen in lysosomes. Normal blood sugar. Enlarged liver and heart; muscle weakness and heart problems in severe forms
III – Cori disease[a]	Glycogen debranching enzyme (4:4 transferase)	Enlarged liver, growth delay, fasting hypoglycemia, abnormal glycogen structure, elevated fat in blood, possible muscle weakness
IV – Andersen disease	Glycogen branching enzyme (4:6 transferase)	Growth delay, enlarged liver, myopathy; death by age 5 usually
V – McArdle disease[a]	Muscle glycogen phosphorylase (myophosphorylase)	Muscle weakness and cramping after exercise; usually a relatively benign, chronic condition
VI – Hers disease	Liver glycogen phosphorylase	Liver enlargement; hypoglycemia; developmental delay
VII – Tarui disease	Muscle phosphofructokinase	Exercise-induced muscle cramps, developmental delay, hemolytic anemia in some

[a]This describes 7 of the 15 types of GSDs. See also Figure 11.3.

Lysosomal storage diseases are genetic disorders characterized by the accumulation of abnormal amounts of carbohydrates or lipids primarily due to their decreased lysosomal degradation resulting from absence, or decreased activity or amount of the specific lysosomal acid hydrolase that is normally responsible for its degradation.

Glycogenesis and Glycogenolysis Regulation

Listen

Because of the importance of maintaining blood glucose levels, the synthesis and degradation of its glycogen storage form are tightly regulated. In the liver, glycogenesis accelerates during periods when the body has been well fed, whereas glycogenolysis accelerates during periods of fasting. In skeletal muscle, glycogenolysis occurs during active exercise, and glycogenesis begins as soon as the muscle is again at rest.

Regulation of synthesis and degradation is accomplished on two levels. First, glycogen synthase and glycogen phosphorylase are hormonally regulated (by covalent phosphorylation/dephosphorylation) to meet the needs of the body as a whole. Second, these same enzymes are allosterically regulated (by effector molecules) to meet the needs of a particular tissue.

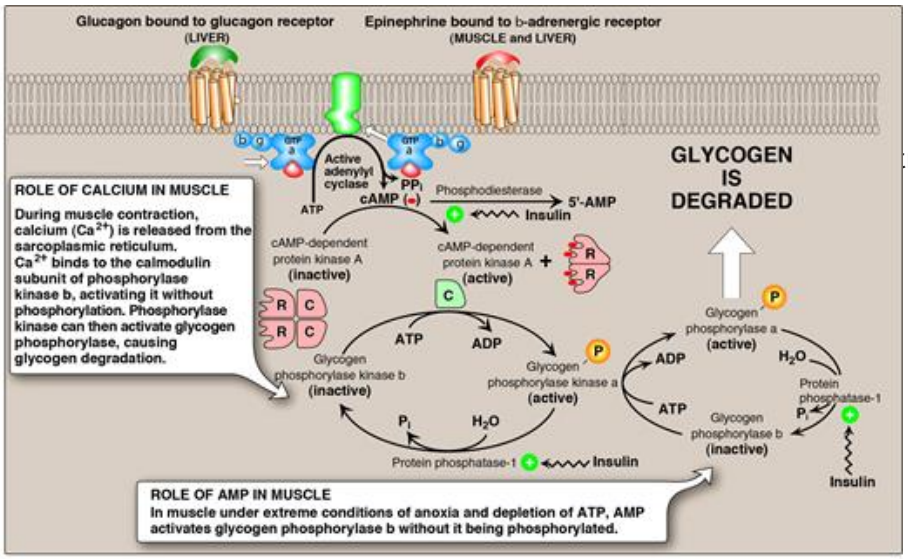
Covalent activation of glycogenolysis

The binding of hormones, such as glucagon or epinephrine, to plasma membrane G protein–coupled receptors signals the need for glycogen to be degraded, either to elevate blood glucose levels or to provide energy for exercising muscle.

Protein kinase A activation

Binding of glucagon or epinephrine to their specific hepatocyte GPCR, or of epinephrine to a specific myocyte GPCR, results in the G protein–mediated activation of adenylyl cyclase. This enzyme catalyzes the synthesis of cyclic adenosine monophosphate (cAMP), which activates cAMP-dependent protein kinase A (PKA). cAMP binds the two regulatory subunits of tetrameric PKA, releasing two individual catalytic subunits that are active (Fig. 11.9). PKA then phosphorylates several enzymes of glycogen metabolism, affecting their activity. (Note: When cAMP is removed, the inactive PKA tetramer reforms.)

FIGURE 11.9



riphosphate; P = phosphate; PP_i

Phosphorylase kinase activation

Phosphorylase kinase exists in two forms: an inactive “b” form and an active “a” form. Active PKA phosphorylates the inactive “b” form of phosphorylase kinase, producing the active “a” form (see Fig. 11.9).

Glycogen phosphorylase activation

Glycogen phosphorylase also exists in a dephosphorylated, inactive “b” form and a phosphorylated, active “a” form. Phosphorylase kinase a is the only enzyme that phosphorylates glycogen phosphorylase b to its active “a” form, which then begins glycogenolysis (see Fig. 11.9).

Signal amplification

The cascade of reactions described above activates glycogenolysis. The large number of sequential steps serves to amplify the effect of the hormonal signal, that is, a few hormone molecules binding to their GPCR result in a number of PKA molecules being activated that can each activate many phosphorylase kinase molecules. This causes the production of many molecules of active glycogen phosphorylase a that can degrade glycogen.

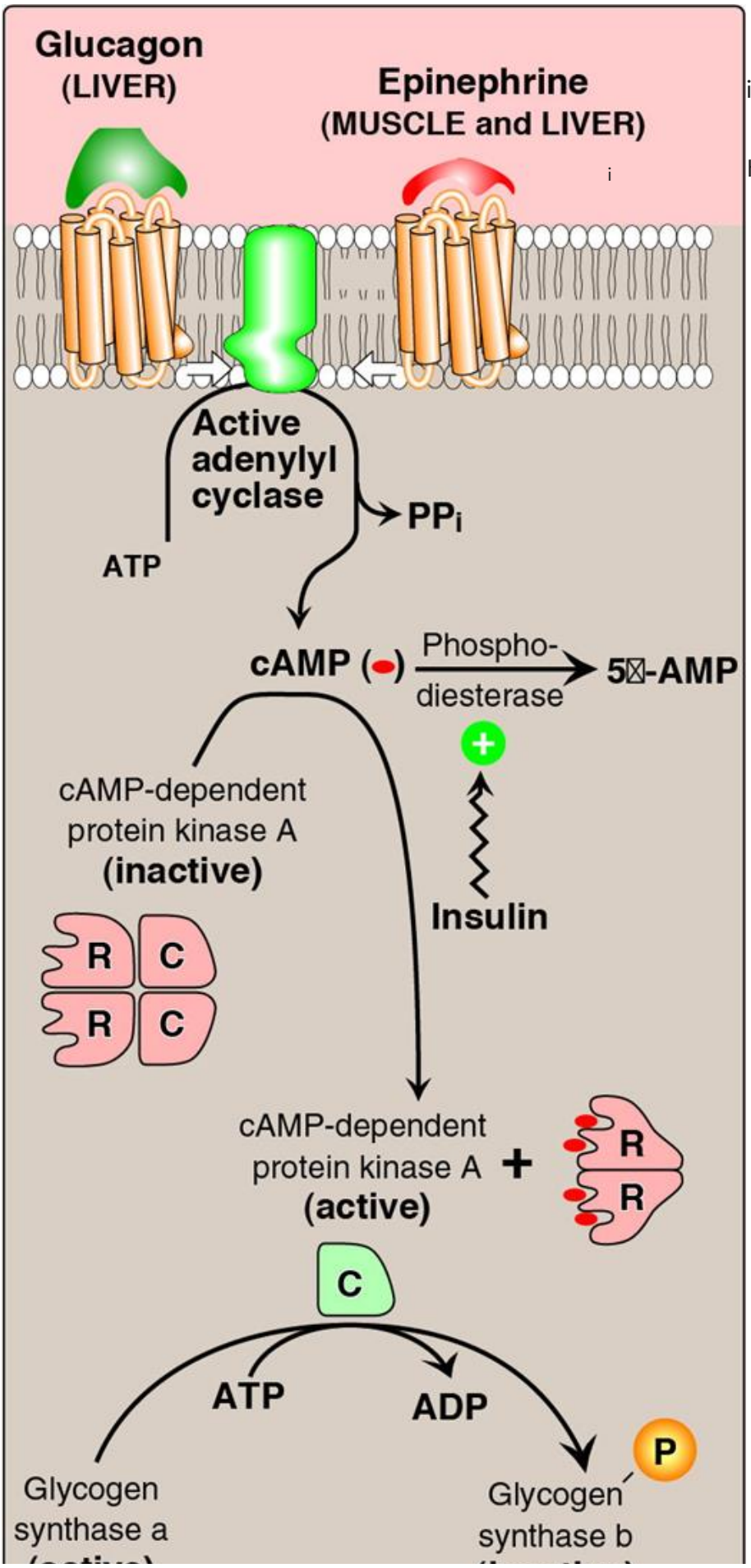
Phosphorylated state maintenance

The phosphate groups added to phosphorylase kinase and phosphorylase in response to cAMP are maintained because the enzyme that hydrolytically removes the phosphate, protein phosphatase-1 (PP1), is inactivated by inhibitor proteins that are also phosphorylated and activated in response to cAMP (see Fig. 11.9). Because insulin also activates the phosphodiesterase that degrades cAMP, it opposes the effects of glucagon and epinephrine.

Covalent inhibition of glycogenesis

The regulated enzyme in glycogenesis, glycogen synthase, also exists in two forms, the active “a” form and the inactive “b” form. However, in contrast to phosphorylase kinase and phosphorylase, the active form of glycogen synthase is dephosphorylated, whereas the inactive form is phosphorylated at several sites on the enzyme, with the level of inactivation proportional to the degree of phosphorylation (Fig. 11.10). Phosphorylation is catalyzed by several different protein kinases in response to cAMP (for example, PKA and phosphorylase kinase) or other signaling mechanisms (see C. below). Glycogen synthase b can be reconverted to the “a” form by PP1. Figure 11.11 summarizes the covalent regulation of glycogen metabolism.

FIGURE 11.10



ivated by phosphorylation.) cAMP =

hate; R = regulatory subunit; C =

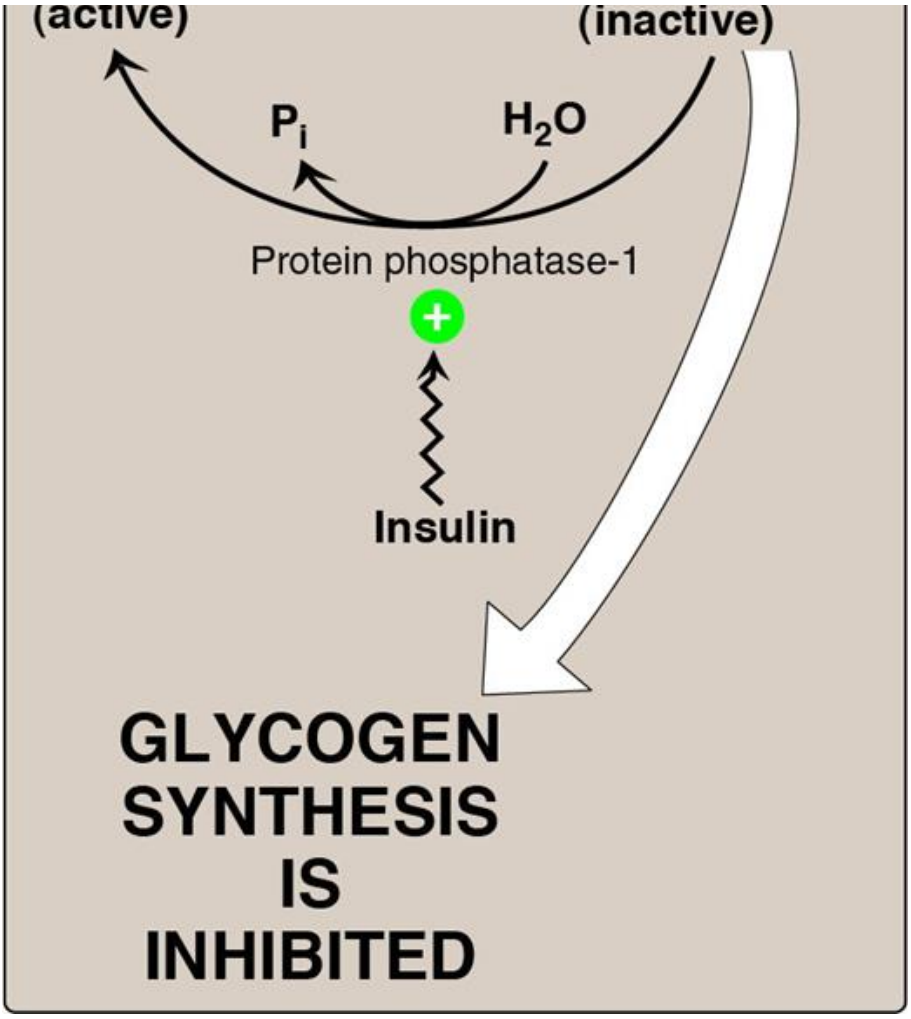
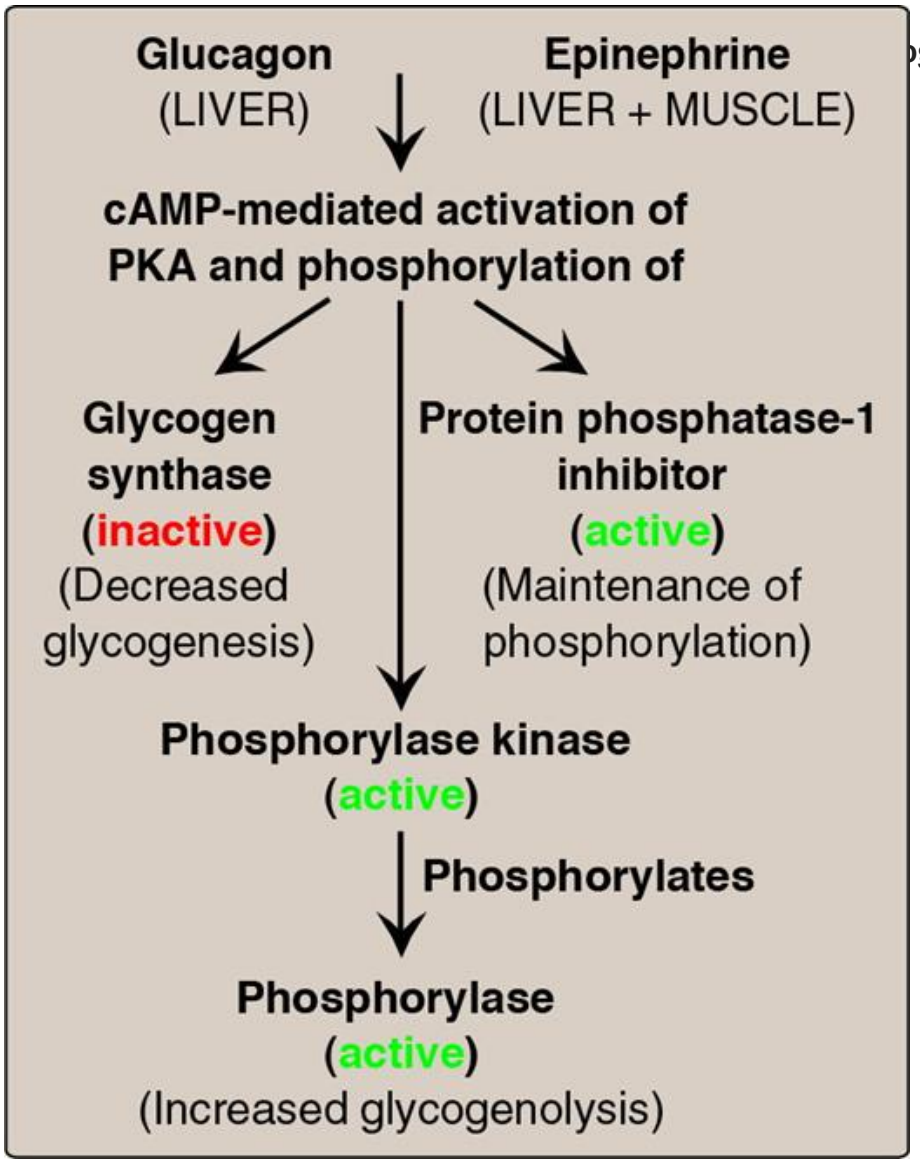

(active)
(inactive)
P_i
H_2O
Protein phosphatase-1
+
Insulin
GLYCOGEN SYNTHESIS IS INHIBITED

FIGURE 11.11



ogen metabolism.

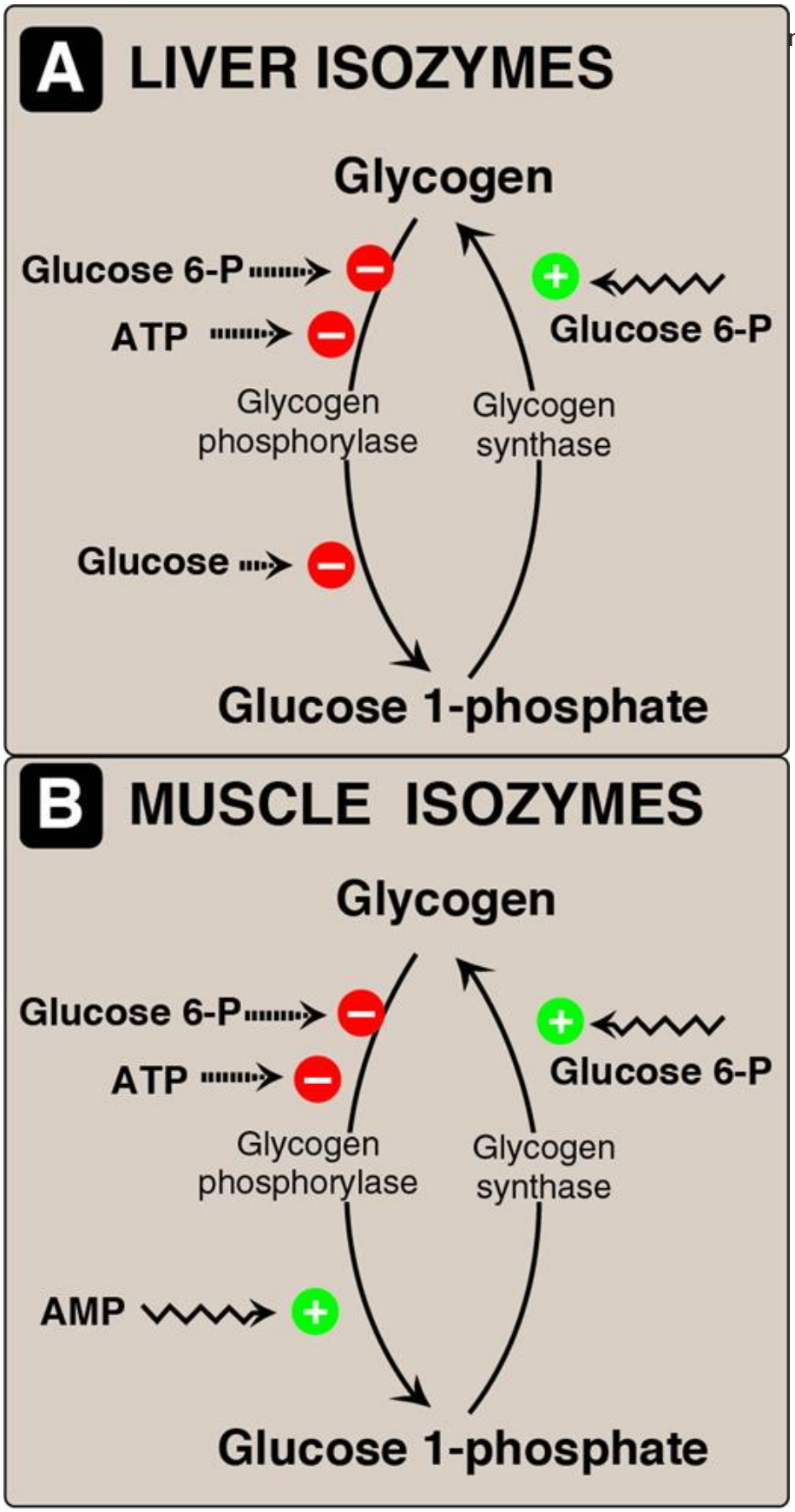
Allosteric regulation of glycogenesis and glycogenolysis

In addition to hormonal signals, glycogen synthase and glycogen phosphorylase respond to the levels of metabolites and energy needs of the cell. Glycogenesis is stimulated when glucose and energy levels are high, whereas glycogenolysis is increased when glucose and energy levels are low. This allosteric regulation allows a rapid response to the needs of a cell and can override the effects of hormone-mediated covalent regulation. (Note: The “a” and “b” forms of the allosteric enzymes of glycogen metabolism are each in an equilibrium between the R [relaxed, more active] and T [tense, less active] conformations [see p. 29]. The binding of effectors shifts the equilibrium and alters enzymic activity without directly altering the covalent modification.)

Regulation in the well-fed state

In the well-fed state, glycogen synthase b in both liver and muscle is allosterically activated by glucose 6-phosphate, which is present in elevated concentrations (Fig. 11.12). In contrast, glycogen phosphorylase a is allosterically inhibited by glucose 6-phosphate, as well as by ATP, a high-energy signal. Note that in liver, but not muscle, free glucose is also an allosteric inhibitor of glycogen phosphorylase a.

FIGURE 11.12



muscle, (**B**). P = phosphate; AMP =

Glycogenolysis activation by AMP

Muscle glycogen phosphorylase (myophosphorylase), but not the liver isozyme, is active in the presence of the high AMP concentrations that occur under extreme conditions of anoxia and ATP depletion. AMP binds to glycogen phosphorylase b, causing its activation without phosphorylation (see Fig. 11.9). Recall that AMP also activates phosphofructokinase-1 of glycolysis, allowing glucose from glycogenolysis to be oxidized.

Glycogenolysis activation by calcium

Calcium (Ca^{2+}) is released into the sarcoplasm in muscle cells (myocytes) in response to neural stimulation and in the liver in response to epinephrine binding to α_1-adrenergic receptors. The Ca^{2+} binds to calmodulin (CaM), the most widely distributed member of a family of small, Ca^{2+}-binding proteins. The binding of four molecules of Ca^{2+} to CaM triggers a conformational change such that the activated Ca^{2+}–CaM complex binds to and activates protein molecules, often enzymes that are inactive in the absence of this complex (Fig. 11.13). Thus, CaM functions as an essential subunit of many complex proteins. One such protein is the tetrameric phosphorylase kinase, whose "b" form is activated by the binding of Ca^{2+} to its δ subunit (CaM) without the need for the kinase to be phosphorylated by PKA. (Note: Epinephrine at β-adrenergic receptors signals through a rise in cAMP, not via a rise in Ca^{2+}.)

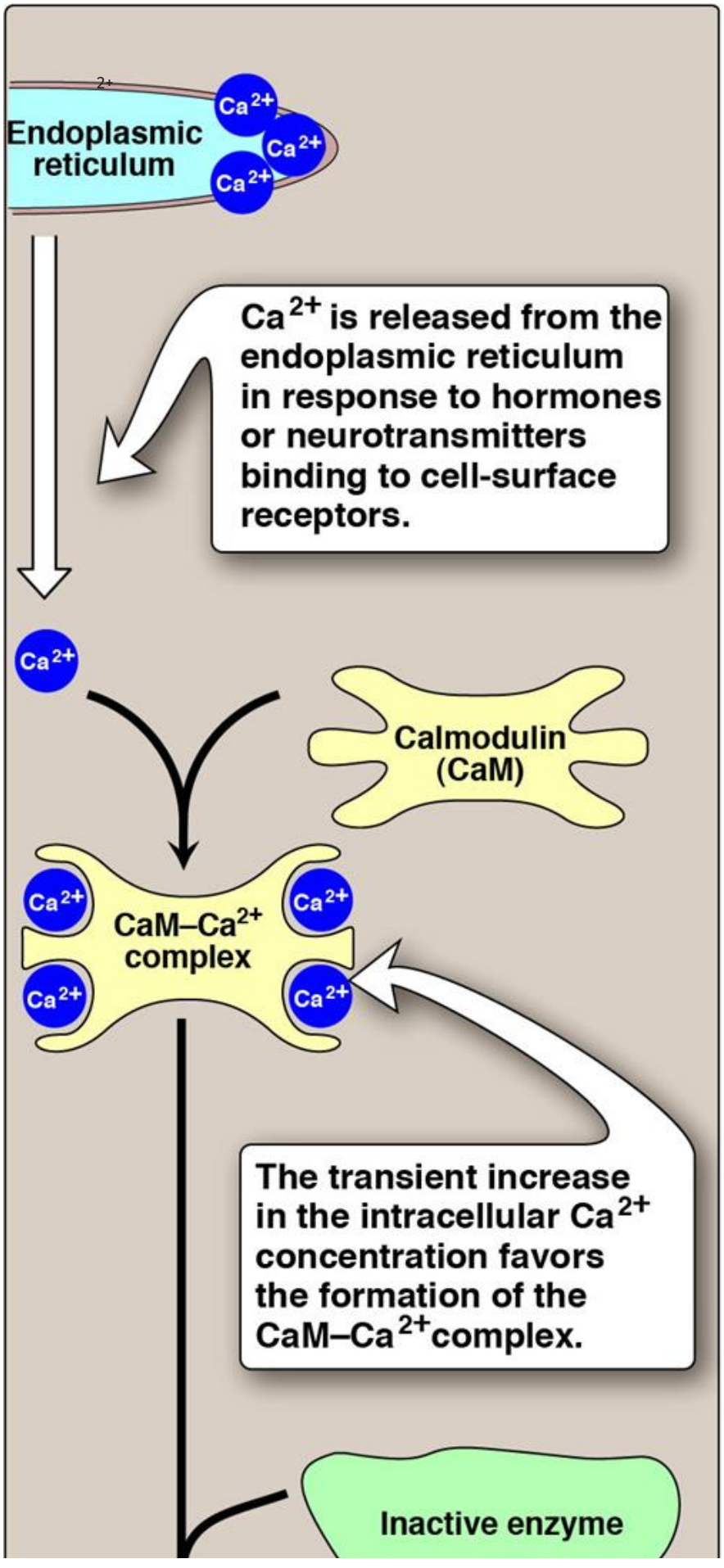
Muscle phosphorylase kinase activation

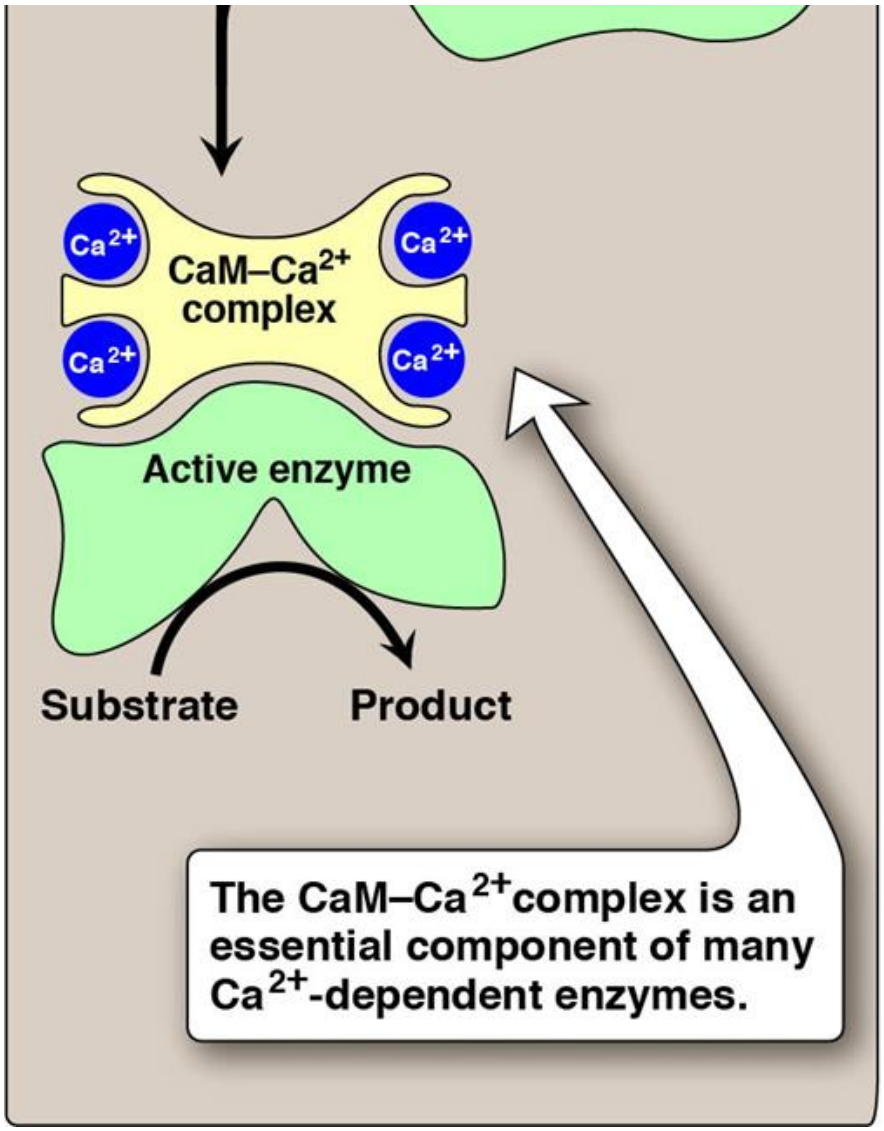
During muscle contraction, there is a rapid and urgent need for ATP. It is supplied by the degradation of muscle glycogen to glucose 6-phosphate, which enters glycolysis. Nerve impulses cause membrane depolarization, which promotes Ca^{2+} release from the sarcoplasmic reticulum into the sarcoplasm of myocytes. The Ca^{2+} binds the CaM subunit, and the complex activates muscle phosphorylase kinase b (see Fig. 11.9).

Liver phosphorylase kinase activation

During physiologic stress, epinephrine is released from the adrenal medulla and signals the need for blood glucose. This glucose initially comes from hepatic glycogenolysis. Binding of epinephrine to hepatocyte α_1-adrenergic GPCR activates a phospholipid-dependent cascade that results in movement of Ca^{2+} from the ER into the cytoplasm. A Ca^{2+}–CaM complex forms and activates hepatic phosphorylase kinase b. Note that the released Ca^{2+} also helps to activate protein kinase C that can phosphorylate and inactivate glycogen synthase a.

FIGURE 11.13


Endoplasmic reticulum
Ca2+
Ca2+
Ca2+
Ca2+ is released from the endoplasmic reticulum in response to hormones or neurotransmitters binding to cell-surface receptors.
Ca2+
Calmodulin (CaM)
Ca2+
Ca2+
CaM–Ca2+ complex
Ca2+
Ca2+
The transient increase in the intracellular Ca2+ concentration favors the formation of the CaM–Ca2+complex.
Inactive enzyme



Glycogen Storage Diseases

Listen

GSDs are a group of genetic diseases caused by defects in enzymes required for glycogen degradation or, more rarely, glycogen synthesis. The most common symptoms are hypoglycemia (low blood glucose), enlarged liver, slow growth, and muscle weakness or cramping.

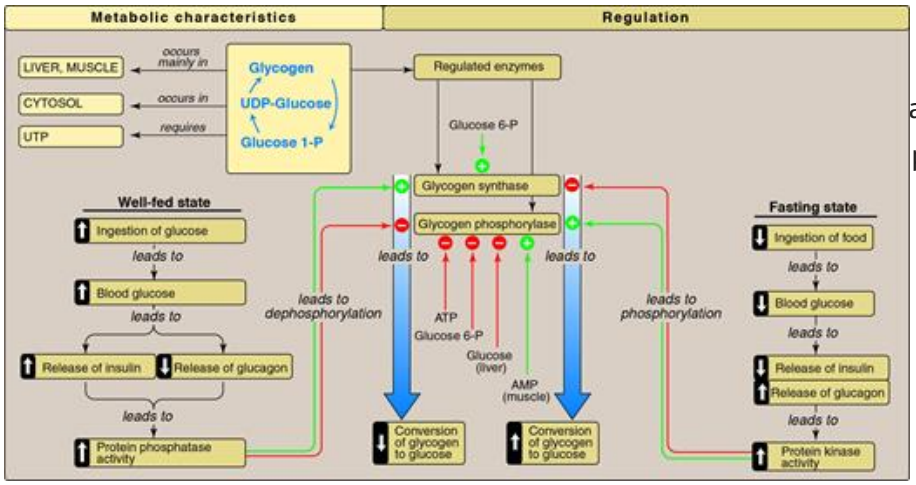
These disorders result either in formation of glycogen that has an abnormal structure or in the accumulation of excessive amounts of normal glycogen in specific tissues as a result of impaired degradation. A particular enzyme may be defective in a single tissue, such as the liver (resulting in hypoglycemia) or muscle (causing muscle weakness), or the defect may be more generalized, affecting a variety of tissues, such as the heart and kidneys. Severity ranges from fatal in early childhood to mild disorders that are not life threatening. Overall there are 15 recognized types of GSD; some are quite rare. The more prevalent types of GSD are described in Table 11.1 and three of the most common GSD are illustrated in Figure 11.8.

Chapter Summary

Listen

- The main stores of **glycogen** in the body are found in **skeletal muscle**, where they serve as a fuel reserve for the synthesis of **ATP** during muscle **contraction**, and in the **liver**, where they are used to maintain the **blood glucose** concentration, particularly during the early stages of a **fast**.
- Glycogen is a highly **branched polymer** of **α-d-glucose**.
- **UDP-glucose**, the building block of glycogen, is synthesized from **glucose 1-phosphate** and **UTP** by **UDP–glucose pyrophosphorylase** (Fig. 11.14).

FIGURE 11.14



ase, the “b” form of which can be phosphate; AMP = adenosine

- **Glucose** from UDP-glucose is transferred to the **nonreducing ends** of glycogen chains by primer-requiring **glycogen synthase**, which makes the α(1→4) linkages. The **primer** is made by **glycogenin**. Branches are formed by **amylo-α(1→4)→α(1→6)-transglycosylase** (a **4:6 transferase**), which transfers a set of six to eight glucosyl residues from the nonreducing end of the glycogen chain (breaking an α[1→4] linkage), and making an α(1→6) linkage to another residue in the chain.
- G**lycogen phosphorylase** cleaves the α(1→4) bonds between glucosyl residues at the nonreducing ends of the glycogen chains, producing **glucose 1-phosphate**.
- Glucose 1-phosphate is converted to **glucose 6-phosphate** by **phosphoglucomutase**.
- In **muscle**, glucose 6-phosphate enters glycolysis. In **liver**, the phosphate is removed by **glucose 6-phosphatase**, releasing free glucose that can be used to maintain blood glucose levels at the beginning of a fast.
- A deficiency of the phosphatase causes **von Gierke disease** and results in an inability of the liver to provide free glucose to the body during a fast. It affects both glycogen degradation and gluconeogenesis.
- Glycogen synthesis and degradation are **reciprocally regulated** to meet whole-body needs by the same hormonal signals, namely, an **elevated insulin** level results in overall **increased glycogenesis** and **decreased glycogenolysis**, whereas an **elevated glucagon**, or **epinephrine**, level causes the opposite effects.
- Key enzymes are phosphorylated by **protein kinases**, some of which are dependent on **cAMP**, a compound increased by glucagon and epinephrine. Phosphate groups are removed by **PP-1**.

- In addition to this **covalent regulation**, **glycogen synthase**, **phosphorylase kinase**, and **phosphorylase** are **allosterically regulated** to meet tissues' needs.
- In the well-fed state, glycogen synthase is activated by glucose 6-phosphate, but glycogen phosphorylase is inhibited by glucose 6-phosphate as well as by ATP.
- In the liver, free glucose also serves as an allosteric inhibitor of glycogen phosphorylase.
- The rise in **calcium** in muscle during exercise and in liver in response to epinephrine activates phosphorylase kinase by binding to the enzyme's C**aM** subunit. This allows the enzyme to activate glycogen phosphorylase, thereby causing glycogen degradation.

Study Questions

Listen

Choose the ONE best answer.

For Questions 11.1 to 11.4, match the deficient enzyme to the clinical finding in selected glycogen storage diseases (GSDs).

Choice	GSD	Deficient Enzyme
A	Von Gierke disease Type Ia	Glucose 6-phosphatase
B	Pompe disease Type II	Acid maltase
C	Cori disease Type III	4:4 Transferase
D	Andersen disease Type IV	4:6 Transferase
E	McArdle disease Type V	Myophosphorylase
F	Hers disease Type VI	Liver phosphorylase

11.1. Exercise intolerance, with no rise in blood lactate during exercise

Correct answer = E. Myophosphorylase (the muscle isozyme of glycogen phosphorylase) deficiency (or, McArdle disease) prevents glycogen degradation in muscle, depriving muscle of glycogen-derived glucose, resulting in decreased glycolysis and its anaerobic product, lactate.

11.2. Fatal, progressive cirrhosis and glycogen with longer-than-normal outer chains

Correct answer = D. 4:6 Transferase (branching enzyme) deficiency (Andersen disease), a defect in glycogen synthesis, results in glycogen with fewer branches and decreased solubility.

11.3. Generalized accumulation of glycogen, severe hypotonia, and death from heart failure

Correct answer = B. Acid maltase (acid α[1→4]-glucosidase) deficiency (or, Pompe disease) prevents degradation of any glycogen brought into lysosomes. A variety of tissues are affected, with the most severe pathology resulting from heart damage.

11.4. Severe fasting hypoglycemia, lactic acidemia, hyperuricemia, and hyperlipidemia

Correct answer = A. Glucose 6-phosphatase deficiency (von Gierke disease) prevents the liver from releasing free glucose into the blood, causing severe fasting hypoglycemia, lactic acidemia, hyperuricemia, and hyperlipidemia.

11.5. Both epinephrine and glucagon have which effect on hepatic glycogen metabolism?

A. Both phosphorylate and activate glycogen phosphorylase and glycogen synthase.

B. Both phosphorylate and inactivate glycogen phosphorylase and glycogen synthase.

C. Both cause increased glycogen degradation and decreased synthesis in the liver.

D. Both cause the synthesis of glycogen to have a net increase.

Correct answer = C. Epinephrine and glucagon both cause increased glycogen degradation and decreased synthesis in the liver through covalent modification (phosphorylation) of key enzymes of glycogen metabolism. Glycogen phosphorylase is phosphorylated and active (“a” form), whereas glycogen synthase is phosphorylated and inactive (“b” form). Glucagon does not cause a rise in calcium.

11.6. In contracting skeletal muscle, a sudden elevation of the sarcoplasmic calcium concentration will result in:

A. activation of cyclic adenosine monophosphate (cAMP)-dependent protein kinase A.

B. conversion of cAMP to AMP by phosphodiesterase.

C. direct activation of glycogen synthase b.

D. direct activation of phosphorylase kinase b.

E. inactivation of phosphorylase kinase a by the action of protein phosphatase-1.

Correct answer = D. Calcium (Ca^{2+}) released from the sarcoplasmic reticulum during exercise binds to the calmodulin subunit of phosphorylase kinase, thereby allosterically activating the dephosphorylated “b” form of this enzyme. The other choices are not caused by an elevation of cytosolic Ca^{2+}. (Note: Ca^{2+} also activates hepatic phosphorylase kinase b.)

11.7. Explain why the hypoglycemia seen with type 1 von Gierke disease (glucose 6-phosphatase deficiency) is severe, whereas that seen with type VI Hers disease (liver phosphorylase deficiency) is mild.

With von Gierke disease, the liver is unable to generate free glucose either from glycogenolysis or gluconeogenesis because both processes produce glucose 6-phosphate. With Hers disease, the liver is still able to produce free glucose from gluconeogenesis, but glycogenolysis is inhibited.