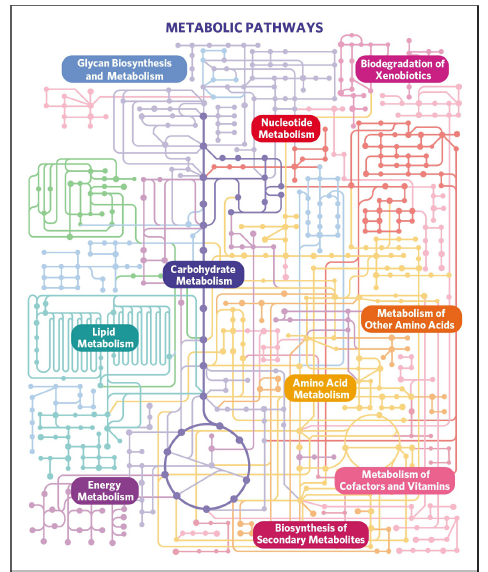
**Chapter 15 Principles of Metabolic Regulation**

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





* 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**

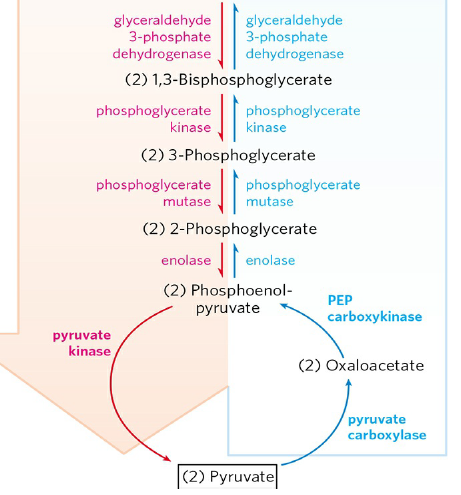
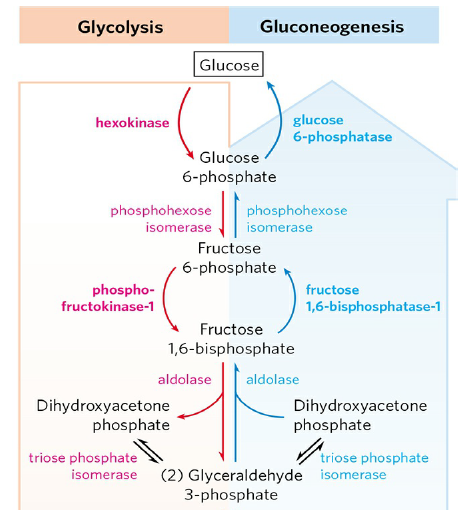
* Cells and organisms maintain a dynamic steady state.
* For each metabolic reaction in a pathway, the substrate is provided by the preceding reaction at the same rate at which it is converted to product.
* Both the amount and the catalytic activity of an enzyme can be regulated.
* Such changes occur 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**

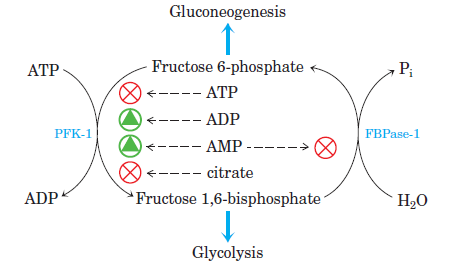
* Hexokinase is a regulatory enzyme.
* Hexokinase isozymes are allosterically inhibited by their product, glucose 6-phosphate, so whenever the cellular concentration of glucose 6-phosphate rises above its normal level, these isozymes are inhibited.





**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)**.



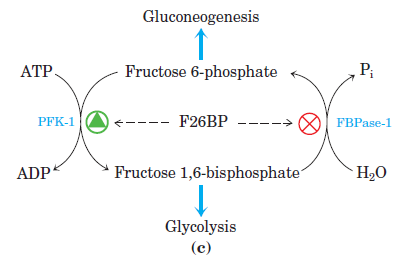


**Fructose 2,6-Bisphosphate Is a Potent Allosteric Regulator of PFK-1 and FBPase-1**

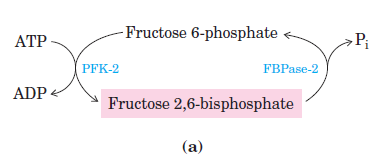
* The special role of liver in maintaining a constant blood glucose level requires additional regulatory mechanisms to coordinate glucose production and consumption.
* When the blood glucose level decreases, the hormone **glucagon** signals the liver to produce and release more glucose and to stop consuming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

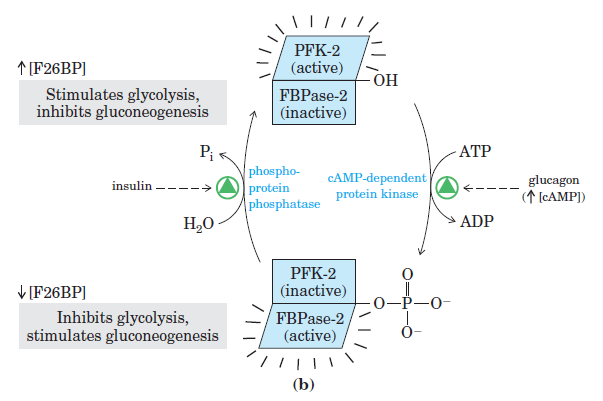


* It is an allosteric effector for the enzymes PFK-1 and FBPase-1 **(Fig. 15–18c)**.
* Fructose 2,6-bisphosphate has the opposite effect on PFK-1 and FBPase-1.

* 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)**.

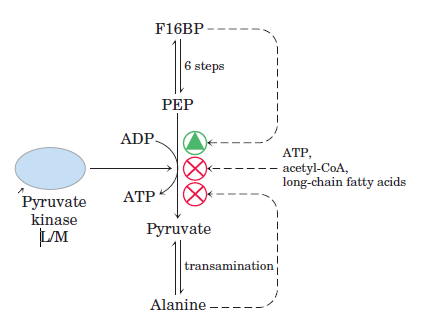






**The Glycolytic Enzyme Pyruvate Kinase Is Allosterically Regulated**

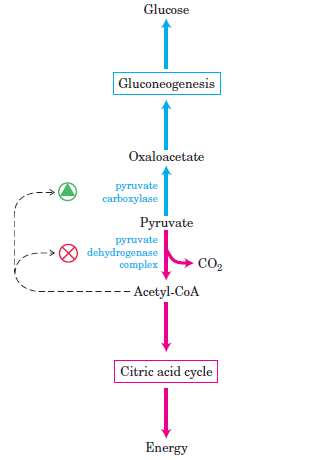
* ATP, acetyl-CoA, long-chain fatty acids and alanine allosterically inhibit and fructose 1,6- bisphosphate activities all isozymes of pyruvate kinase **(Fig. 15–21)**.





**The Gluconeogenic Enzyme Pyruvate Carboxylase Is Allosterically Regulated**

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



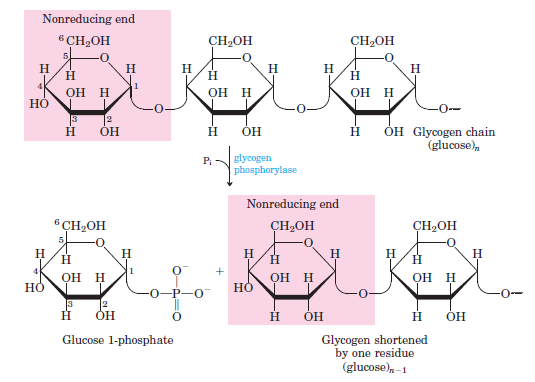


**15.4 The Metabolism of Glycogen in Animals**

* 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**.

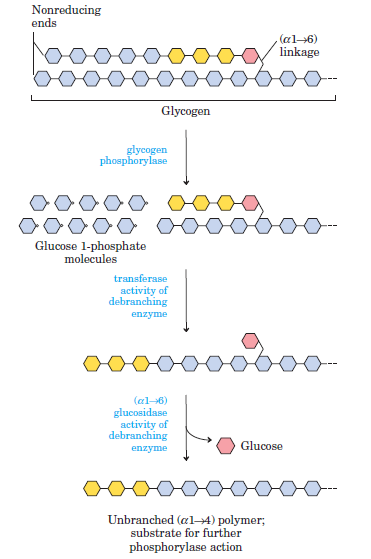
**Glycogen Breakdown Is Catalyzed by Glycogen Phosphorylase**

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





* Glycogen phosphorylase acts repetitively on the nonreducing ends of glycogen branches until it reaches a point four glucose residues away from an (1 6) branch point **(Fig. 15–28)**.





* Further degradation by glycogen phosphorylase can occur only after the **debranching enzyme**, formally known as **(1** **6) to (1** **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 (1 4) linkage.
* The single glucose residue remaining at the branch point, in (1 6) linkage, is then released as free glucose by the debranching enzyme’s **(1**   **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**.



* **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**

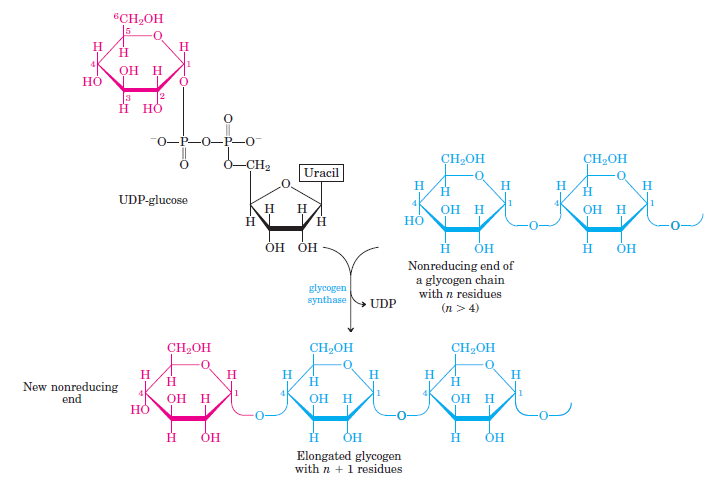
* The starting point for synthesis of glycogen is glucose 6-phosphate.
* To initiate glycogen synthesis, the glucose 6-phosphate is converted to glucose 1-phosphate by **phosphoglucomutase**.



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

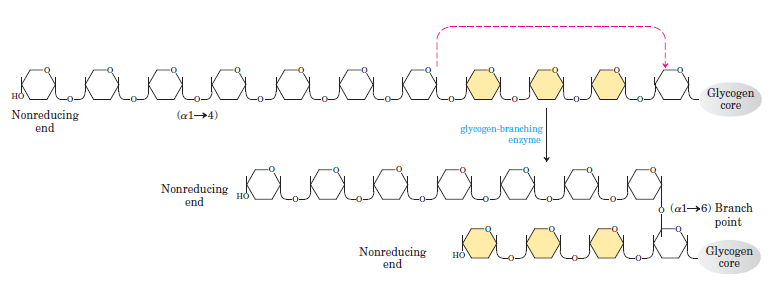


* The transfer of the glucose residue from UDP-glucose to a nonreducing end of a branched glycogen molecule is catalyzed by **glycogen synthase** **(Fig. 15–30)**.





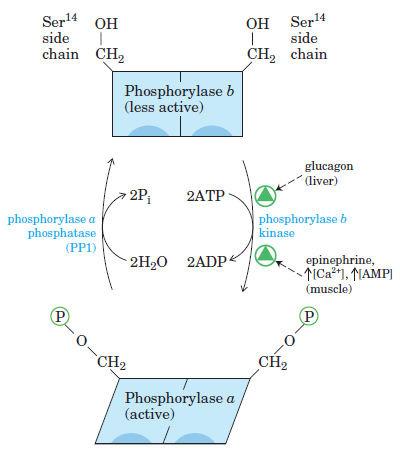
* Glycogen synthase cannot make the (1 6) bonds found at the branch points of glycogen: these are formed by the glycogen-branching enzyme, also called **amylo (1 4) to (1 6) transglycosylase**, or **glycosyl-(4 6) transferase**.
* The glycogen-branching enzyme catalyzes transfer of a terminal fragment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





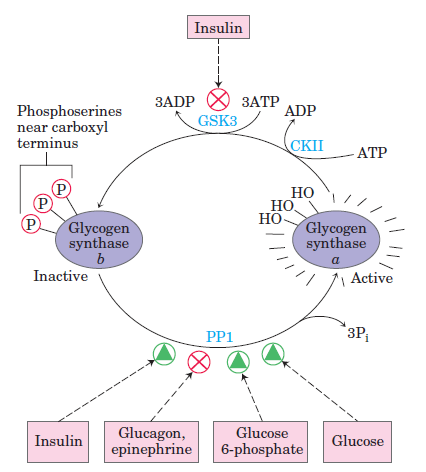
**15.5 Coordinated Regulation of Glycogen Synthesis and Breakdown**

* 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)**.





* 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**.