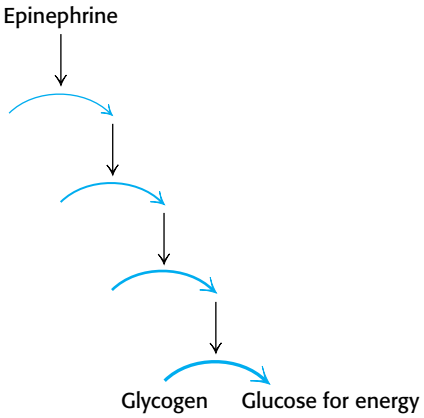
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CHAPTER

16

Glycogen Metabolism





Signaling cascades lead to the mobilization of glycogen to produce glucose, an energy source for cyclists. [(Left) Jonathan Devich/Epic Images.]

Glucose is an important fuel and, as we will see, a key precursor for the biosynthesis of many molecules. However, glucose cannot be stored, because high concentrations of glucose disrupt the osmotic balance of the cell, which would cause cell damage or death. How can adequate stores of glucose be maintained without damaging the cell? The solution to this problem is to store glucose as a nonosmotically active polymer called *glycogen*.

Glycogen is a *readily mobilized storage form of glucose.* It is a very large, branched polymer of glucose residues that can be broken down to yield glucose molecules when energy is needed (Figure 21.1). A glycogen molecule has approximately 12 layers of glucose molecules and can be as large as 40 nm, containing approximately 55,000 glucose residues. Most of the glucose residues in glycogen are linked by α-1,4-glycosidic bonds (Figure 21.2). Branches at about every 12 residues are created by α-1,6-glycosidic bonds. Recall that α-glycosidic linkages form open helical polymers, whereas β linkages produce nearly straight strands that form structural fibrils, as in cellulose (Figure 11.14).

Glycogen is not as reduced as fatty acids are and consequently are not as energy rich. Why isn't all excess fuel stored as fatty acids rather than as glycogen? The controlled release of glucose from glycogen maintains blood-glucose concentration between meals. The circulating blood keeps the brain supplied with glucose, which is virtually the only fuel used by the brain, except during prolonged starvation (Chapter 27). Moreover, the readily mobilized glucose from glycogen is a good source of energy for sudden, strenuous activity. Unlike fatty acids, the released glucose can be metabolized in the absence of oxygen and can thus supply energy for anaerobic activity (Section 16.1).

OUTLINE

21.1 Glycogen Breakdown Requires the Interplay of Several Enzymes

21.2 Phosphorylase Is Regulated by Allosteric Interactions and Reversible Phosphorylation

21.3 Epinephrine and Glucagon Signal the Need for Glycogen Breakdown

21.4 Glycogen Is Synthesized and Degraded by Different Pathways

21.5 Glycogen Breakdown and Synthesis Are Reciprocally Regulated

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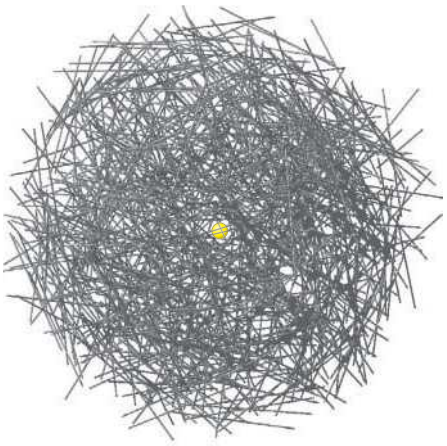


FIGURE 21.1 Glycogen. At the core of the glycogen molecule is the protein glycogenin (yellow). Each line represents glucose molecules joined by an α-1,4-glycosidic linkage. The nonreducing ends of the glycogen molecule form the surface of the glycogen granule. Degradation takes place at this surface. [Information from R. Melendez et al. *Biophys. J.* 77:1327–1332, 1999.]

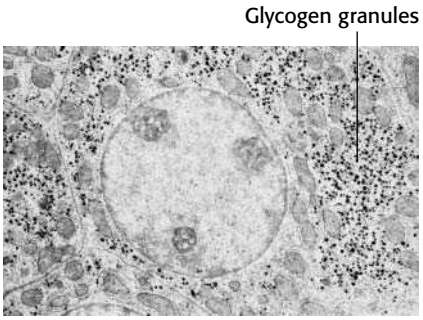


FIGURE 21.3 Electron micrograph of a liver cell. The dark particles in the cytoplasm are glycogen granules. [Courtesy of Dr. George Palade.]

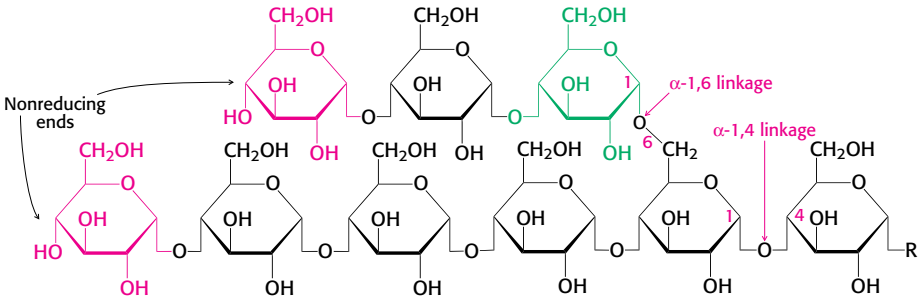


FIGURE 21.2 Glycogen structure. In this structure of two outer branches of a glycogen molecule, the residues at the nonreducing ends are shown in red and the residue that starts a branch is shown in green. The rest of the glycogen molecule is represented by R.

Glycogen is present in bacteria, archae, and eukaryotes. Recall that plants store glucose as starch, a similar chemical. Thus, storing energy as glucose polymers is common to all forms of life. In humans, most tissues have some glycogen, although the two major sites of glycogen storage are the liver and skeletal muscle. The concentration of glycogen is higher in the liver than in muscle (10% versus 2% by weight), but more glycogen is stored in skeletal muscle overall because of muscle's much greater mass. Glycogen is present in the cytoplasm, with the molecule appearing as granules (Figure 21.3). In the liver, glycogen synthesis and degradation are regulated to maintain blood-glucose levels as required to meet the needs of the organism as a whole. In contrast, in muscle, these processes are regulated to meet the energy needs of the muscle itself.

Glycogen metabolism is the regulated release and storage of glucose

Glycogen degradation and synthesis are simple biochemical processes. Glycogen degradation consists of three steps: (1) the release of glucose 1-phosphate from glycogen, (2) the remodeling of the glycogen substrate to permit further degradation, and (3) the conversion of glucose 1-phosphate into glucose 6-phosphate for further metabolism. The glucose 6-phosphate derived from the breakdown of glycogen has three possible fates (Figure 21.4): (1) It can be metabolized by glycolysis, (2) it can be converted into free

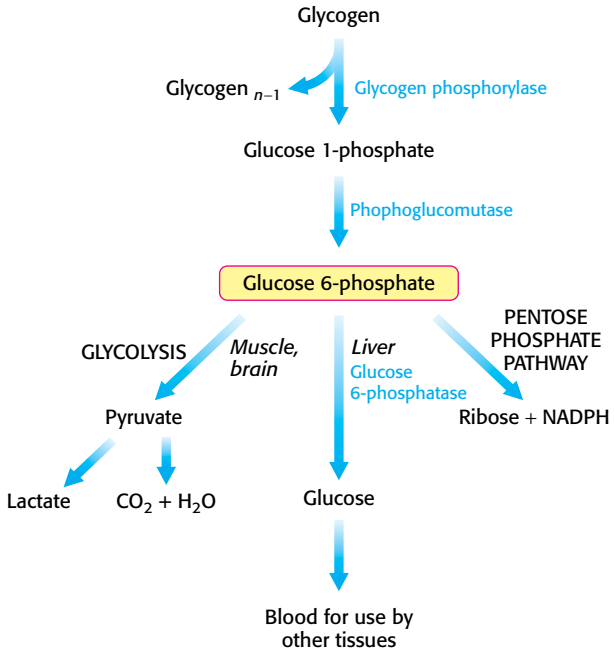


FIGURE 21.4 Fates of glucose 6-phosphate. Glucose 6-phosphate derived from glycogen can (1) be used as a fuel for anaerobic or aerobic metabolism as in, for instance, muscle; (2) be converted into free glucose in the liver and subsequently released into the blood; (3) be processed by the pentose phosphate pathway to generate NADPH or ribose in a variety of tissues.

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glucose for release into the bloodstream, and (3) it can be processed by the pentose phosphate pathway to yield NADPH and ribose derivatives. The conversion of glycogen into free glucose takes place mainly in the liver.

Glycogen synthesis, which takes place when glucose is abundant, requires an activated form of glucose, uridine diphosphate glucose (UDP-glucose), formed by the reaction of UTP and glucose 1-phosphate. As is the case for glycogen degradation, the glycogen molecule must be remodeled for continued synthesis.

The regulation of glycogen degradation and synthesis is complex and is facilitated by the fact that all of the enzymes involved in glycogen metabolism and its regulation are associated with the glycogen particle. Several enzymes taking part in glycogen metabolism allosterically respond to metabolites that signal the energy needs of the cell. *Through these allosteric responses, enzyme activity is adjusted to meet the needs of the cell.* In addition, hormones may initiate signal cascades that lead to the reversible phosphorylation of enzymes, which alters their catalytic rates. *Regulation by hormones adjusts glycogen metabolism to meet the needs of the entire organism.*

21.1 Glycogen Breakdown Requires the Interplay of Several Enzymes

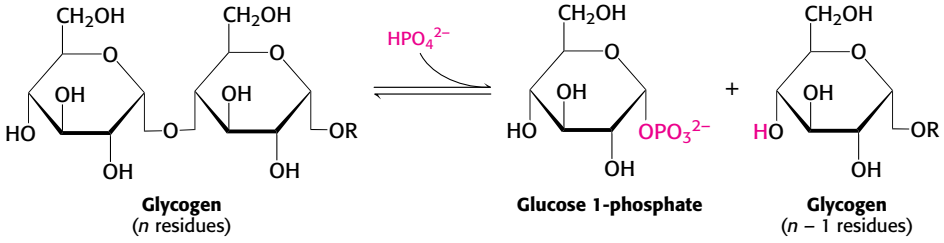
The efficient breakdown of glycogen to provide glucose 6-phosphate for further metabolism requires four enzyme activities: one to degrade glycogen, two to remodel glycogen so that it can remain a substrate for degradation, and one to convert the product of glycogen breakdown into a form suitable for further metabolism. We will examine each of these activities in turn.

Phosphorylase catalyzes the phosphorolytic cleavage of glycogen to release glucose 1-phosphate

Glycogen phosphorylase, the key enzyme in glycogen breakdown, cleaves its substrate by the addition of orthophosphate (P_i) to yield *glucose 1-phosphate.* The cleavage of a bond by the addition of orthophosphate is referred to as *phosphorolysis*.

$$\underset{(n \text{ residues})}{\text{Glycogen}} + P_i \rightleftharpoons \text{glucose 1-phosphate} + \underset{(n-1 \text{ residues})}{\text{glycogen}}$$

Phosphorylase catalyzes the sequential removal of glucosyl residues from the nonreducing ends of the glycogen molecule (the ends with a free OH group on carbon 4). Orthophosphate splits the glycosidic linkage between C-1 of the terminal residue and C-4 of the adjacent one. Specifically, it cleaves the bond between the C-1 carbon atom and the glycosidic oxygen atom, and the α configuration at C-1 is retained.



Glucose 1-phosphate released from glycogen can be readily converted into glucose 6-phosphate, an important metabolic intermediate, by the enzyme phosphoglucomutase.

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The reaction catalyzed by phosphorylase is readily reversible in vitro. At pH 6.8, the equilibrium ratio of orthophosphate to glucose 1-phosphate is 3.6. The value of $\Delta G^{\circ\prime}$ for this reaction is small because a glycosidic bond is replaced by a phosphoryl ester bond that has a nearly equal transfer potential. However, phosphorolysis proceeds far in the direction of glycogen breakdown in vivo because the $[P_i]/[\text{glucose 1-phosphate}]$ ratio is usually greater than 100, substantially favoring phosphorolysis. We see here an example of how the cell can alter the free-energy change to favor a reaction's occurrence by altering the ratio of substrate and product.

The phosphorolytic cleavage of glycogen is energetically advantageous because the released sugar is already phosphorylated. In contrast, a hydrolytic cleavage would yield glucose, which would then have to be phosphorylated at the expense of a molecule of ATP to enter the glycolytic pathway. An additional advantage of phosphorolytic cleavage for muscle cells is that no transporters exist for glucose 1-phosphate, which is negatively charged under physiological conditions, and so it cannot be transported or diffuse out of the cell.

Mechanism: Pyridoxal phosphate participates in the phosphorolytic cleavage of glycogen

The special challenge faced by phosphorylase is to cleave glycogen phosphorolytically rather than hydrolytically to save the ATP required to phosphorylate free glucose. Thus, water must be excluded from the active site. Phosphorylase is a dimer of two identical 97-kDa subunits. Each subunit is compactly folded into an *amino-terminal domain* (480 residues) containing a *glycogen-binding site* and a *carboxyl-terminal domain* (360 residues; Figure 21.5). The catalytic site in each subunit is located in a deep crevice formed by residues from both domains. Substrates bind synergistically, causing the crevice to narrow, thereby excluding water. What is the mechanistic basis of the phosphorolytic cleavage of glycogen?

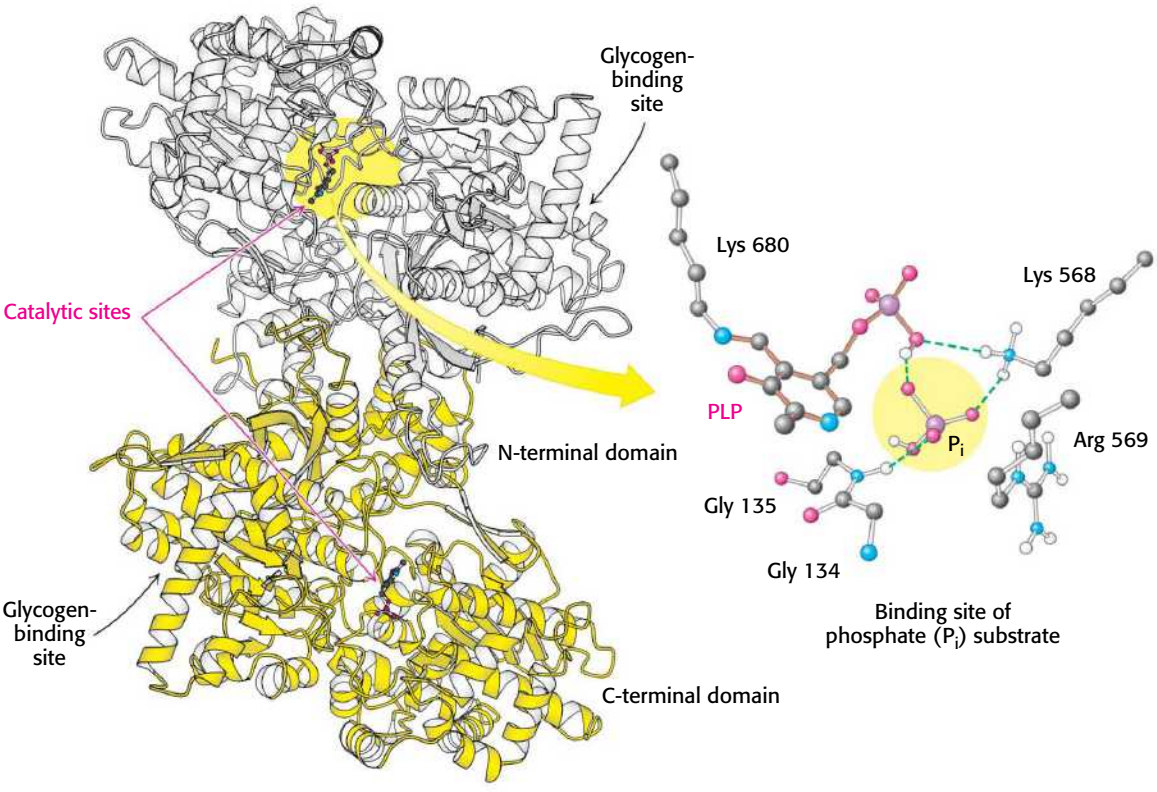


FIGURE 21.5 Structure of glycogen phosphorylase. This enzyme forms a homodimer: one subunit is shown in white and the other in yellow. Each catalytic site includes a pyridoxal phosphate (PLP) group, linked to lysine 680 of the enzyme. The binding site for the phosphate (P_i) substrate is shown. *Notice* that the catalytic site lies between the C-terminal domain and the glycogen-binding site. A narrow crevice, which binds four or five glucose units of glycogen, connects the two sites. The separation of the sites allows the catalytic site to phosphorolyze several glucose units before the enzyme must rebind the glycogen substrate. [Drawn from 1NOI.pdb.]

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Several clues suggest a mechanism. First, both the glycogen substrate and the glucose 1-phosphate product have an α configuration at C-1. A direct attack by phosphate on C-1 of a sugar would invert the configuration at this carbon atom because the reaction would proceed through a pentacovalent transition state. The fact that the glucose 1-phosphate formed has an α rather than a β configuration suggests that an even number of steps (most simply, two) is required. A likely explanation for these results is that a *carbonium ion intermediate* is formed from the glucose residue.

A second clue to the catalytic mechanism of phosphorylase is its requirement for the coenzyme *pyridoxal phosphate* (PLP), a derivative of pyridoxine (vitamin B_6, Section 15.4). The aldehyde group of this coenzyme forms a Schiff-base linkage with a specific lysine side chain of the enzyme (Figure 21.6). Structural studies indicate that the reacting orthophosphate group takes a position between the 5′-phosphate group of PLP and the glycogen substrate (Figure 21.7). *The 5′-phosphate group of PLP acts in tandem with orthophosphate by serving as a proton donor and then as a proton acceptor (i.e., as a general acid–base catalyst).* Orthophosphate (in the HPO_4^{2-} form) donates a proton to the oxygen atom attached to carbon 4 of the departing glycogen chain and simultaneously acquires a proton from PLP. The carbonium ion intermediate formed in this step is then attacked by orthophosphate to form α-glucose 1-phosphate, with the concomitant return of a proton to pyridoxal phosphate. The special role of pyridoxal phosphate in the reaction is necessary because water is excluded from the active site.

The glycogen-binding site is 30 Å away from the catalytic site (Figure 21.5), but it is connected to the catalytic site by a narrow crevice able to accommodate four or five glucose units. The large separation between the binding site and the catalytic site enables the enzyme to phosphorolyze many residues without having to dissociate and reassociate after each catalytic cycle. An enzyme that can catalyze many reactions without having to dissociate and reassociate after each catalytic step is said to be *processive*—a property of enzymes that synthesize and degrade large polymers. We will see such enzymes again when we consider DNA and RNA synthesis.

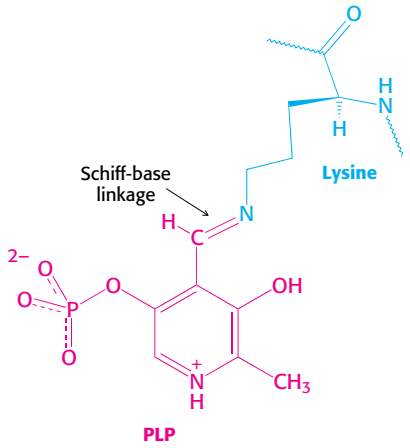


FIGURE 21.6 PLP–Schiff-base linkage. A pyridoxal phosphate (PLP) group (red) forms a Schiff base with a lysine residue (blue) at the active site of phosphorylase, where it functions as a general acid–base catalyst.

A Schiff base, also called an *imine,* is a compound containing a carbon–nitrogen double bond with the nitrogen atom bonded to an organic compound, not a hydrogen atom. A Schiff base is formed by the reaction of a primary amine with an aldehyde or ketone.

A debranching enzyme also is needed for the breakdown of glycogen

Glycogen phosphorylase acting alone degrades glycogen to a limited extent. The enzyme can break α-1,4-glycosidic bonds on glycogen branches but soon encounters an obstacle. The α-1,6-glycosidic bonds at the branch points are not susceptible to cleavage by phosphorylase. Indeed, phosphorylase stops cleaving α-1,4 linkages when it reaches a terminal residue four residues away from a branch point. Because about 1 in 12 residues is branched, cleavage by the phosphorylase alone would come to a halt after the release of eight glucose molecules per branch.

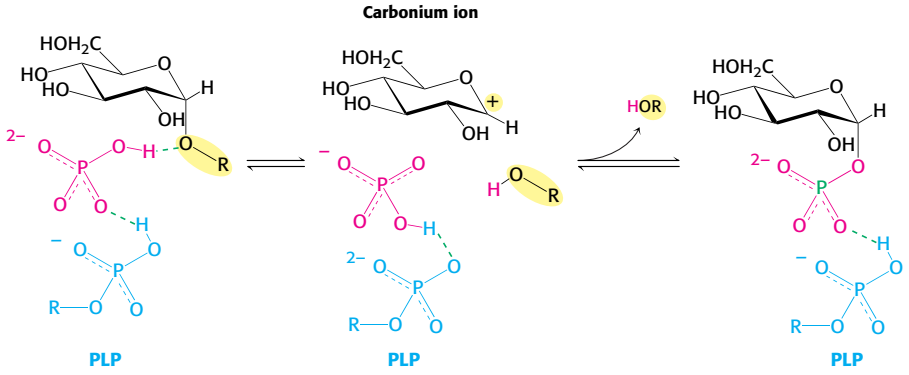
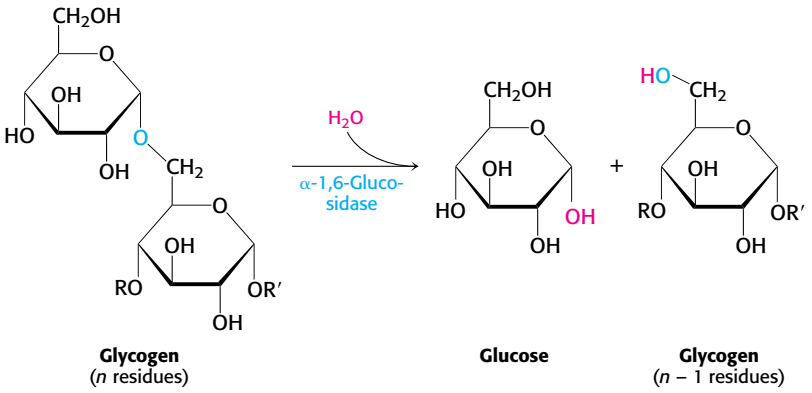


FIGURE 21.7 Phosphorylase mechanism. A bound HPO_4^{2-} group (red) favors the cleavage of the glycosidic bond by donating a proton to the C-4 oxygen of the departing glycosyl group (black). This reaction results in the formation of a carbonium ion and is favored by the transfer of a proton from the protonated phosphate group of the bound pyridoxal phosphate (PLP) group (blue). The carbonium ion and the orthophosphate combine to form glucose 1-phosphate.

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How can the remainder of the glycogen molecule be mobilized for use as a fuel? Two additional enzymes, a *transferase* and α-*1,6-glucosidase,* remodel the glycogen for continued degradation by the phosphorylase (Figure 21.8). *The transferase shifts a block of three glucosyl residues from one outer branch to another.* This transfer exposes a single glucose residue joined by an α-1,6-glycosidic linkage. α-1,6-Glucosidase, also known as the debranching enzyme, hydrolyzes the α-1,6-glycosidic bond.



A free glucose molecule is released and then phosphorylated by the glycolytic enzyme hexokinase. Thus, the transferase and α-1,6-glucosidase convert the branched structure into a linear one, which paves the way for further cleavage by phosphorylase. In eukaryotes, the transferase and the α-1,6-glucosidase activities are present in a single 160-kDa polypeptide chain, providing yet another example of a bifunctional enzyme (Figure 16.29).

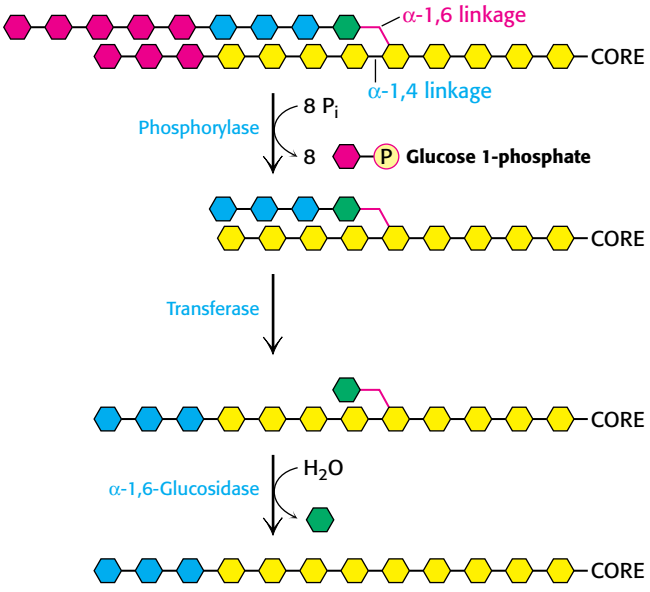


FIGURE 21.8 Glycogen remodeling. First, α-1,4-glycosidic bonds on each branch are cleaved by phosphorylase, leaving four residues along each branch. The transferase shifts a block of three glucosyl residues from one outer branch to the other. In this reaction, the α-1,4-glycosidic link between the blue and the green residues is broken and a new α-1,4 link between the blue and the yellow residues is formed. The green residue is then removed by α-1,6-glucosidase, leaving a linear chain with all α-1,4 linkages, suitable for further cleavage by phosphorylase.

Phosphoglucomutase converts glucose 1-phosphate into glucose 6-phosphate

Glucose 1-phosphate formed in the phosphorolytic cleavage of glycogen must be converted into glucose 6-phosphate to enter the metabolic mainstream. This shift of a phosphoryl group is catalyzed by *phosphoglucomutase.* Recall that this enzyme is also used in galactose metabolism (Section 16.1). To effect this shift, the enzyme exchanges a phosphoryl group with the substrate (Figure 21.9). The catalytic site of an active mutase molecule contains a phosphorylated serine residue. The phosphoryl group is transferred from the serine residue to the C-6 hydroxyl group of glucose 1-phosphate to form glucose 1,6-bisphosphate. The C-1 phosphoryl group of this intermediate is then shuttled to the same serine residue, resulting in the formation of glucose 6-phosphate and the regeneration of the phosphoenzyme.

These reactions are like those of *phosphoglycerate mutase,* a glycolytic enzyme (Section 16.1). The role of glucose 1,6-bisphosphate in the interconversion of the phosphoglucoses is like that of 2,3-bisphosphoglycerate (2,3-BPG) in the interconversion of 2-phosphoglycerate and 3-phosphoglycerate in glycolysis. A phosphoenzyme intermediate participates in both reactions.

The liver contains glucose 6-phosphatase, a hydrolytic enzyme absent from muscle

A major function of the liver is to maintain a nearly constant level of glucose in the blood. The liver releases glucose into the blood between meals and

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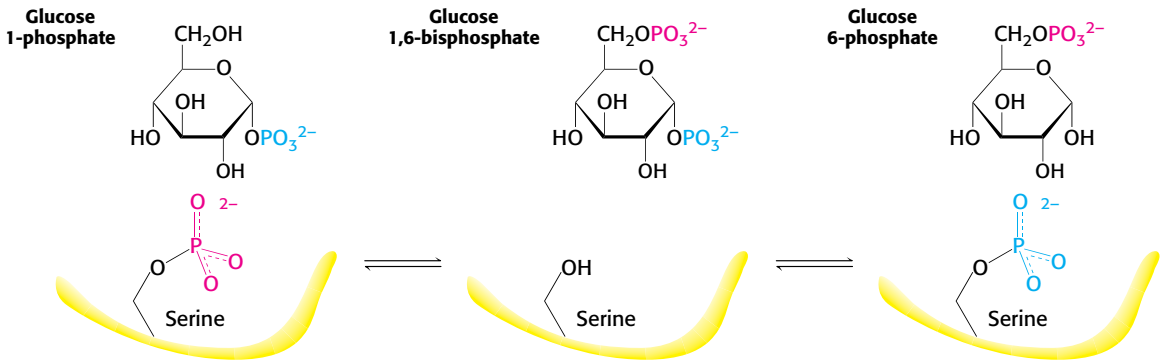


FIGURE 21.9 Reaction catalyzed by phosphoglucomutase. A phosphoryl group is transferred from the enzyme to the substrate, and a different phosphoryl group is transferred back to restore the enzyme to its initial state.

during muscular activity. The released glucose is taken up primarily by the brain, skeletal muscle, and red blood cells. In contrast with unmodified glucose, however, the phosphorylated glucose produced by glycogen breakdown is not transported out of cells. The liver contains a hydrolytic enzyme, *glucose 6-phosphatase,* that enables glucose to leave that organ. This enzyme cleaves the phosphoryl group to form free glucose and orthophosphate. This glucose 6-phosphatase is the same enzyme that releases free glucose at the conclusion of gluconeogenesis. It is located on the lumenal side of the smooth endoplasmic reticulum membrane. Recall that glucose 6-phosphate is transported into the endoplasmic reticulum; glucose and orthophosphate formed by hydrolysis are then shuttled back into the cytoplasm (Section 16.1).

$$\text{Glucose 6-phosphate} + H_2O \longrightarrow \text{glucose} + P_i$$

Glucose 6-phosphatase is absent from most other tissues. Muscle tissues retain glucose 6-phosphate for the generation of ATP. In contrast, glucose is not a major fuel for the liver.

21.2 Phosphorylase Is Regulated by Allosteric Interactions and Reversible Phosphorylation

Glycogen degradation is precisely controlled by multiple interlocking mechanisms. The focus of this control is the enzyme glycogen phosphorylase. *Phosphorylase is regulated by several allosteric effectors that signal the energy state of the cell as well as by reversible phosphorylation, which is responsive to hormones such as insulin, epinephrine, and glucagon.* We will examine the differences in the control of two isozymic forms of glycogen phosphorylase: one specific to liver and one specific to skeletal muscle. These differences are due to the fact that *the liver maintains glucose homeostasis of the organism as a whole, whereas the muscle uses glucose to produce energy for itself.*

Liver phosphorylase produces glucose for use by other tissues

The dimeric phosphorylase exists in two interconvertible forms: a *usually active* phosphorylase *a* and a *usually inactive* phosphorylase *b* (Figure 21.10). Each of these two forms exists in equilibrium between an active relaxed (R) state and a much less active tense (T) state, but the equilibrium for phosphorylase *a* favors the active R state, whereas the equilibrium for phosphorylase *b* favors the less-active T state (Figure 21.11). The role of glycogen degradation in the liver is to form glucose for export to other tissues when the blood-glucose level is low. Consequently, we can think of the

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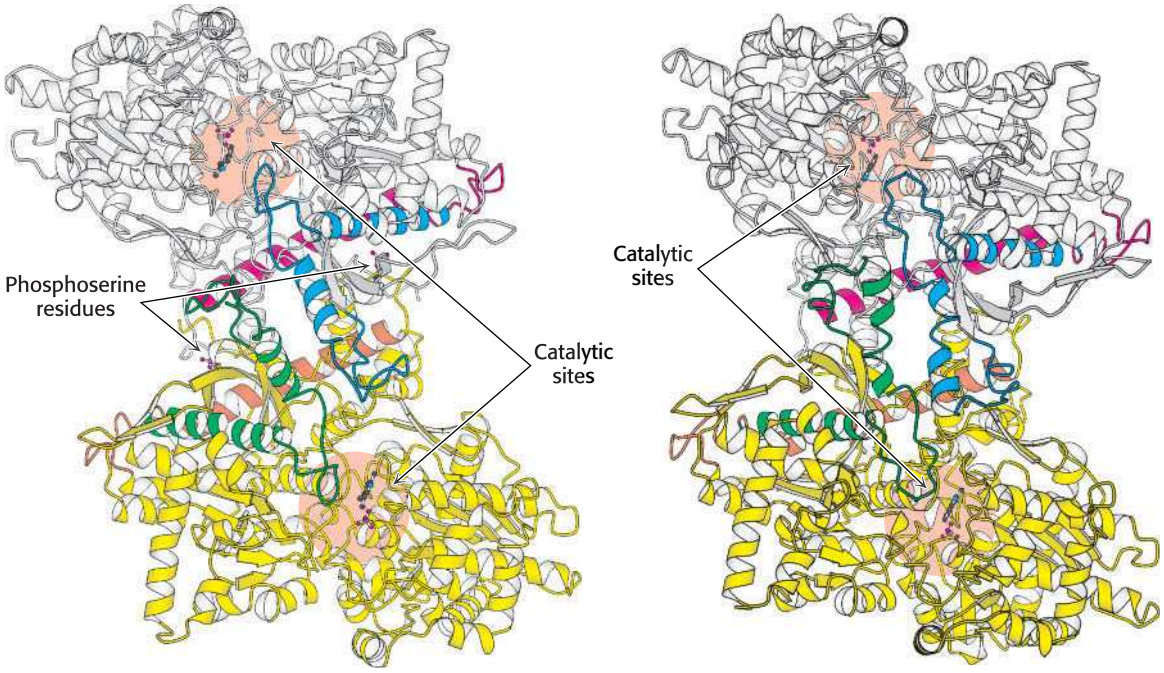


FIGURE 21.10 Structures of phosphorylase *a* and phosphorylase *b*. Phosphorylase *a* is phosphorylated on serine 14 of each subunit. This modification favors the structure of the more-active R state. One subunit is shown in white, with helices and loops important for regulation shown in blue and red. The other subunit is shown in yellow, with the regulatory structures shown in orange and green. Phosphorylase *b* is not phosphorylated and exists predominantly in the T state. *Notice* that the catalytic sites are partly occluded in the T state. [Drawn from 1GPA.pdb and 1NOJ.pdb.]

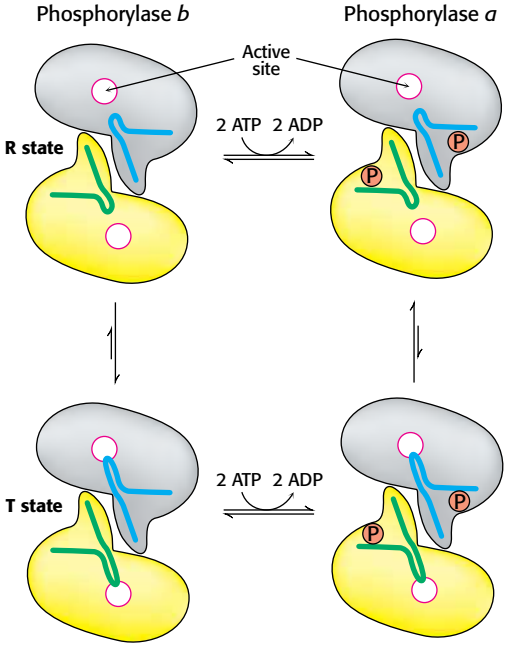


FIGURE 21.11 Phosphorylase regulation. Both phosphorylase *b* and phosphorylase *a* exist as equilibria between an active R state and a less-active T state. Phosphorylase *b* is usually inactive because the equilibrium favors the T state. Phosphorylase *a* is usually active because the equilibrium favors the R state. Regulatory structures are shown in blue and green.

default state of liver phosphorylase as being the *a* form: glucose is to be generated unless the enzyme is signaled otherwise. The liver phosphorylase *a* form thus exhibits the most responsive R ↔ T transition (Figure 21.12). The binding of glucose to the active site shifts the *a* form from the active R state to the less-active T state. In essence, the enzyme reverts to the low-activity T state only when it detects the presence of sufficient glucose. If glucose is present in the diet, there is no need to degrade glycogen.

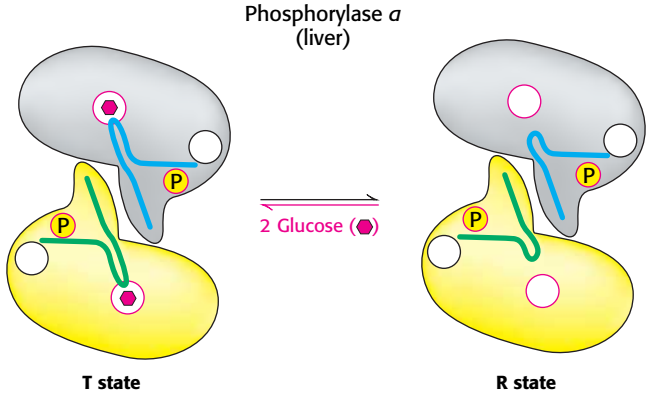


FIGURE 21.12 Allosteric regulation of liver phosphorylase. The binding of glucose to phosphorylase *a* shifts the equilibrium to the T state and inactivates the enzyme. Thus, glycogen is not mobilized when glucose is already abundant.

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Muscle phosphorylase is regulated by the intracellular energy charge

In contrast to the liver isozyme, the default state of muscle phosphorylase is the *b* form, owing to the fact that, for muscle, phosphorylase must be active primarily during muscle contraction. Muscle phosphorylase *b* is activated by the presence of high concentrations of AMP, which binds to a nucleotide-binding site and stabilizes the conformation of phosphorylase *b* in the active R state (Figure 21.13). Thus, when a muscle contracts and ATP is converted into AMP by the sequential action of myosin (Section 9.4) and adenylate kinase (Section 16.2), the phosphorylase is signaled to degrade glycogen. ATP acts as a negative allosteric effector by competing with AMP. Thus, *the transition of phosphorylase* b *between the active R state and the less-active T state is controlled by the energy charge of the muscle cell.* Glucose 6-phosphate also binds at the same site as ATP and stabilizes the less-active state of phosphorylase *b,* an example of feedback inhibition. Under most physiological conditions, *phosphorylase* b *is inactive because of the inhibitory effects of ATP and glucose 6-phosphate.* In contrast, *phosphorylase* a *is fully active,* regardless of the levels of AMP, ATP, and glucose 6-phosphate. In resting muscle, nearly all the enzyme is in the inactive *b* form.

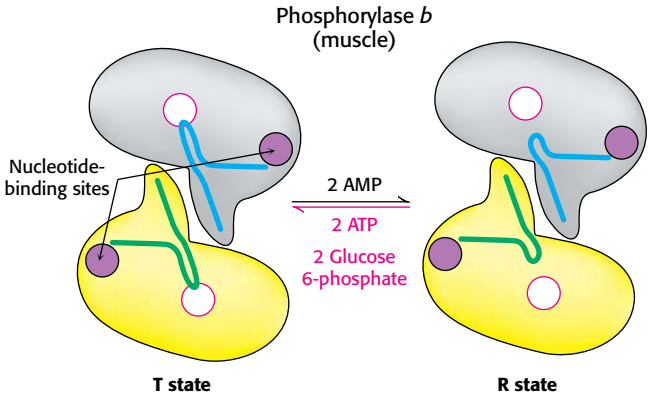


FIGURE 21.13 Allosteric regulation of muscle phosphorylase. A low energy charge, represented by high concentrations of AMP, favors the transition to the R state. ATP and glucose 6-phosphate stabilize the T state.

Unlike the enzyme in muscle, the liver phosphorylase is insensitive to regulation by AMP because the liver does not undergo the dramatic changes in energy charge seen in a contracting muscle. We see here a clear example of the use of isozymes to establish the tissue-specific biochemical properties of the liver and muscle. In human beings, liver phosphorylase and muscle phosphorylase are approximately 90% identical in amino acid sequence, yet the 10% difference results in subtle but important shifts in the stability of various forms of the enzyme.

Biochemical characteristics of muscle fiber types differ

Not only do the biochemical needs of liver and muscle differ with respect to glycogen metabolism, but the biochemical needs of different muscle fiber types also vary. Skeletal muscle consists of three different fiber types: type I, or slow-twitch muscle; type IIb (also called type IIx), or fast-twitch fibers; and type IIa fibers that have properties intermediate between the other two fiber types. Type I fibers rely predominantly on cellular respiration to derive energy. These fibers are powered by fatty acid degradation and are rich in mitochondria, the site of fatty acid degradation and the citric acid cycle. As we will see in Chapter 22, fatty acids are an excellent energy storage form, but generating ATP from fatty acids is slower than from glycogen. Glycogen is not an important fuel for type I fibers, and consequently the amount of glycogen phosphorylase is low. Type I fibers power endurance activities. Type IIb fibers use glycogen as their main fuel. Consequently, the glycogen and glycogen phosphorylase are abundant. These fibers are also rich in glycolytic enzymes needed to process glucose quickly in the absence of oxygen and poor in mitochondria. Type IIb fibers power burst activities such as sprinting and weight lifting. No amount of training can interconvert type I fibers and type IIb fibers. However, there is some evidence that type IIa fibers are "trainable"; that is, endurance training enhances the oxidative capacity of type IIa fibers while burst activity training enhances the glycolytic capacity. Table 21.1 shows the biochemical profile of the fiber types.

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TABLE 21.1 Biochemical characteristics of muscle fiber types

Characteristic	Type I	Type IIa	Type IIb
Fatigue resistance	High	Intermediate	Low
Mitochondrial density	High	Intermediate	Low
Metabolic type	Oxidative	Oxidative/glycolytic	Glycolytic
Myoglobin content	High	Intermediate	Low
Glycogen content	Low	Intermediate	High
Triacylglycerol content	High	Intermediate	Low
Glycogen phosphorylase activity	Low	Intermediate	High
Phosphofructokinase activity	Low	Intermediate	High
Citrate synthase activity	High	Intermediate	Low

Phosphorylation promotes the conversion of phosphorylase *b* to phosphorylase *a*

In both liver and muscle, phosphorylase *b* is converted into phosphorylase *a* by the phosphorylation of a single serine residue (serine 14) in each subunit. This conversion is initiated by hormones. Low blood levels of glucose lead to the secretion of the hormone glucagon. Fear or the excitement of exercise will cause levels of the hormone epinephrine to increase. The rise in glucagon and epinephrine levels results in phosphorylation of the enzyme to the phosphorylase *a* form in liver and muscle respectively. The regulatory enzyme *phosphorylase kinase* catalyzes this covalent modification.

Comparison of the structures of phosphorylase *a* in the R state and phosphorylase *b* in the T state reveals that subtle structural changes at the subunit interfaces are transmitted to the active sites (Figure 21.10). The transition from the T state (the prevalent state of phosphorylase *b*) to the R state (the prevalent state of phosphorylase *a*) entails a 10-degree rotation around the twofold axis of the dimer. Most important, this transition is associated with structural changes in α helices that move a loop out of the active site of each subunit. Thus, the T state is less active because the catalytic site is partly blocked. In the R state, the catalytic site is more accessible and a binding site for orthophosphate is well organized.

Phosphorylase kinase is activated by phosphorylation and calcium ions

Phosphorylase kinase activates phosphorylase *b* by attaching a phosphoryl group. The subunit composition of phosphorylase kinase in skeletal muscle is $(\alpha\beta\gamma\delta)_4$, and the mass of this very large protein is 1300 kDa. The enzyme consists of two $(\alpha\beta\gamma\delta)_2$ lobes that are joined by a β_4 bridge that is the core of the enzyme and serves as a scaffold for the remaining subunits. The γ subunit contains the active site, while all of the remaining subunits (≈90% by mass) play regulatory roles. The δ subunit is the calcium binding protein *calmodulin*, a calcium sensor that stimulates many enzymes in eukaryotes (Section 14.1). The α and β subunits are targets of protein kinase A. The β subunit is phosphorylated first, followed by the phosphorylation of the α subunit.

Activation of phosphorylase kinase is initiated when Ca^{2+} binds to the δ subunit. This mode of activation of the kinase is especially noteworthy in muscle, where contraction is triggered by the release of Ca^{2+} from the sarcoplasmic reticulum (Figure 21.14). Maximal activation is achieved with the phosphorylation of the β and α subunits of the Ca^{2+}-bound kinase. The stimulation of phosphorylase kinase is one step in a signal-transduction cascade initiated by signal molecules such as glucagon and epinephrine.

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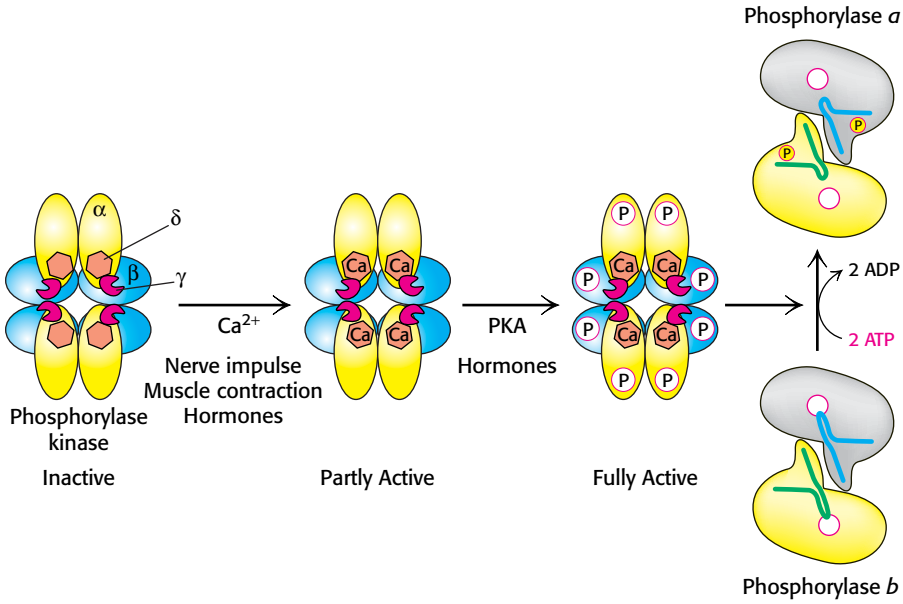


FIGURE 21.14 Activation of phosphorylase kinase. Phosphorylase kinase, an $(\alpha\beta\gamma\delta)_4$ assembly, is partly activated by Ca^{2+} binding to the δ subunit. Activation is maximal when the β and α subunits are phosphorylated in response to hormonal signals. When active, the enzyme converts phosphorylase *b* into phosphorylase *a*.

21.3 Epinephrine and Glucagon Signal the Need for Glycogen Breakdown

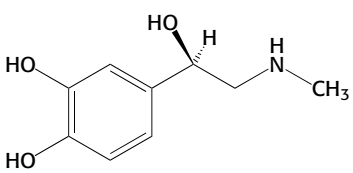
Protein kinase A activates phosphorylase kinase, which in turn activates glycogen phosphorylase. What activates protein kinase A? What is the signal that ultimately triggers an increase in glycogen breakdown?

G proteins transmit the signal for the initiation of glycogen breakdown

Several hormones greatly affect glycogen metabolism. Glucagon and epinephrine trigger the breakdown of glycogen. Muscular activity or its anticipation leads to the release of *epinephrine (adrenaline),* a catecholamine derived from tyrosine, from the adrenal medulla. Epinephrine markedly stimulates glycogen breakdown in muscle and, to a lesser extent, in the liver. The liver is more responsive to *glucagon,* a polypeptide hormone secreted by the α cells of the pancreas when the blood-sugar level is low. Physiologically, glucagon signifies the starved state (Figure 21.15).

How do hormones trigger the breakdown of glycogen? They initiate a cyclic AMP signal-transduction cascade, already discussed in Section 14.1 (Figure 21.16).

1. The signal molecules epinephrine and glucagon bind to specific seven-transmembrane (7TM) receptors in the plasma membranes of target cells (Section 14.1). Epinephrine binds to the β-adrenergic receptor in muscle, whereas glucagon binds to the glucagon receptor in the liver. These binding events activate the G_s protein. *A specific external signal has been transmitted into the cell through structural changes,* first in the receptor and then in the G protein.



Epinephrine

5 10
$^{+}H_3N$–His–Ser–Glu–Gly–Thr–Phe–Thr–Ser–Asp–Tyr–
15 20
–Ser–Lys–Tyr–Leu–Asp–Ser–Arg–Arg–Ala–Gln–
25 29
–Asp–Phe–Val–Gln–Trp–Leu–Met–Asn–Thr–COO^{-}

Glucagon

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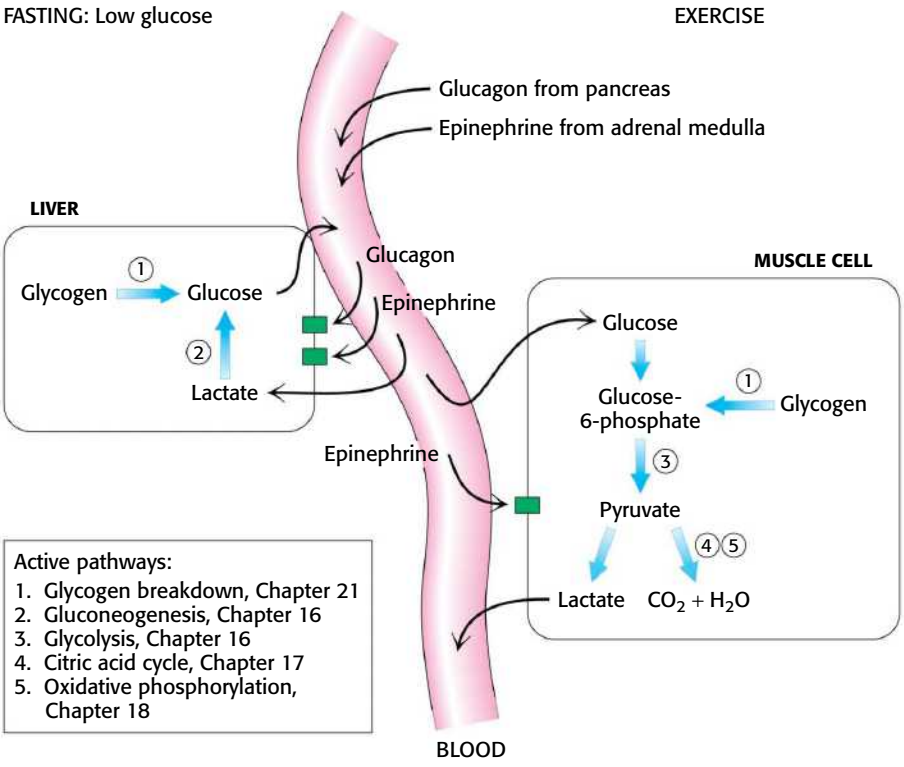


FIGURE 21.15 PATHWAY INTEGRATION: Hormonal control of glycogen breakdown. Glucagon stimulates liver-glycogen breakdown when blood glucose is low. Epinephrine enhances glycogen breakdown in muscle and the liver to provide fuel for muscle contraction.

2. The GTP-bound subunit of G_s activates the transmembrane protein adenylate cyclase. This enzyme catalyzes the formation of the second messenger cyclic AMP (cAMP) from ATP.

3. The elevated cytoplasmic level of cAMP activates *protein kinase A* (Section 10.3). The binding of cAMP to inhibitory regulatory subunits

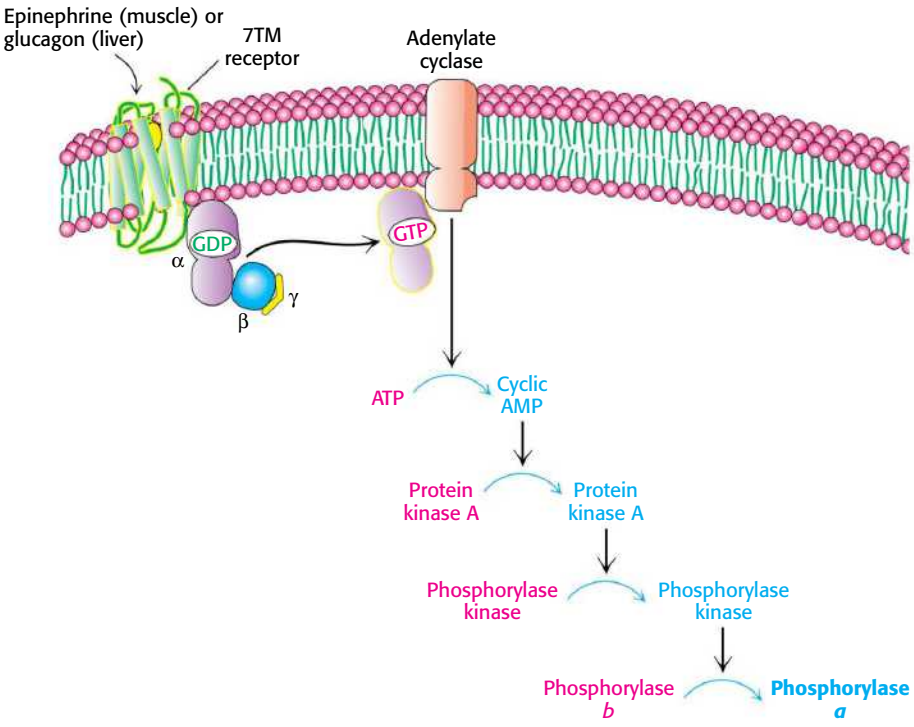


FIGURE 21.16 Regulatory cascade for glycogen breakdown. Glycogen degradation is stimulated by hormone binding to 7TM receptors. Hormone binding initiates a G-protein-dependent signal-transduction pathway that results in the phosphorylation and activation of glycogen phosphorylase.

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triggers their dissociation from the catalytic subunits. The free catalytic subunits are now active.

4. Protein kinase A phosphorylates phosphorylase kinase, first on the β subunit and then on the α subunit, which activates glycogen phosphorylase.

The cyclic AMP cascade highly amplifies the effects of hormones. The binding of a small number of hormone molecules to cell-surface receptors leads to the release of a very large number of sugar units. Indeed, much of the stored glycogen would be mobilized within seconds were it not for a counterregulatory system.

The signal-transduction processes in the liver are more complex than those in muscle. Epinephrine can also elicit glycogen degradation in the liver. However, in addition to binding to the β-adrenergic receptor, it binds to the 7TM α-adrenergic receptor, which then initiates the *phosphoinositide cascade* (Section 14.2) that induces the release of Ca^{2+} from endoplasmic reticulum stores. Recall that the δ subunit of phosphorylase kinase is the Ca^{2+} sensor calmodulin. The binding of Ca^{2+} to calmodulin leads to a partial activation of phosphorylase kinase. Stimulation by both glucagon and epinephrine leads to maximal mobilization of liver glycogen.

Glycogen breakdown must be rapidly turned off when necessary

It is crucial that the high-gain system of glycogen breakdown be terminated quickly to prevent the wasteful depletion of glycogen after energy needs have been met. When glucose needs have been satisfied, phosphorylase kinase and glycogen phosphorylase are dephosphorylated and inactivated. Simultaneously, glycogen synthesis is activated.

The signal-transduction pathway leading to the activation of glycogen phosphorylase is shut down automatically when secretion of the initiating hormone ceases. The inherent GTPase activity of the G protein converts the bound GTP into inactive GDP, and phosphodiesterases always present in the cell convert cyclic AMP into AMP. Protein phosphatase 1 (PP1) removes the phosphoryl groups from phosphorylase kinase, thereby inactivating the enzyme. Finally, PP1 also removes the phosphoryl group from glycogen phosphorylase, converting the enzyme into the usually inactive *b* form.

The regulation of glycogen phosphorylase became more sophisticated as the enzyme evolved

Analyses of the primary structures of glycogen phosphorylase from human beings, rats, *Dictyostelium* (slime mold), yeast, potatoes, and *E. coli* have enabled inferences to be made about the evolution of this important enzyme. The 16 residues that come into contact with glucose at the active site are identical in nearly all the enzymes. There is more variation but still substantial conservation of the 15 residues at the pyridoxal phosphate-binding site. Likewise, the glycogen-binding site is well conserved in all the enzymes. The high degree of similarity among these three sites shows that the catalytic mechanism has been maintained throughout evolution.

Differences arise, however, when we compare the regulatory sites. The simplest type of regulation would be feedback inhibition by glucose 6-phosphate. Indeed, the glucose 6-phosphate regulatory site is highly conserved among most of the phosphorylases. The crucial amino acid residues that participate in regulation by phosphorylation and nucleotide binding are well conserved only in the mammalian enzymes. Thus, this level of regulation was a later evolutionary acquisition.

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