Chapter 15 Principles of Metabolic Regulation

- Every pathway is inextricably intertwined with all the other cellular pathways **(Fig. 15–1)**.

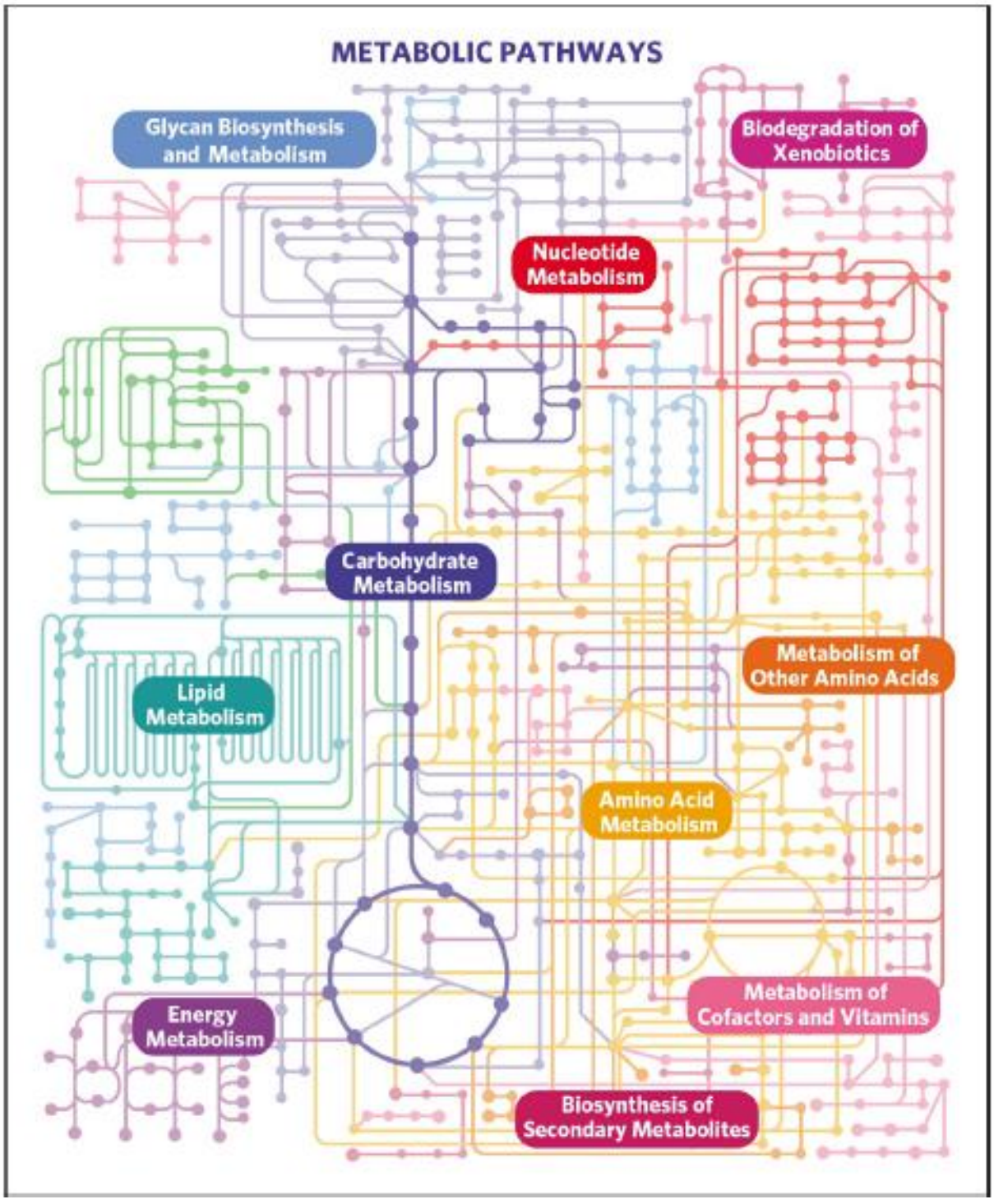


FIGURE 15-1 Metabolism as a three-dimensional meshwork.

- A typical eukaryotic cell has the capacity to make about 30,000 different proteins
    - they catalyze thousands of different reactions involving many hundreds of metabolites, most shared by more than one “pathway.”

15.1 Regulation of Metabolic Pathways

- Cells and organisms maintain a dynamic steady state.
    - For each metabolic reaction in a pathway, the substrate is provided by the preceding reaction at the same rate at which it is converted to product.
- Both the amount and the catalytic activity of an enzyme can be regulated.
    - Such changes occur on time scales from milliseconds to many hours, in response to signals from within or outside the cell.
    - Various signals activate or inactivate transcription factors, which act in the nucleus to regulate gene expression.

15.3 Coordinated Regulation of Glycolysis and Gluconeogenesis

- Glycolysis and gluconeogenesis are different at the three points **(Fig. 15–13)**.
- Three reactions of glycolysis are irreversible: those catalyzed by hexokinase, phosphofructokinase-1 and pyruvate kinase which play a regulatory role.

Hexokinase Isozymes of Muscle and Liver Are Affected Differently by Their Product, Glucose 6-Phosphate

- Hexokinase is a regulatory enzyme.
- Hexokinase isozymes are allosterically inhibited by their product, glucose 6-phosphate, so whenever the cellular concentration of glucose 6-phosphate rises above its normal level, these isozymes are inhibited.

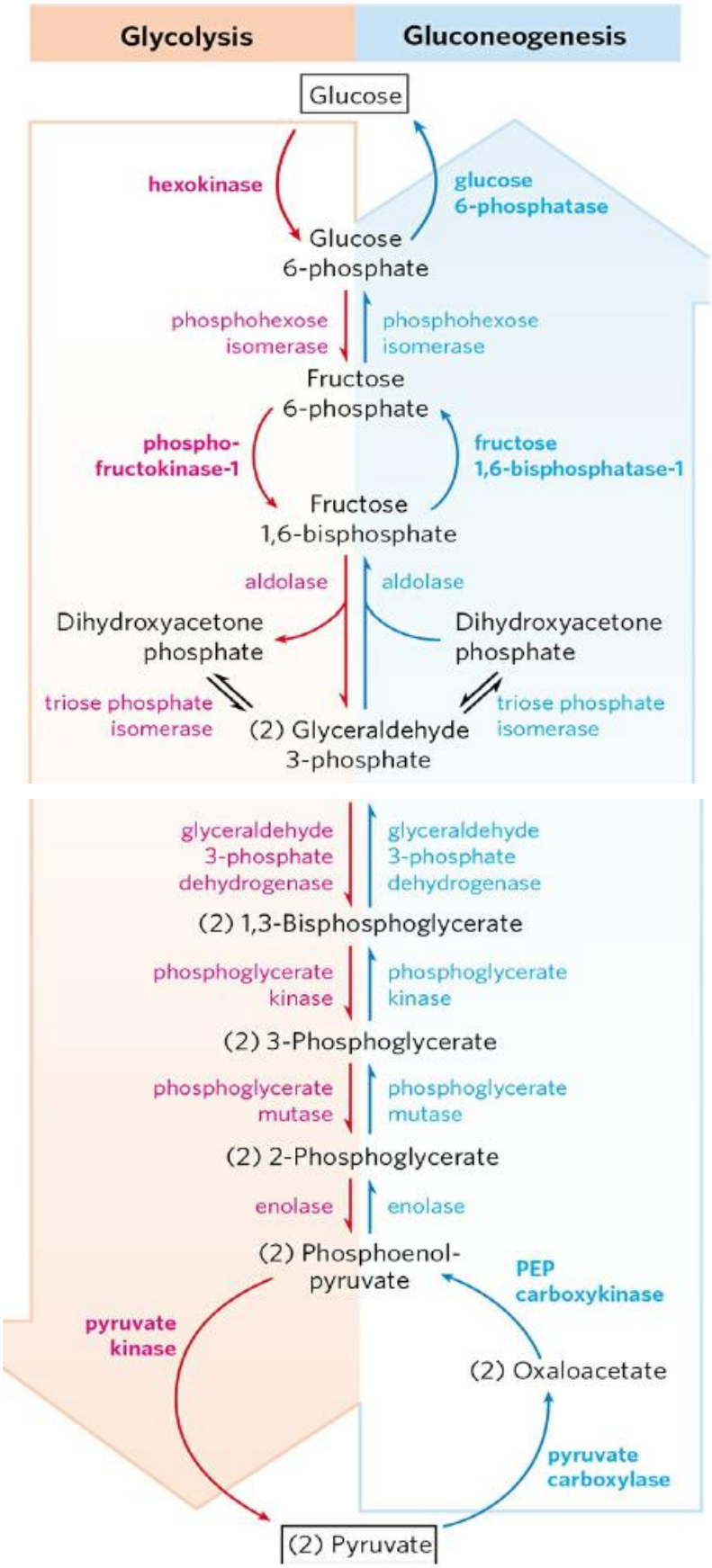


FIGURE 15-13 Glycolysis and gluconeogenesis.

Phosphofructokinase-1 and Fructose 1,6-bisphosphatase Are Reciprocally Regulated

- PFK-1 has several regulatory sites at which allosteric activators or inhibitors bind.
- FBPase-1 is allosterically inhibited by AMP.
- Thus these opposing steps in the glycolytic and gluconeogenic pathways are regulated in a coordinated and reciprocal manner **(Fig. 15–15)**.

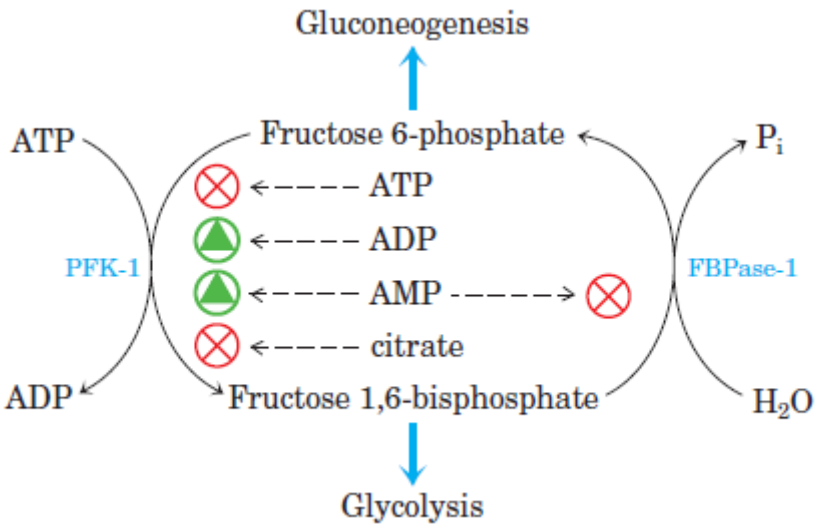
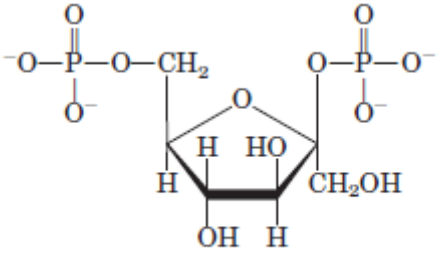


FIGURE 15–15 Regulation of fructose 1,6-bisphosphatase (FBPase-1) and phosphofructokinase-1 (PFK-1).

Fructose 2,6-Bisphosphate Is a Potent Allosteric Regulator of PFK-1 and FBPase-1

- The special role of liver in maintaining a constant blood glucose level requires additional regulatory mechanisms to coordinate glucose production and consumption.
- When the blood glucose level decreases, the hormone **glucagon** signals the liver to produce and release more glucose and to stop consuming it.
- When blood glucose is high, **insulin** signals the liver to use glucose.

- The rapid hormonal regulation of glycolysis and gluconeogenesis is mediated by **fructose 2,6-bisphosphate**.



Fructose 2,6-bisphosphate

- It is an allosteric effector for the enzymes PFK-1 and FBPase-1 **(Fig. 15–18c)**.
- Fructose 2,6-bisphosphate has the opposite effect on PFK-1 and FBPase-1.

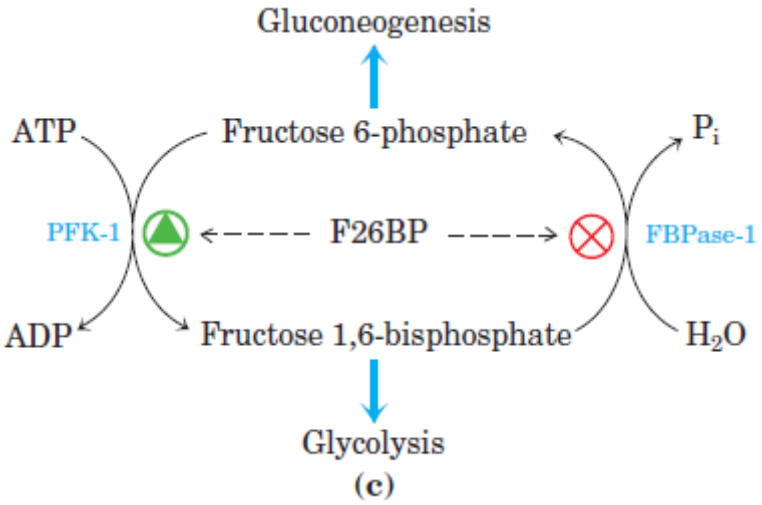


FIGURE 15-18 Role of fructose 2,6-bisphosphate in regulation of glycolysis and gluconeogenesis.

- It is formed by phosphorylation of fructose 6-phosphate, catalyzed by phosphofructokinase- 2 (PFK-2), and is broken down by fructose 2,6-bisphosphatase (FBPase-2) **(Fig. 15–19a)**.
- PFK-2 and FBPase-2 are two separate enzymatic activities of a single, bifunctional protein.

- The balance of these two activities in the liver is regulated by glucagon and insulin **(Fig. 15–19b)**.

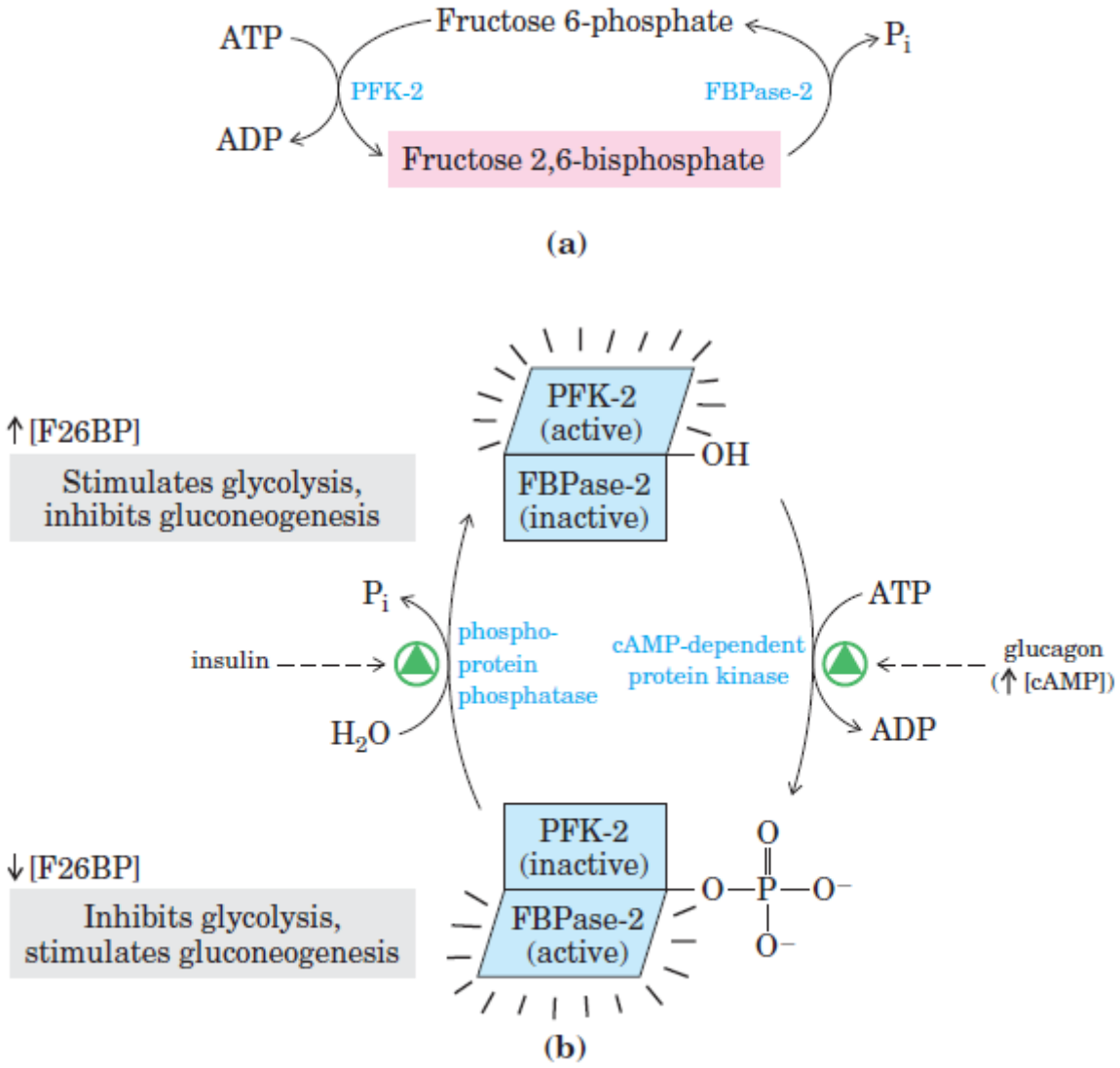


FIGURE 15-19 Regulation of fructose 2,6-bisphosphate level.

The Glycolytic Enzyme Pyruvate Kinase Is Allosterically Regulated

- ATP, acetyl-CoA, long-chain fatty acids and alanine allosterically inhibit and fructose 1,6- bisphosphate activities all isozymes of pyruvate kinase **(Fig. 15–21)**.

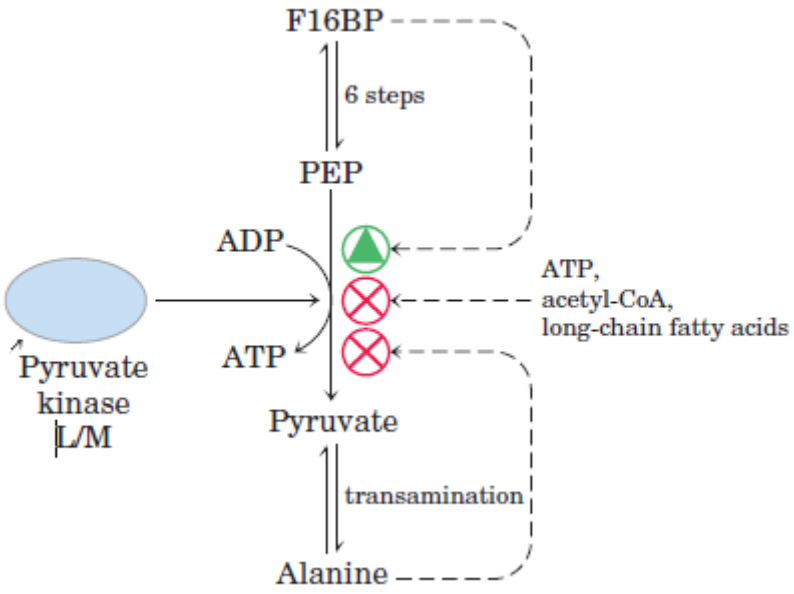


FIGURE 15-21 Regulation of pyruvate kinase.

The Gluconeogenic Enzyme Pyruvate Carboxylase Is Allosterically Regulated

- Acetyl-CoA stimulates pyruvate carboxylase and inhibits pyruvate dehydrogenase **(Fig. 15–22)**.

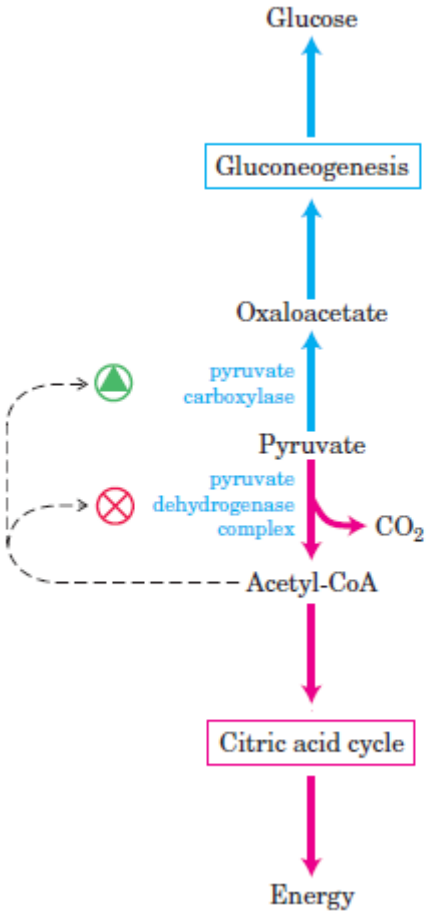


FIGURE 15-22 Two alternative fates for pyruvate.

15.4 The Metabolism of Glycogen in Animals

- Glycogen is found primarily in the liver and skeletal muscle
  - It may represent up to 10% of the weight of liver and 1% to 2% of the weight of muscle.
- The elementary particle of glycogen is about 21 nm in diameter and consists of up to 55,000 glucose residues with about 2,000 nonreducing ends.
- Liver glycogen can be depleted in 12 to 24 hours.
- Glycogen is also obtained in the diet and broken down in the gut, and this involves a separate set of hydrolytic enzymes that convert glycogen to free glucose.

- The breakdown of glycogen to glucose 1-phosphate is called **glycogenolysis**.
- The turn to synthesis of glycogen is called **glycogenesis**.

Glycogen Breakdown Is Catalyzed by Glycogen Phosphorylase

- Glycogen phosphorylase catalyzes glucose 1-phosphate from nonreducing end of glycogen having an (α1 → 4) glycosidic linkage **(Fig. 15–27)**.

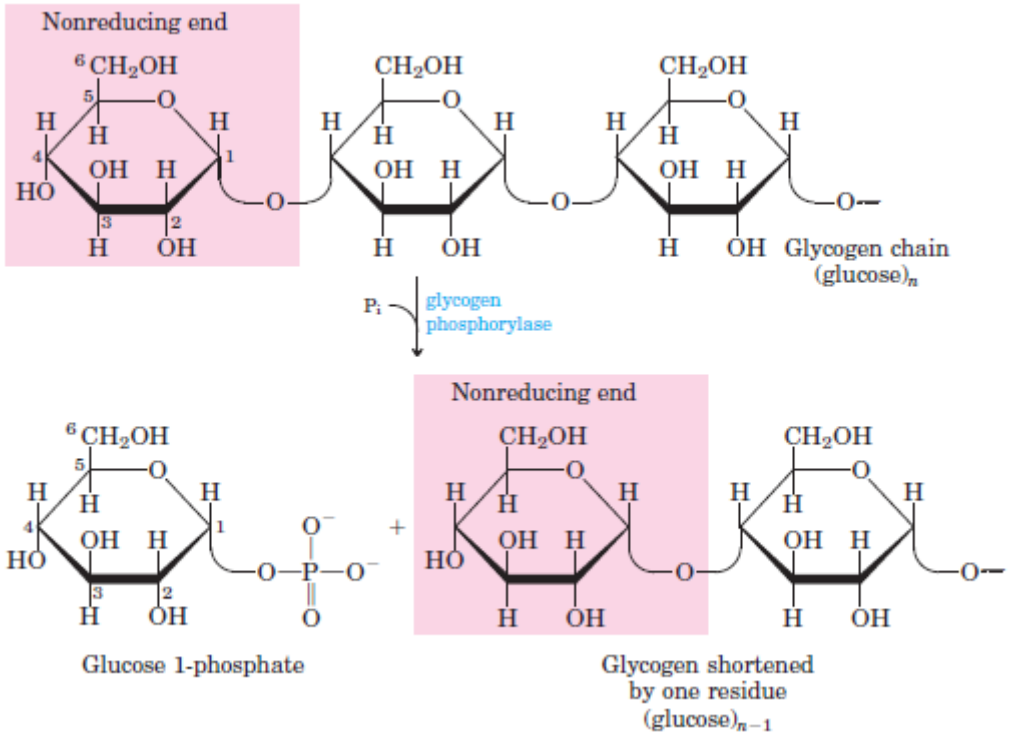


FIGURE 15-27 Removal of a glucose residue from the nonreducing end of a glycogen chain by glycogen phosphorylase.

- Glycogen phosphorylase acts repetitively on the nonreducing ends of glycogen branches until it reaches a point four glucose residues away from an (α1 → 6) branch point **(Fig. 15–28)**.

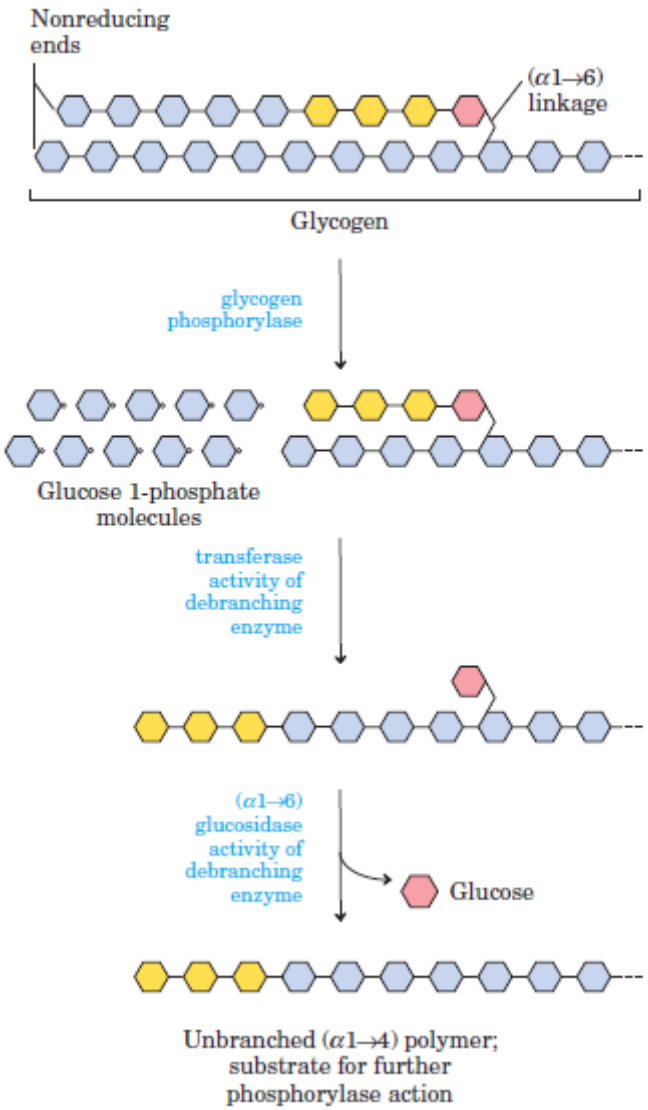


FIGURE 15-28 Glycogen breakdown near an (α1→6) branch point.

- Further degradation by glycogen phosphorylase can occur only after the **debranching enzyme**, formally known as **(α1 → 6) to (α1 → 4) glucan-transferase**, catalyzes two successive reactions that transfer branches.
    - First, the **transferase activity** of the enzyme shifts a block of three glucose residues from the branch to a nearby nonreducing end, to which they are reattached▾ in (α1→ 4) linkage.

- The single glucose residue remaining at the branch point, in ($\alpha 1 \rightarrow 6$) linkage, is then released as free glucose by the debranching enzyme's **($\alpha 1 \rightarrow 6$) glucosidase activity**.

Glucose 1-Phosphate Can Enter Glycolysis or, in Liver, Replenish Blood Glucose

- Glucose 1-phosphate is converted to glucose 6-phosphate by **phosphoglucomutase**.

$$\text{Glucose 1-phosphate} \rightleftharpoons \text{glucose 6-phosphate}$$

- **Glucose 6-phosphatase** present in liver and kidney but not in other tissues. The enzyme is an integral membrane protein of the endoplasmic reticulum.
- Glucose 6- phosphate formed in the cytosol is transported into the ER lumen and hydrolyzed at the lumenal surface by the glucose 6- phosphatase. Glucose is carried back into the cytosol.

The Sugar Nucleotide UDP-Glucose Donates Glucose for Glycogen Synthesis

- The starting point for synthesis of glycogen is glucose 6-phosphate.
- To initiate glycogen synthesis, the glucose 6-phosphate is converted to glucose 1-phosphate by **phosphoglucomutase**.

$$\text{Glucose 6-phosphate} \rightleftharpoons \text{glucose 1-phosphate}$$

- The glucose 1-phosphate is converted to UDP-glucose by **UDP-glucose pyrophosphorylase**.

$$\text{Glucose 1-phosphate} + \text{UTP} \longrightarrow \text{UDP-glucose} + \text{PP}_i$$

- The transfer of the glucose residue from UDP-glucose to a nonreducing end of a branched glycogen molecule is catalyzed by **glycogen synthase (Fig. 15–30)**.

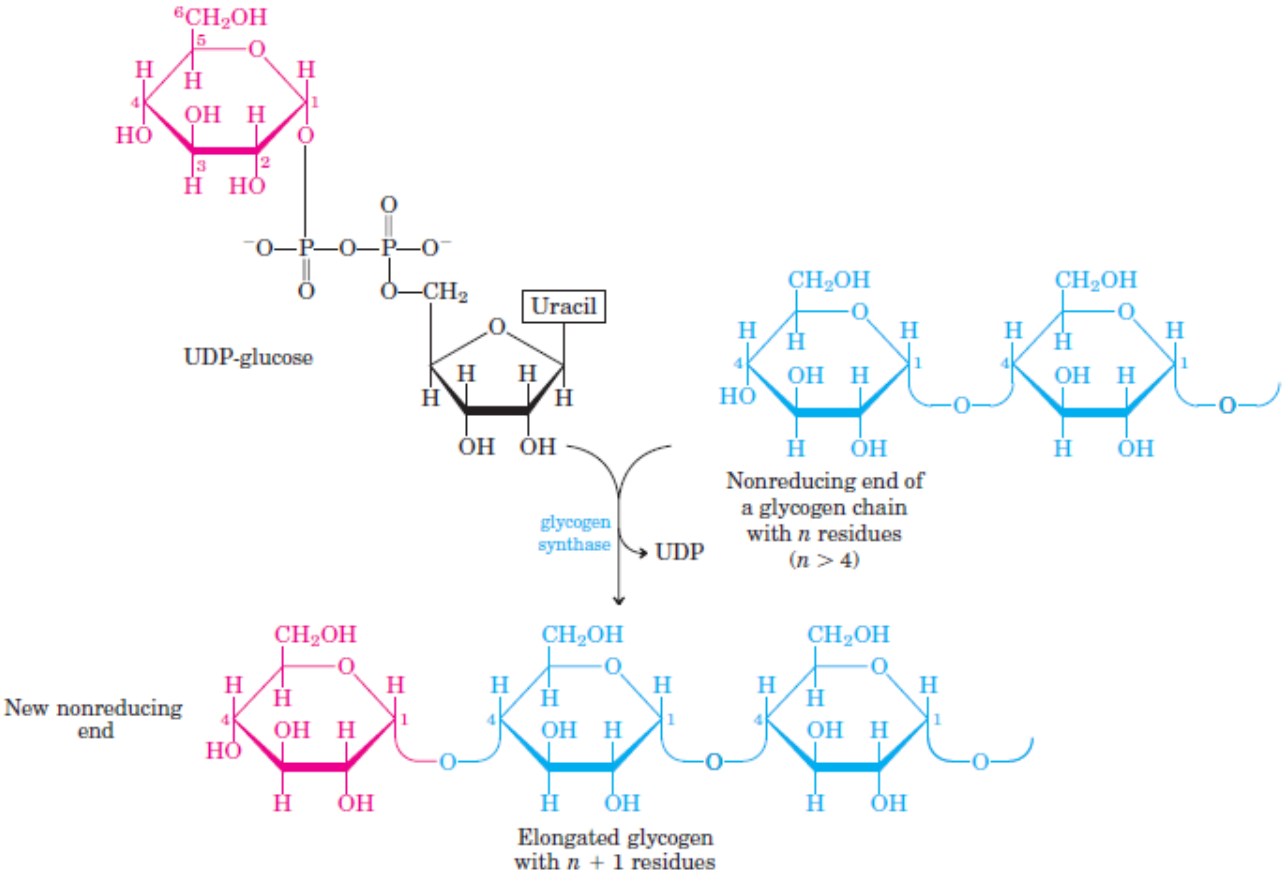


FIGURE 15–30 Glycogen synthesis.

- Glycogen synthase cannot make the (α1→ 6) bonds found at the branch points of glycogen: these are formed by the glycogen-branching enzyme, also called **amylo (1→ 4) to (1 →6) transglycosylase**, or **glycosyl-(4 →6) transferase**.
- The glycogen-branching enzyme catalyzes transfer of a terminal fragment of 6 or 7 glucose residues from the nonreducing end of a glycogen branch having at least 11 residues **(Fig. 15–31)**.

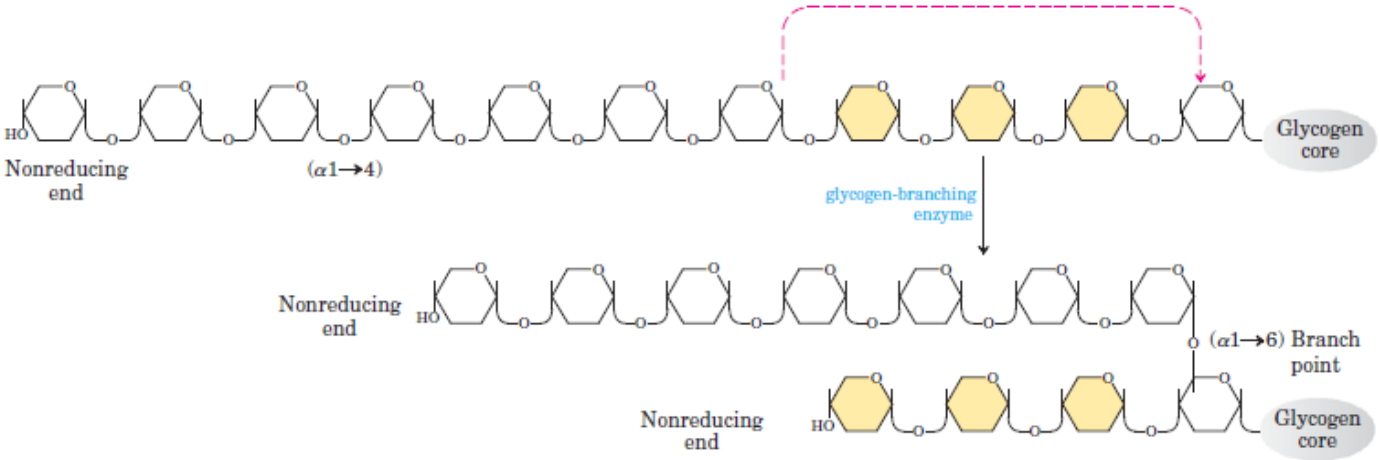


FIGURE 15–31 Branch synthesis in glycogen.

15.5 Coordinated Regulation of Glycogen Synthesis and Breakdown

- Glycogen phosphorylase is regulated allosterically and hormonally. The glycogen phosphorylase of skeletal muscle exists in two interconvertible forms: **glycogen phosphorylase *a***, which is catalytically active, and **glycogen phosphorylase *b***, which is less active **(Fig. 15–34)**.

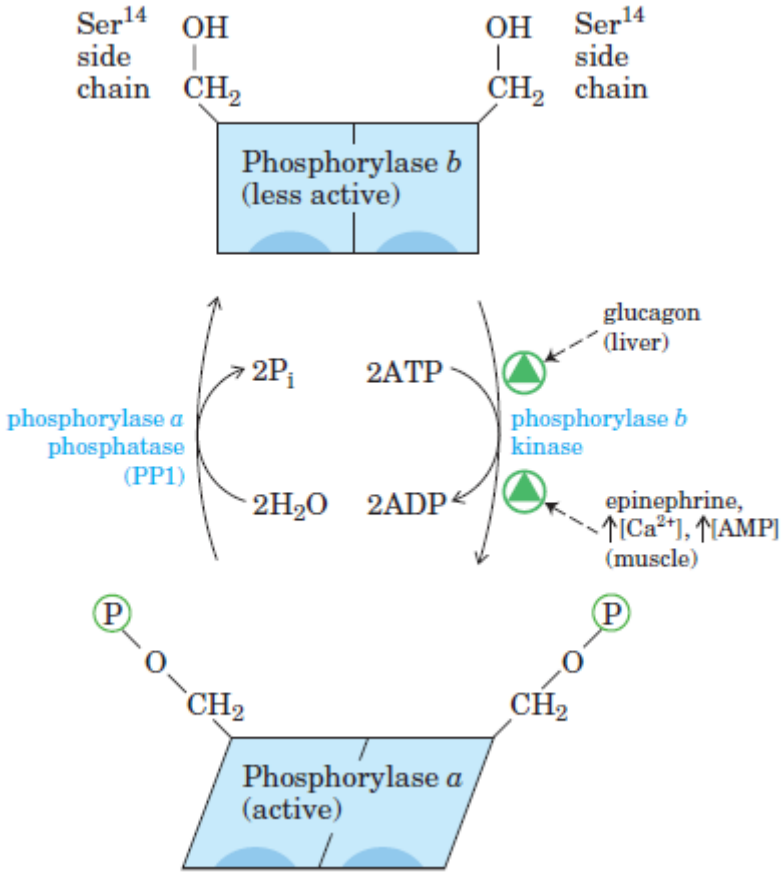


FIGURE 15–34 Regulation of muscle glycogen phosphorylase by covalent modification.

- Glycogen synthase is also regulated by phosphorylation and dephosphorylation. Its active form, **glycogen synthase a**, is unphosphorylated. Phosphorylation converts glycogen synthase a to **glycogen synthase b**, which is inactive **(Fig. 15–36)**.

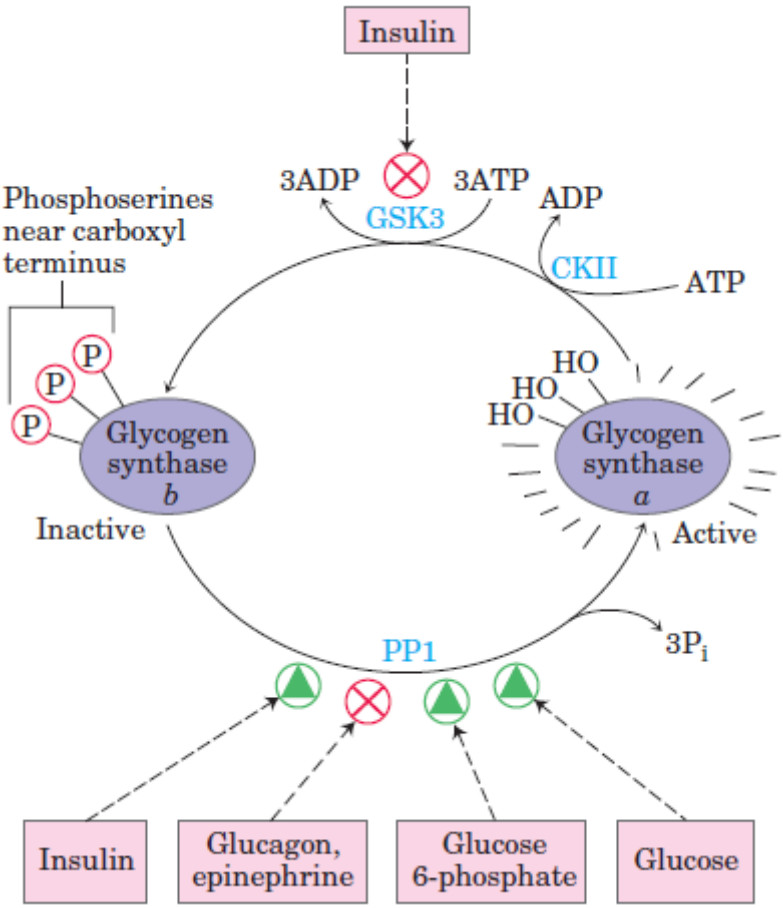


Figure 15-36. Regulation of glycogen synthase by covalent modification.