CHAPTER 15
Principles of Metabolic Regulation

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15.4 The Metabolism of Gylcogen in Animals

p612

单选题 1分

设置

What is glycogen?

A a unbranched polysaccharide of glucose in animal cells

B a multibranched polysaccharide of glucose in animal cells

C a multibranched polysaccharide of glucose in plant cells

D a disaccharide of glucose in animal cells

提交

• Glycogen

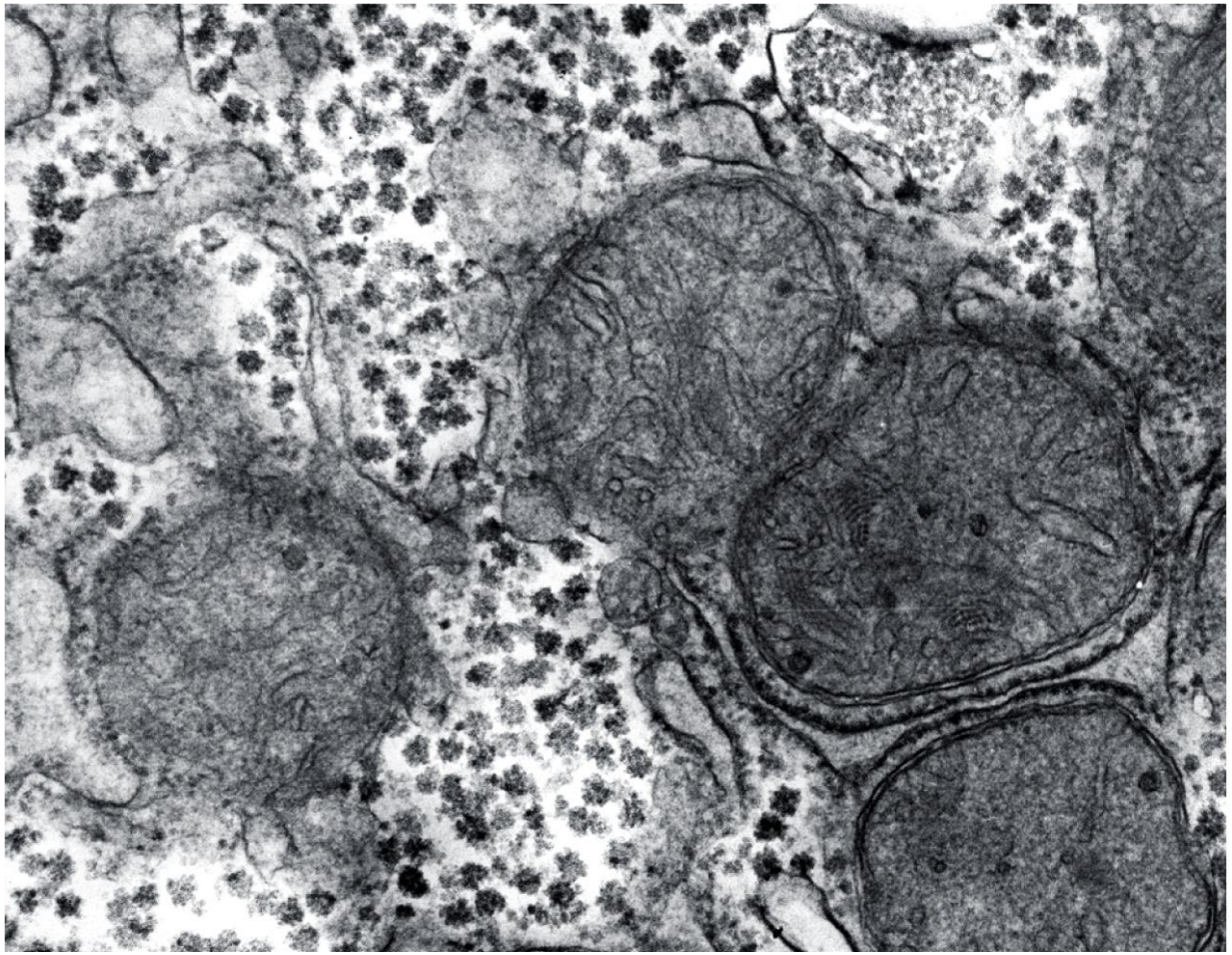
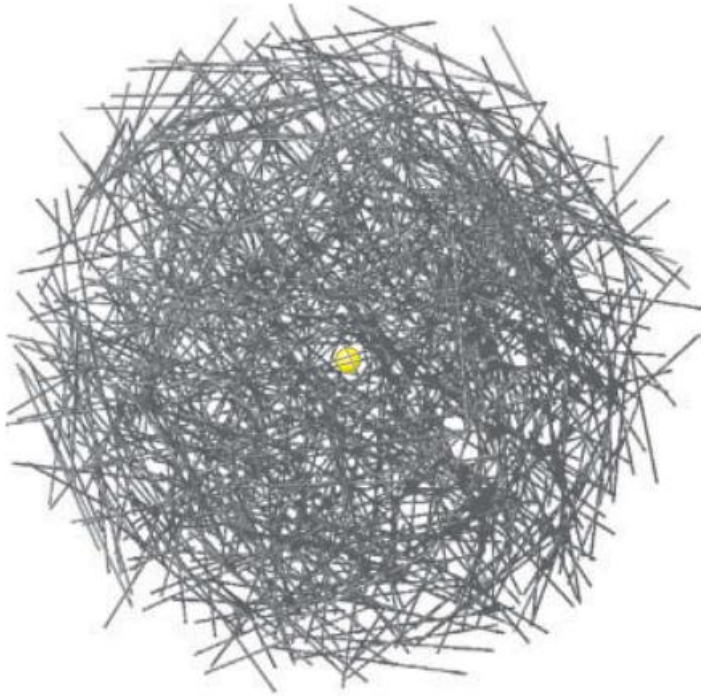
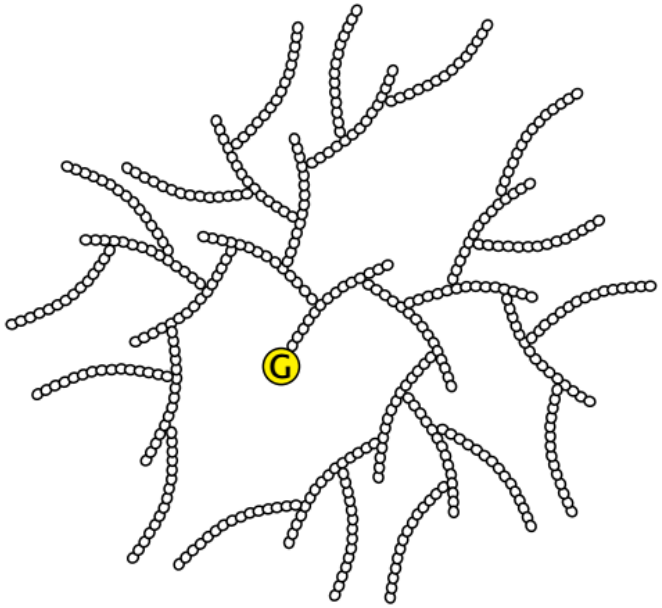


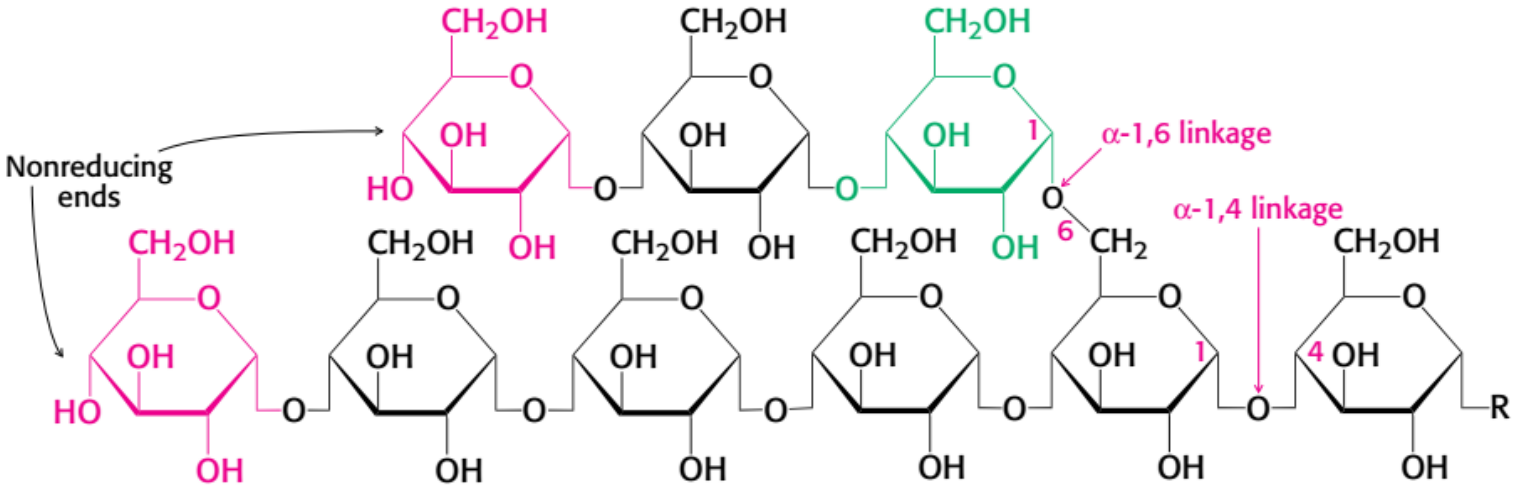
Figure 15-26

The elementary particle of glycogen, the β-particle, is about 21 nm in diameter and consists of up to 55,000 glucose residues with about 2,000 nonreducing ends. Twenty to 40 of these particles cluster together to form α-rosettes.

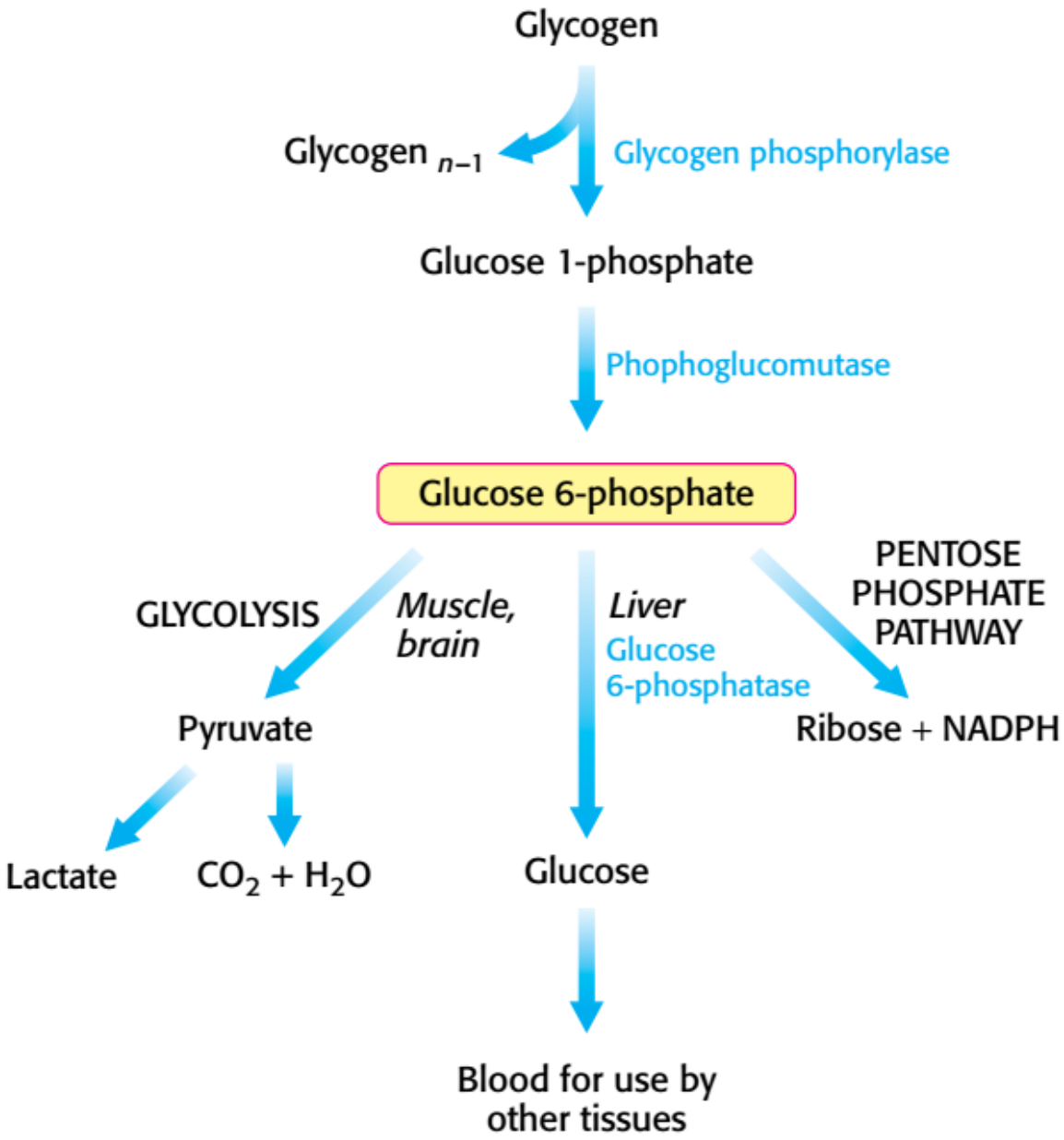
• Glycogen







• Breakdown of Glycogen (glycogenolysis)



• Glycogen Phosphorylase

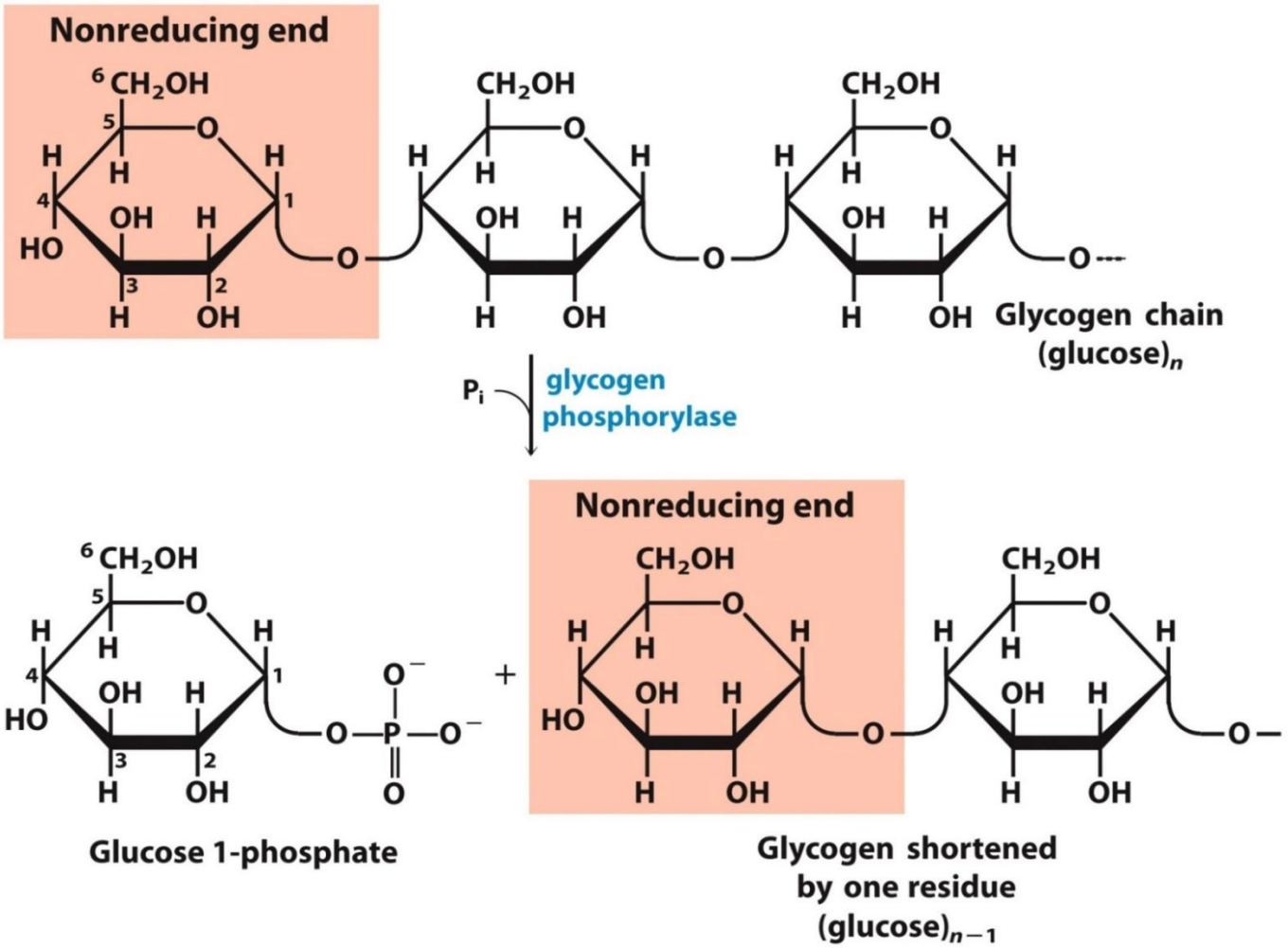
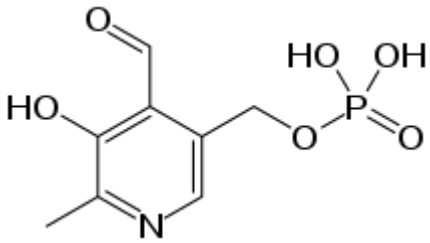


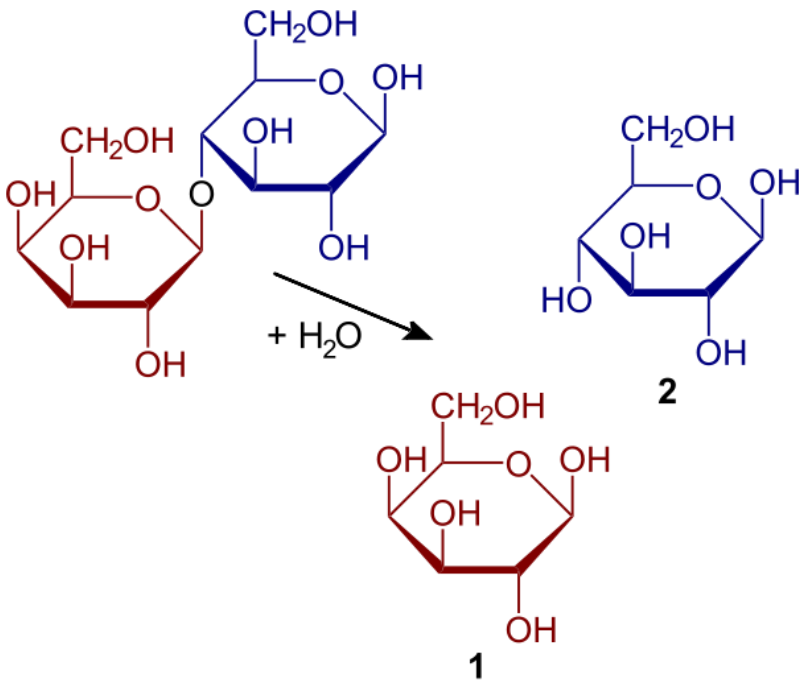
Figure 15-27

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

- **Co-factor:** Pyridoxal phosphate (PLP)



- **Phosphorolysis** *v.s.* **Hydrolysis**



• Phosphorylase & Kinase & Phosphatase

- **Phosphorylase**（磷酸化酶）
  - an enzymes that catalyze the addition of a phosphate group from an inorganic phosphate to an acceptor.
- **Kinase**（激酶）
  - an enzyme that catalyzes the transfer of phosphate groups from high-energy, phosphate-donating molecules to specific substrates
- **Phosphatase**（磷酸酶）
  - an enzyme that uses water to cleave a phosphoric acid monoester into a phosphate ion and an alcohol.

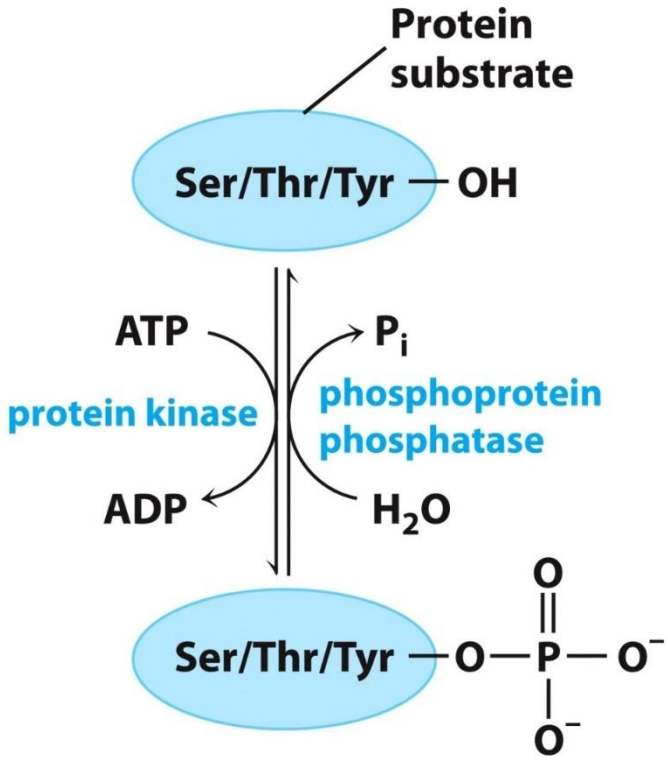


Figure 15-5

• Debranching enzyme

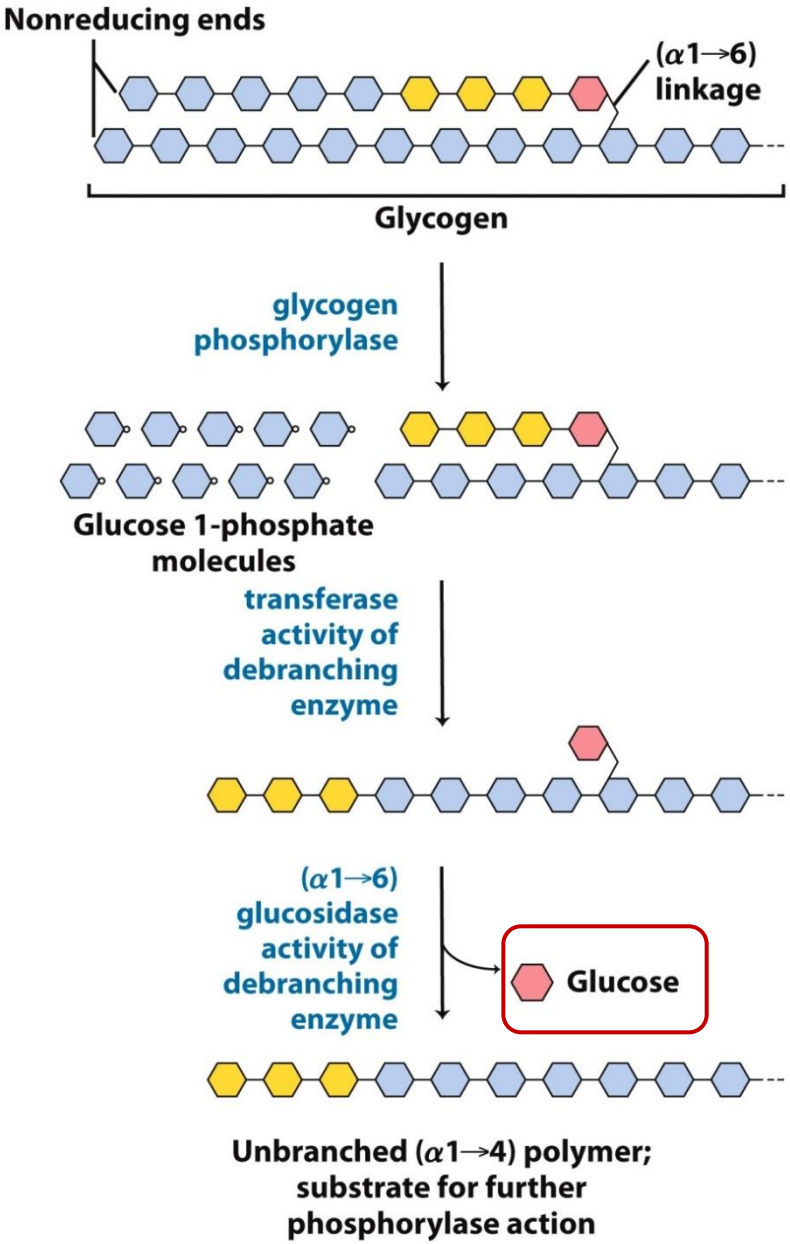


Figure 15-28

Glycogen breakdown near an (α1→6) branch point is catalyzed by a bifunctional **debranching enzyme**

oligo (α1→6) to (α1→ 4) glucantransferase

• phosphoglucomutase

Glucose-1-P $\rightleftharpoons$ Glucose-6-P (phosphoglucomutase)

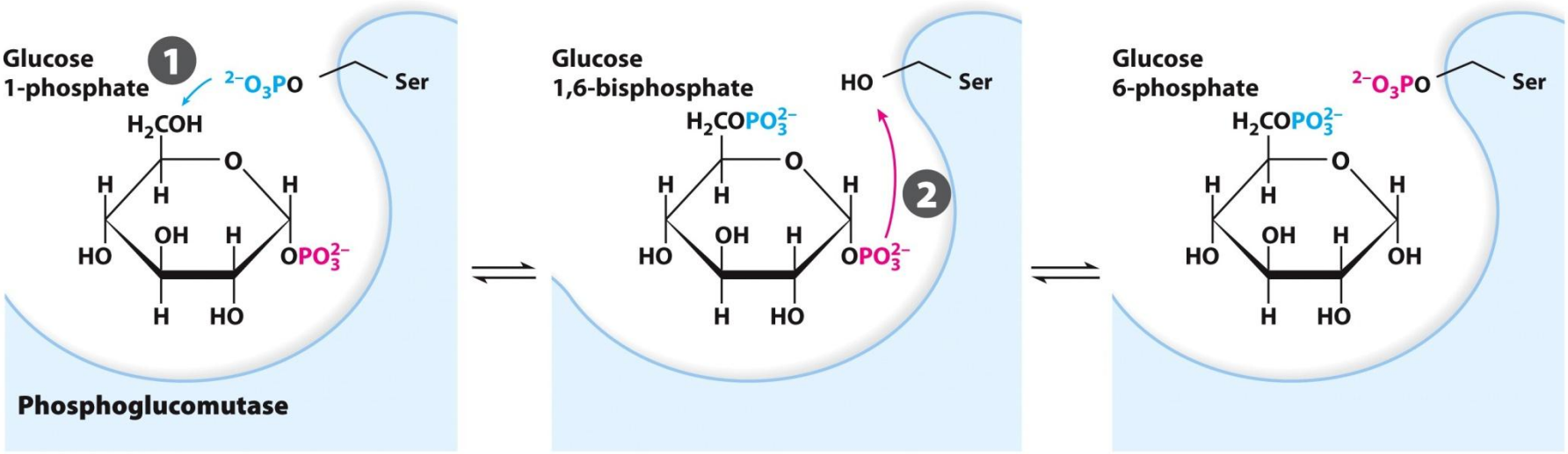
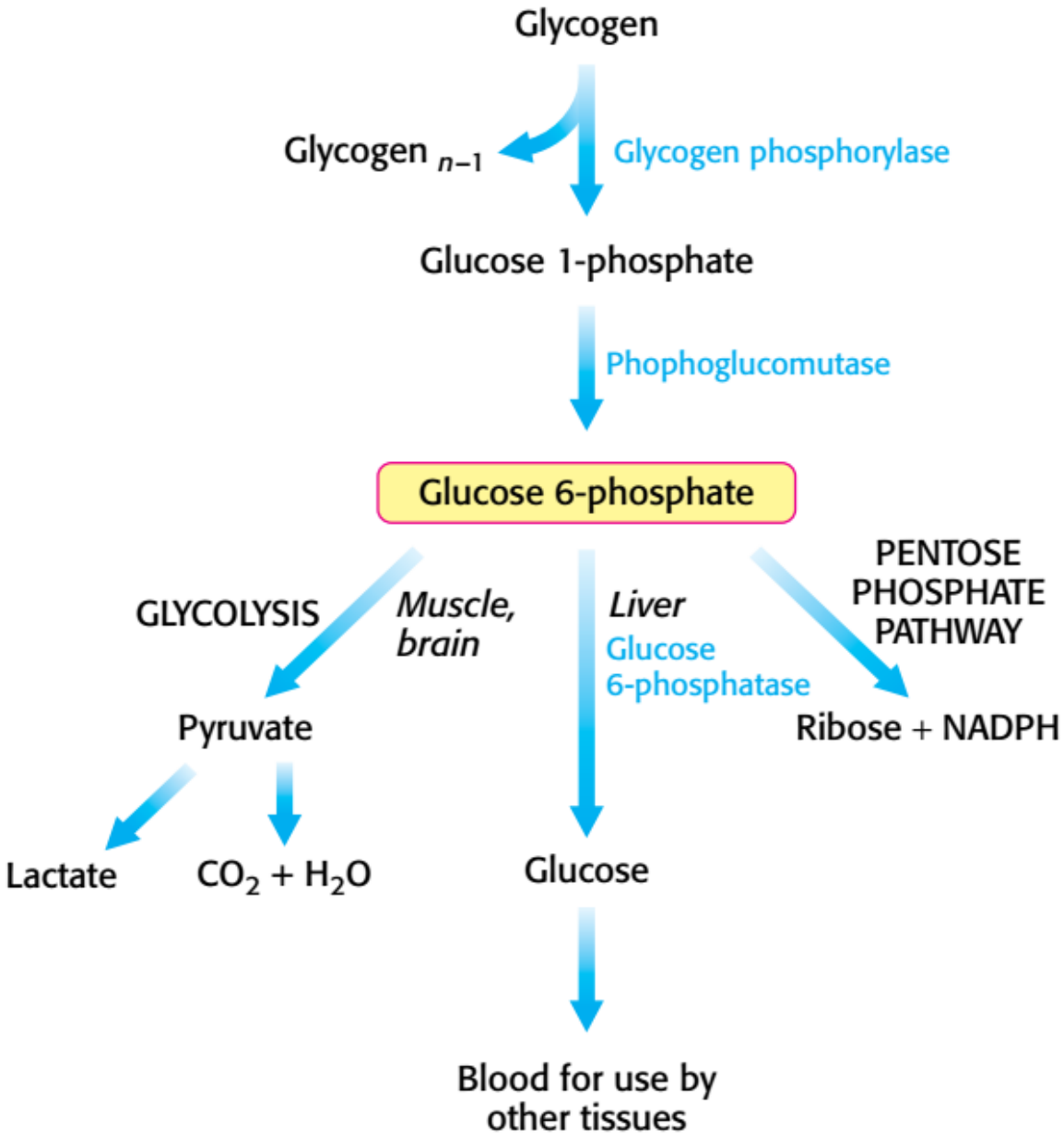


Figure 15-29
Lehninger Principles of Biochemistry, Sixth Edition

• Metabolism of Glucose 6-phosphate



• Glucose 6-phosphatase

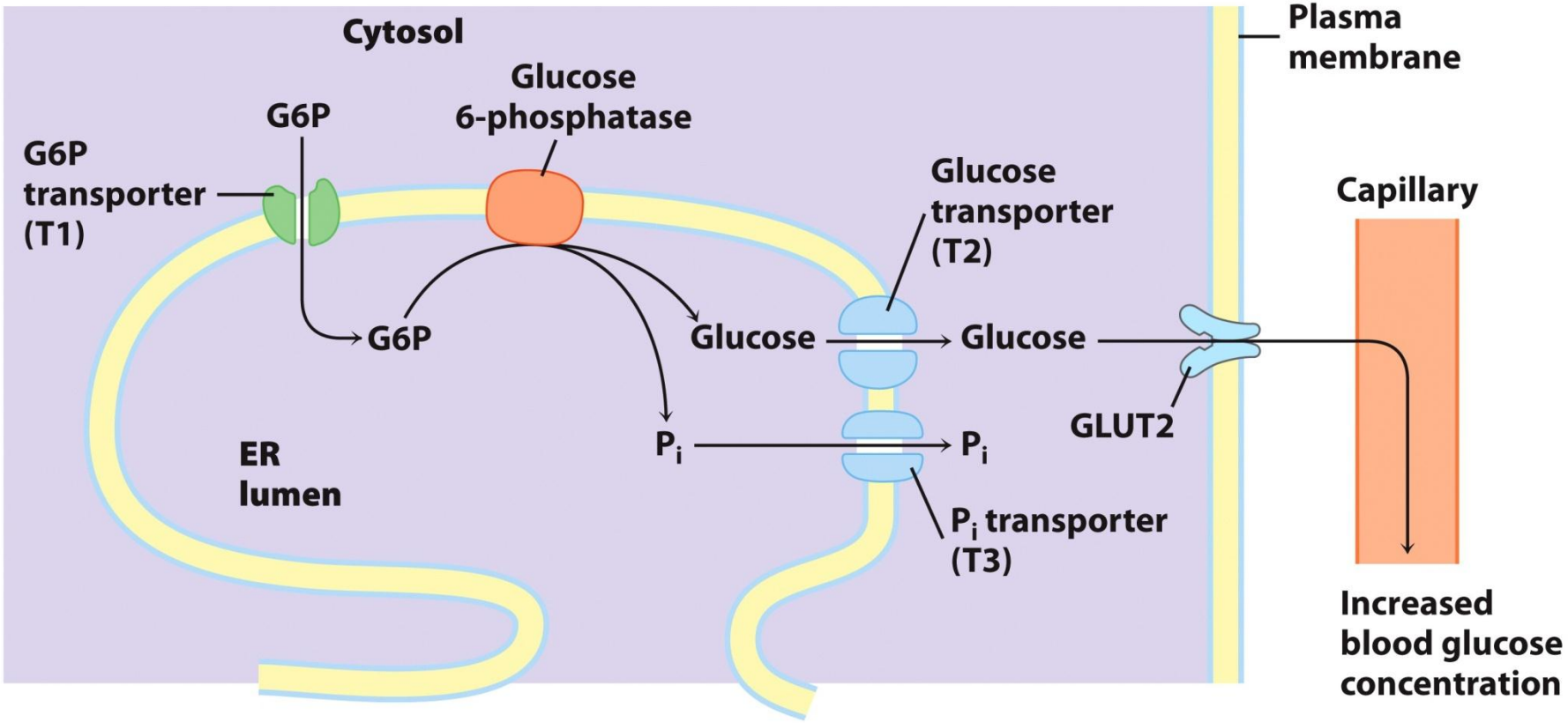


Figure 15-30
Lehninger Principles of Biochemistry, Sixth Edition

Hydrolysis of glucose 6-phosphate by **glucose 6-phosphatase** of the ER

G-6-phosphatase is present in liver and kidney, but is absent in other tissues including muscle and adipose tissue, which determines that liver can release glucose into the blood, on the contrary muscle cannot.

• Carl and Gerty Cori

The Coris in Gerty Cori's laboratory, around 1947.

Box 15-4

Lehninger Principles of Biochemistry, Sixth Edition

Gerty Cori, Carl Cori and Argentine physiologist Bernardo Houssay received the Nobel Prize in 1947 for the discovery of the mechanism by which glycogen—a derivative of glucose—is broken down in muscle tissue into lactic acid and then resynthesized in the body and stored as a source of energy (known as the Cori cycle).

TABLE 1 Glycogen Storage Diseases of Humans

Type (name)	Enzyme affected	Primary organ affected	Symptoms
Type 0	Glycogen synthase	Liver	Low blood glucose, high ketone bodies, early death
Type Ia (von Gierke)	Glucose 6-phosphatase	Liver	Enlarged liver, kidney failure
Type Ib	Microsomal glucose 6-phosphate translocase	Liver	As in type Ia; also high susceptibility to bacterial infections
Type Ic	Microsomal P_i transporter	Liver	As in type Ia
Type II (Pompe)	Lysosomal glucosidase	Skeletal and cardiac muscle	Infantile form: death by age 2; juvenile form: muscle defects (myopathy); adult form: as in muscular dystrophy
Type IIIa (Cori or Forbes)	Debranching enzyme	Liver, skeletal and cardiac muscle	Enlarged liver in infants; myopathy
Type IIIb	Liver debranching enzyme (muscle enzyme normal)	Liver	Enlarged liver in infants
Type IV (Andersen)	Branching enzyme	Liver, skeletal muscle	Enlarged liver and spleen, myoglobin in urine
Type V (McArdle)	Muscle phosphorylase	Skeletal muscle	Exercise-induced cramps and pain; myoglobin in urine
Type VI (Hers)	Liver phosphorylase	Liver	Enlarged liver
Type VII (Tarui)	Muscle PFK-1	Muscle, erythrocytes	As in type V; also hemolytic anemia
Type VIb, VIII, or IX	Phosphorylase kinase	Liver, leukocytes, muscle	Enlarged liver
Type XI (Fanconi-Bickel)	Glucose transporter (GLUT2)	Liver	Failure to thrive, enlarged liver, rickets, kidney dysfunction

Box 15-4 table 1

Lehninger Principles of Biochemistry, Sixth Edition

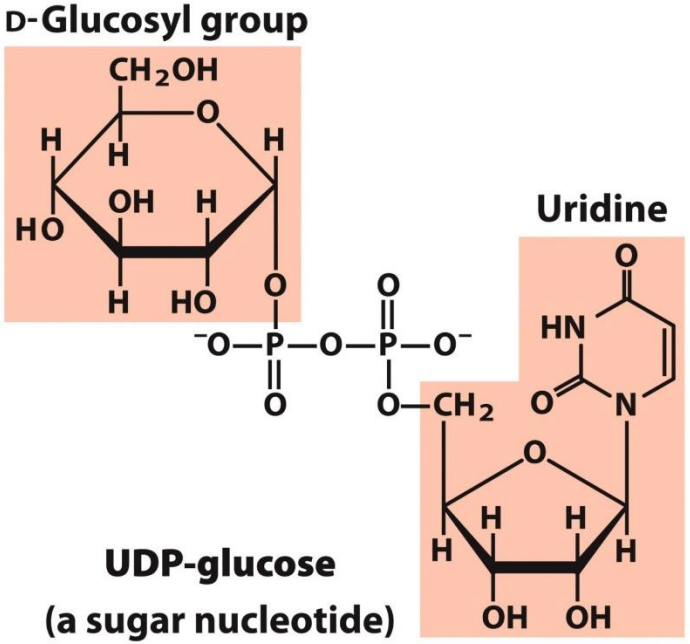
• Glycogen Synthesis (glycogenesis)

- Glycogen is synthesized and degraded by different pathways

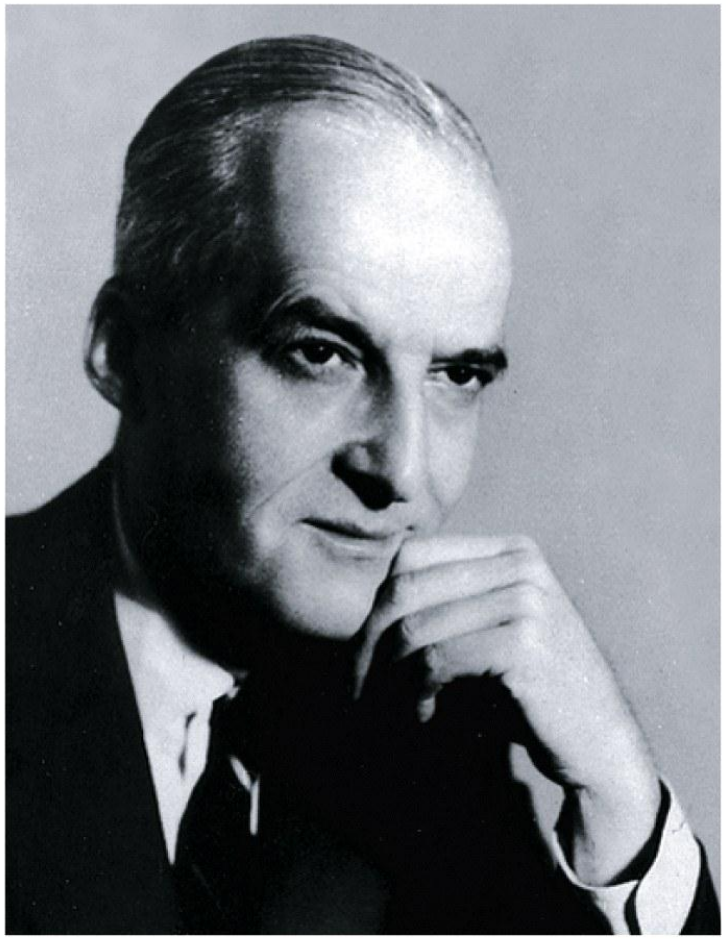
Degradation: $\text{Glycogen}_{n+1} + P_i \longrightarrow \text{glycogen}_n + \text{glucose 1-phosphate}$

Synthesis: $\text{Glycogen}_n + \text{UDP-glucose} \longrightarrow \text{glycogen}_{n+1} + \text{UDP}$

- The sugar nucleotide UDP-glucose donates glucose for glycogen synthesis.



- **Luis Leloir**



Luis Leloir, 1906–1987

The Nobel Prize in Chemistry 1970 was awarded to Luis Leloir "*for his discovery of* ***sugar nucleotides*** *and their role in the* ***biosynthesis of carbohydrates***".

• Synthesis of UDP-glucose

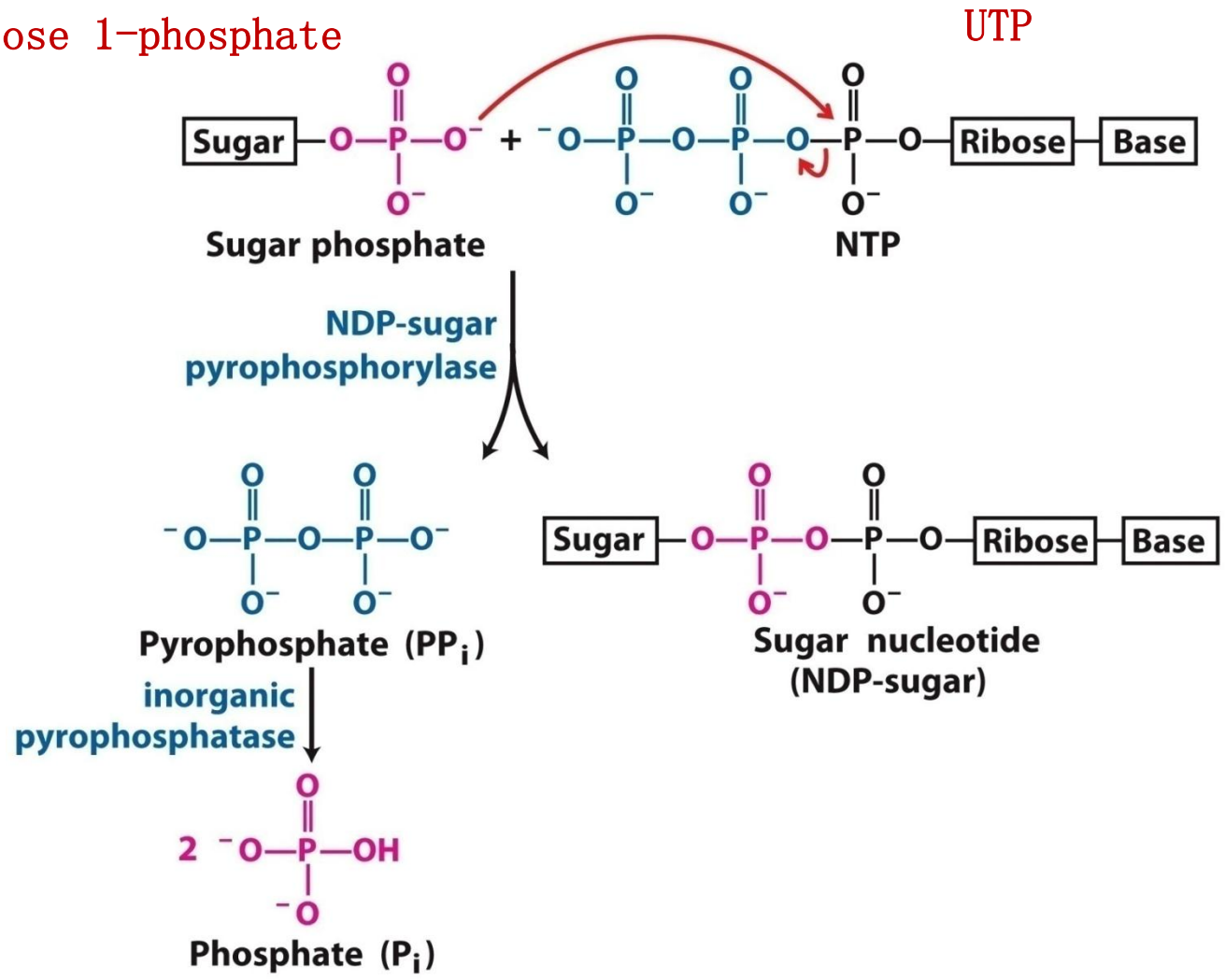


Figure 15-31

• Synthesis of UDP-glucose

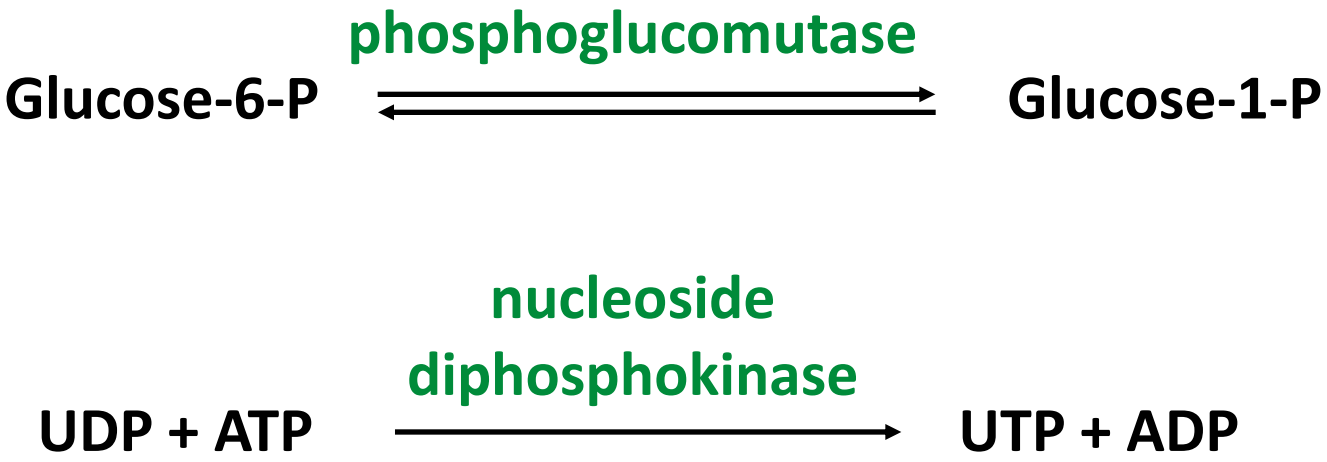
- UDP-glucose pyrophosphorylase

$$\begin{array}{r} \text{Glucose 1-phosphate} + \text{UTP} \rightleftharpoons \text{UDP-glucose} + \text{PP}_i \\ \text{PP}_i + \text{H}_2\text{O} \longrightarrow 2\,\text{P}_i \\ \hline \text{Glucose 1-phosphate} + \text{UTP} + \text{H}_2\text{O} \longrightarrow \text{UDP-glucose} + 2\,\text{P}_i \end{array}$$

- The reaction is pulled in the forward direction by the hydrolysis of PPi.

- *Many biosynthetic reactions are driven by the hydrolysis of pyrophosphate.*

• Synthesis of UDP-glucose



- A glycogen chain is elongated by glycogen synthase

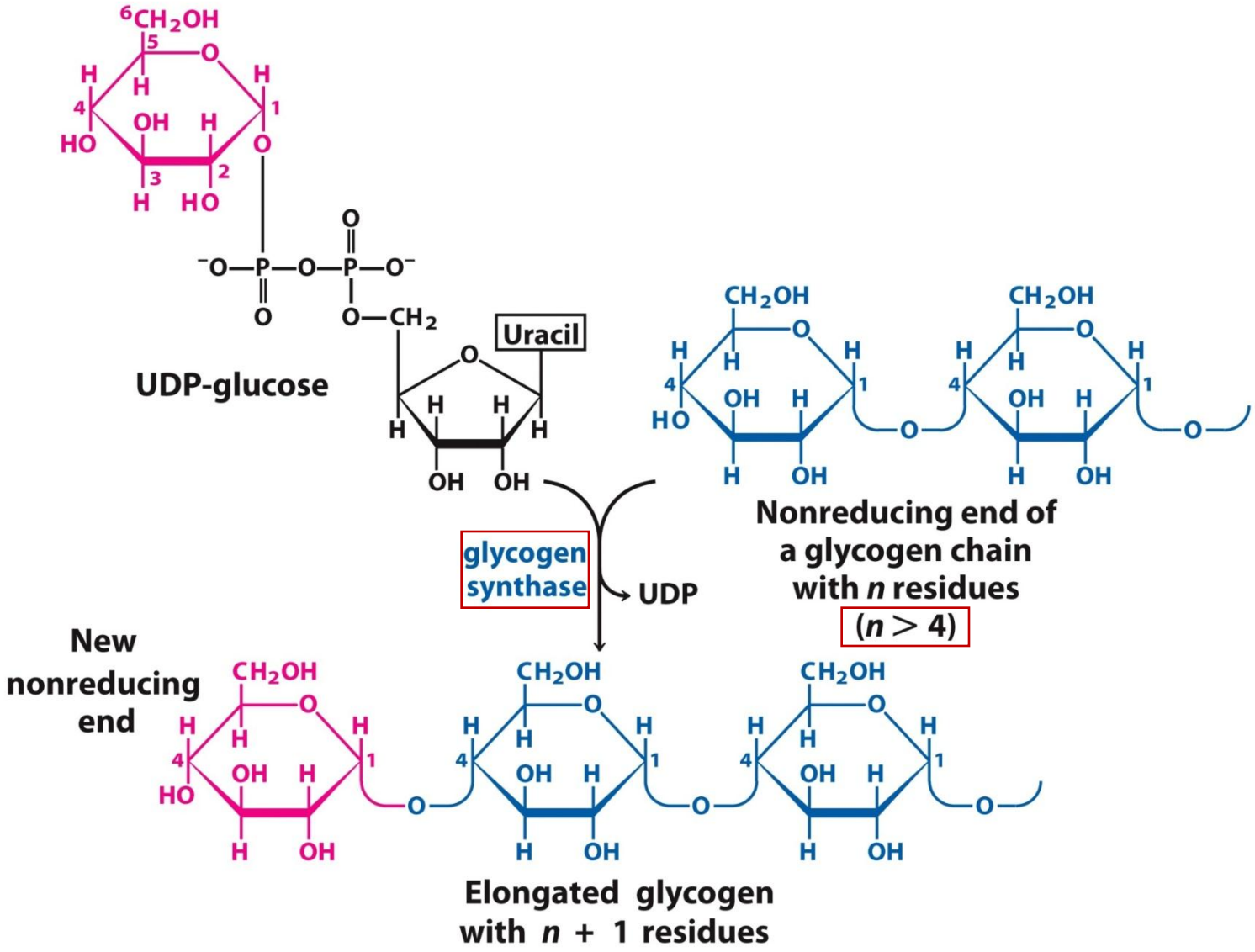


Figure 15-32

• Branch synthesis in glycogen

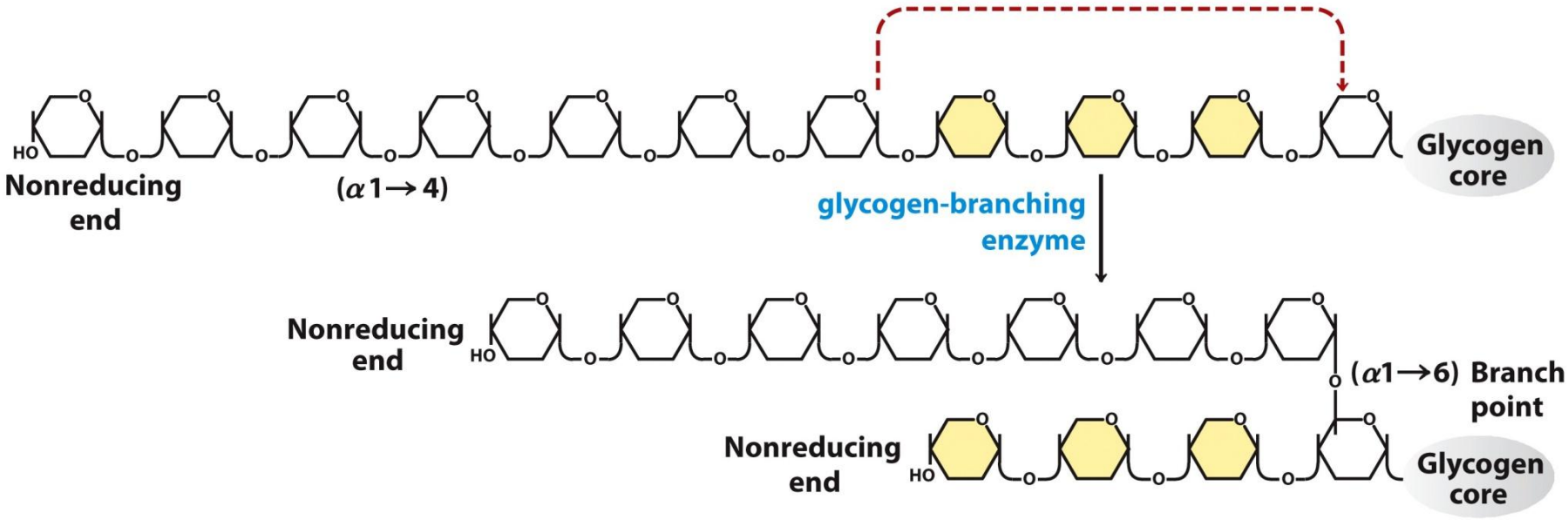


Figure 15-33

The **glycogen-branching enzyme** *(called glycosyl-(4→6)-transferase or amylo (1→4) to (1→6) transglycosylase) forms a new branch point during glycogen synthesis.*

Branching is important because it increases the solubility of glycogen.

• Glycogenin Primes the Initial Sugar Residues

- Glycogenin is both the primer on which new chains are assembled and the enzyme that catalyzes their assembly.

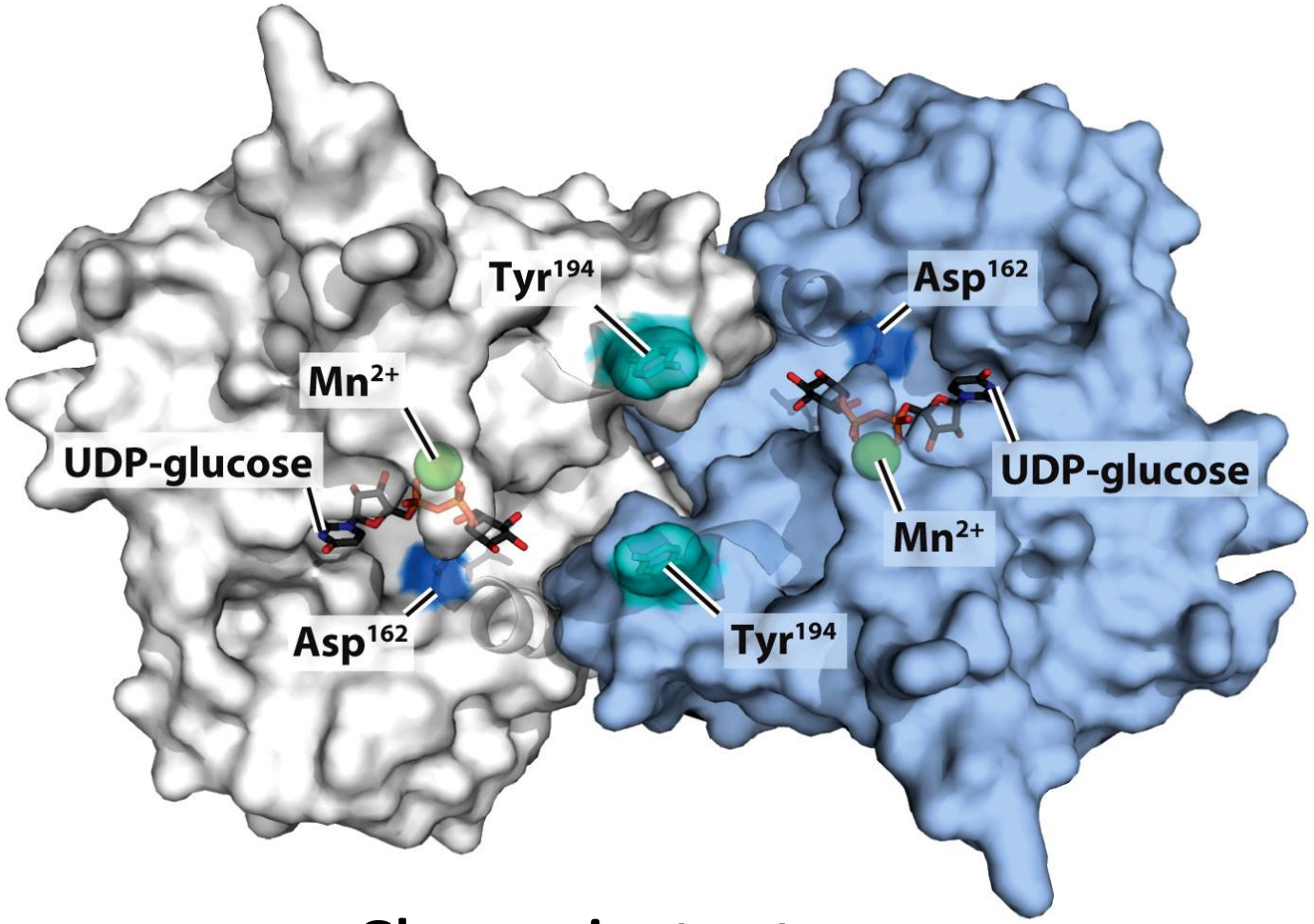
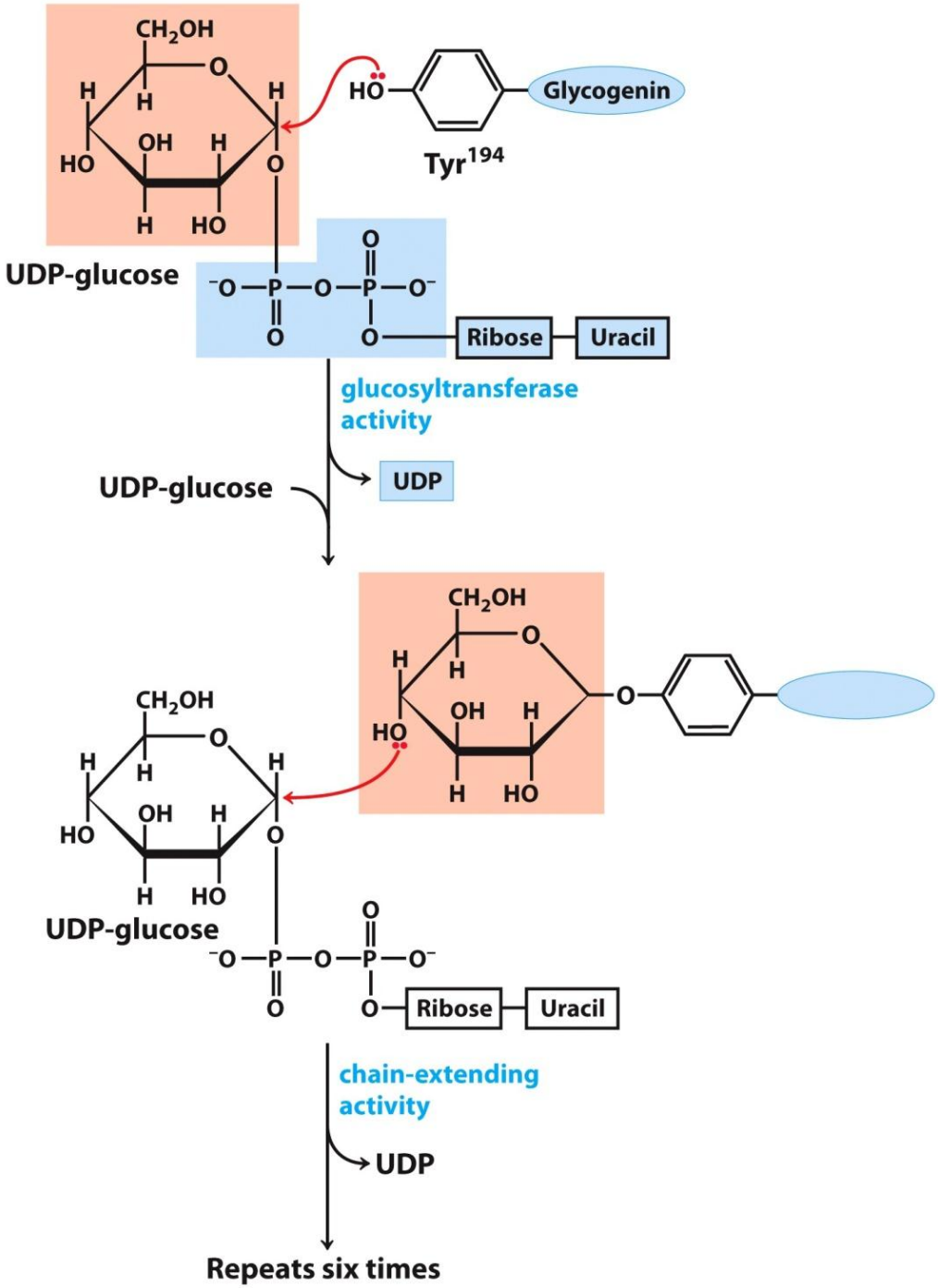


Figure 15-34

Glycogenin structure



Glycogenin catalyzes two distinct reactions

Glucosyltransferase activity

Chain-extending activity

• Structure of the glycogen particle

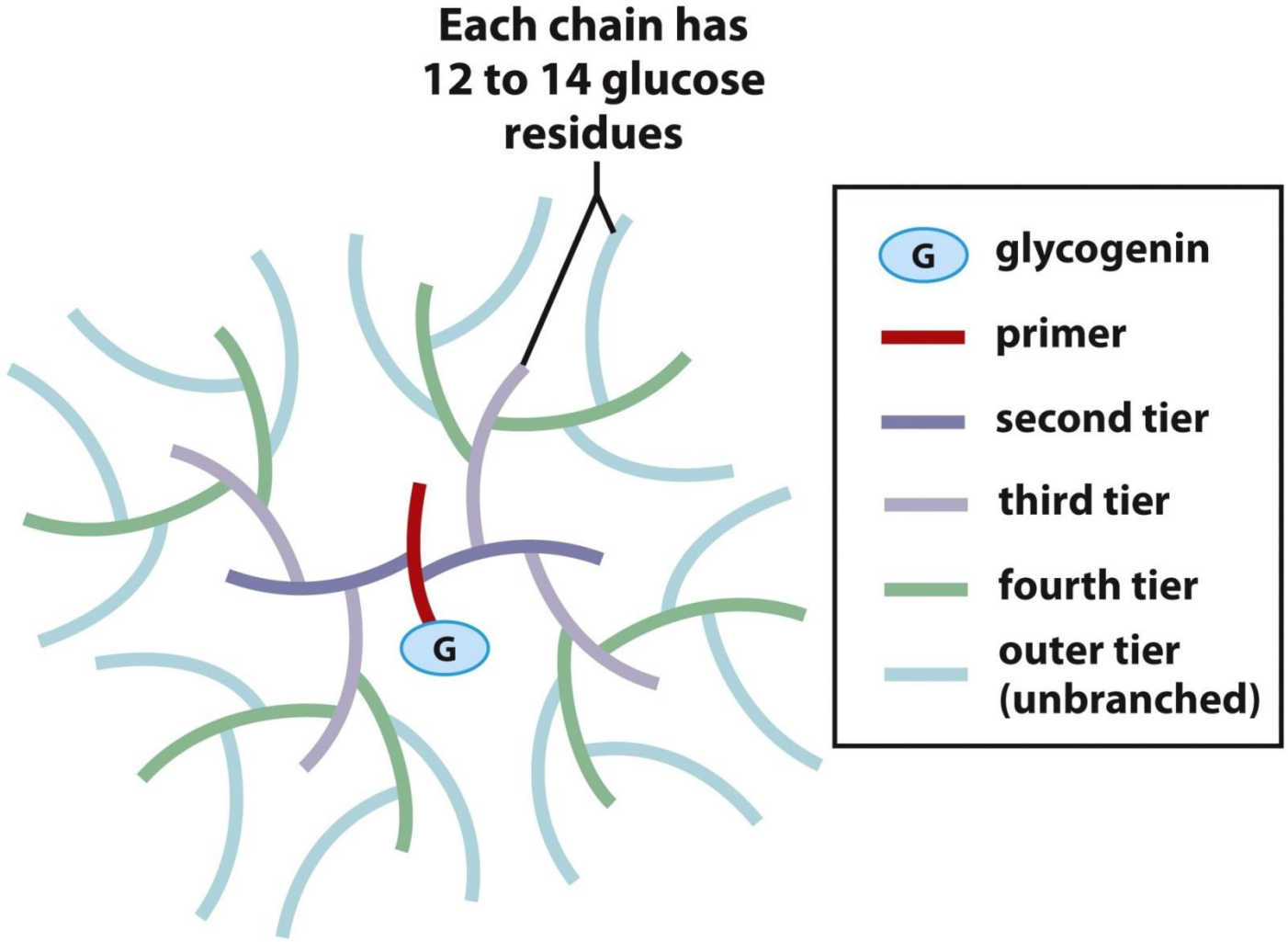


Figure 15-35b

The structure of the glycogen β-particle (12 tiers, 55000 glucose residues)
(20-40 of these particles cluster together to form an α-rosettes)

• Glycogen is an efficient storage form of glucose

$$\text{Glucose 6-phosphate} \longrightarrow \text{glucose 1-phosphate} \quad (1)$$

$$\text{Glucose 1-phosphate} + \text{UTP} \longrightarrow \text{UDP-glucose} + PP_i \quad (2)$$

$$PP_i + H_2O \longrightarrow 2\,P_i \quad (3)$$

$$\text{UDP-glucose} + \text{glycogen}_n \longrightarrow \text{glycogen}_{n+1} + \text{UDP} \quad (4)$$

$$\text{UDP} + \text{ATP} \longrightarrow \text{UTP} + \text{ADP} \quad (5)$$

$$\text{Sum: Glucose 6-phosphate} + \text{ATP} + \text{glycogen}_n + H_2O \longrightarrow \text{glycogen}_{n+1} + \text{ADP} + 2\,P_i$$

- The complete oxidation of glucose 6-phosphate yields about 31 molecules of ATP, and storage consumes slightly more than 1 molecule of ATP per molecule of glucose 6-phosphate; so *the overall efficiency of storage is nearly 97%*.

• SUMMARY 15.4

- Glycogen is stored in muscle and liver as large particles. Contained within the particles are the enzymes that metabolize glycogen, as well as regulatory enzymes.

- Glycogen phosphorylase catalyzes phosphorolytic cleavage at the nonreducing ends of glycogen chains, producing glucose 1-phosphate. The debranching enzyme transfers branches onto main chains and releases the residue at the (α1→6) branch as free glucose.

- Phosphoglucomutase interconverts glucose 1-phosphate and glucose 6-phosphate. Glucose 6-phosphate can enter glycolysis or, in liver, can be converted to free glucose by glucose 6-phosphatase in the endoplasmic reticulum, then released to replenish blood glucose.

• SUMMARY 15.4

- The sugar nucleotide UDP-glucose donates glucose residues to the nonreducing end of glycogen in the reaction catalyzed by glycogen synthase. A separate branching enzyme produces the (α1→6) linkages at branch points.

- New glycogen particles begin with the autocatalytic formation of a glycosidic bond between the glucose of UDP-glucose and a Tyr residue in the protein glycogenin, followed by addition of several glucose residues to form a primer that can be acted on by glycogen synthase.

15.5 Coordinated Regulation of Glycogen Synthesis and Breakdown

• Regulation

- Short term regulation:
  - enzyme modification
  - allosteric effectors
- Long term regulation:
  - Enzyme expression

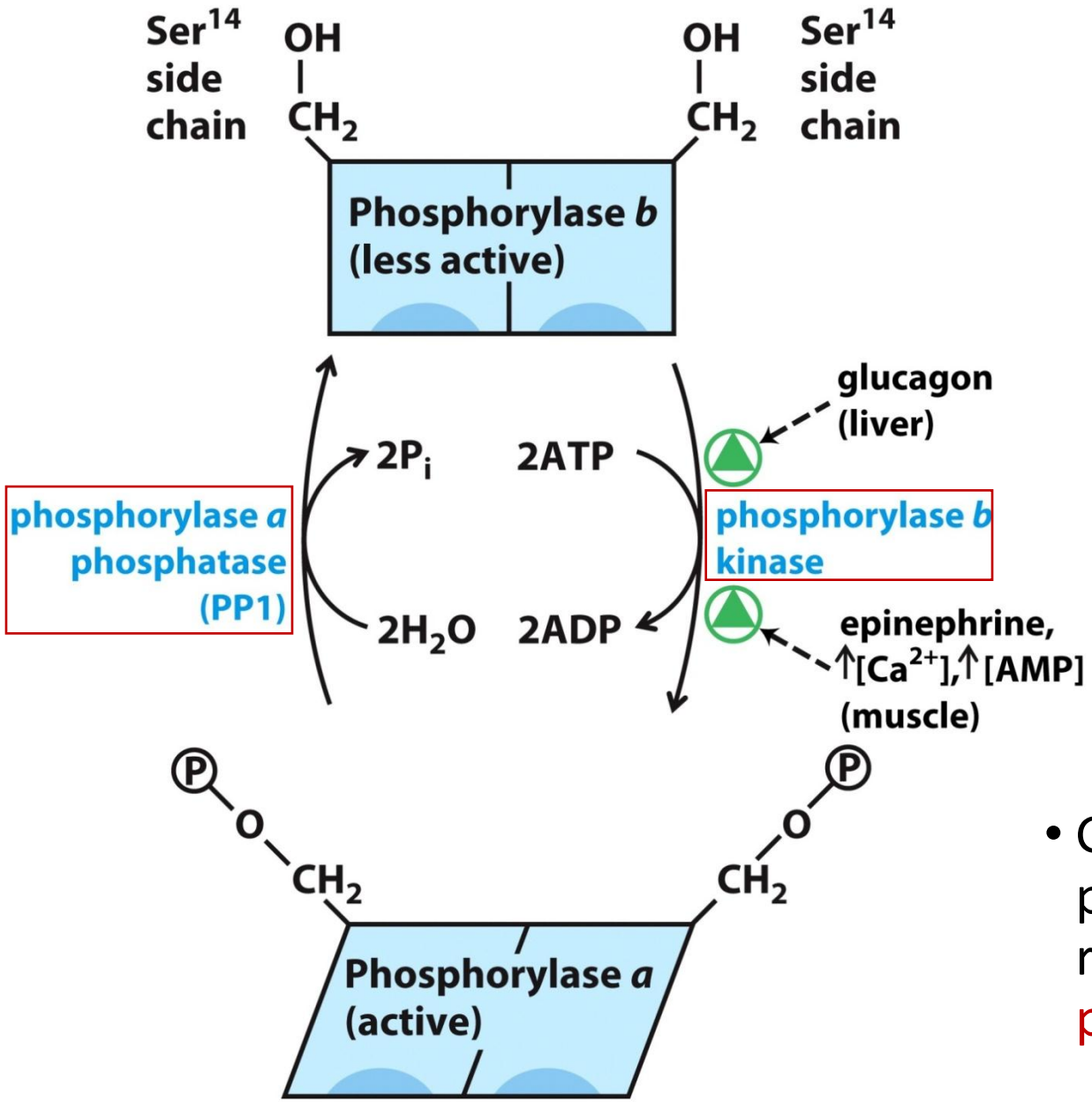
• Earl Sutherland

Earl W. Sutherland, Jr.
1915-1974

Discovered the second messenger **cAMP**, which increases in concentration in response to stimulation by epinephrine (in muslce) or glucagon (in liver).

Nobel Prize winner of 1971 "for his discoveries concerning the mechanisms of the action of hormones,"

• Phosphorylase *a* *v.s.* Phosphorylase *b*

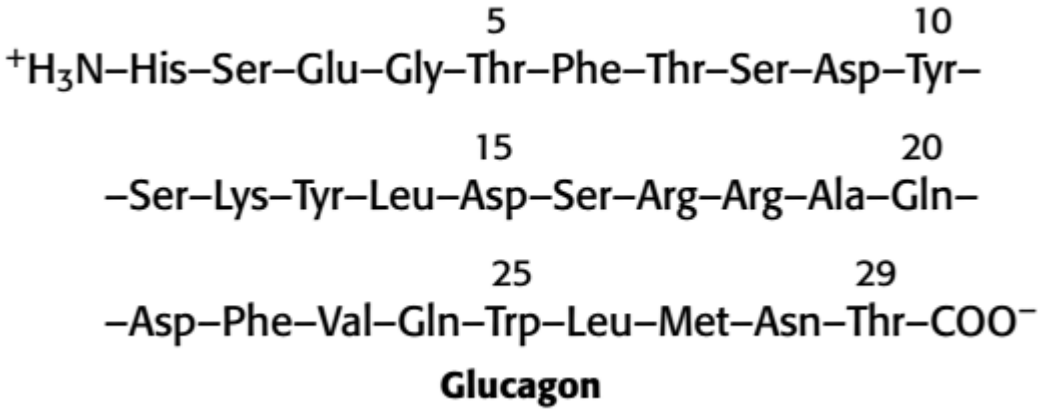


- Glycogen phosphorylase is regulated by phosphorylation.

Figure 15-36

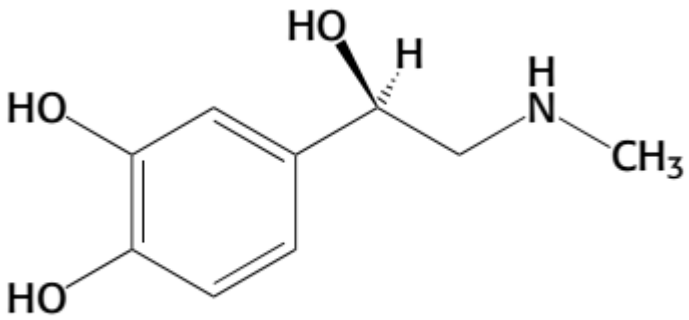
• Hormonal control of glycogen breakdown

- Glucagon (胰高糖素)



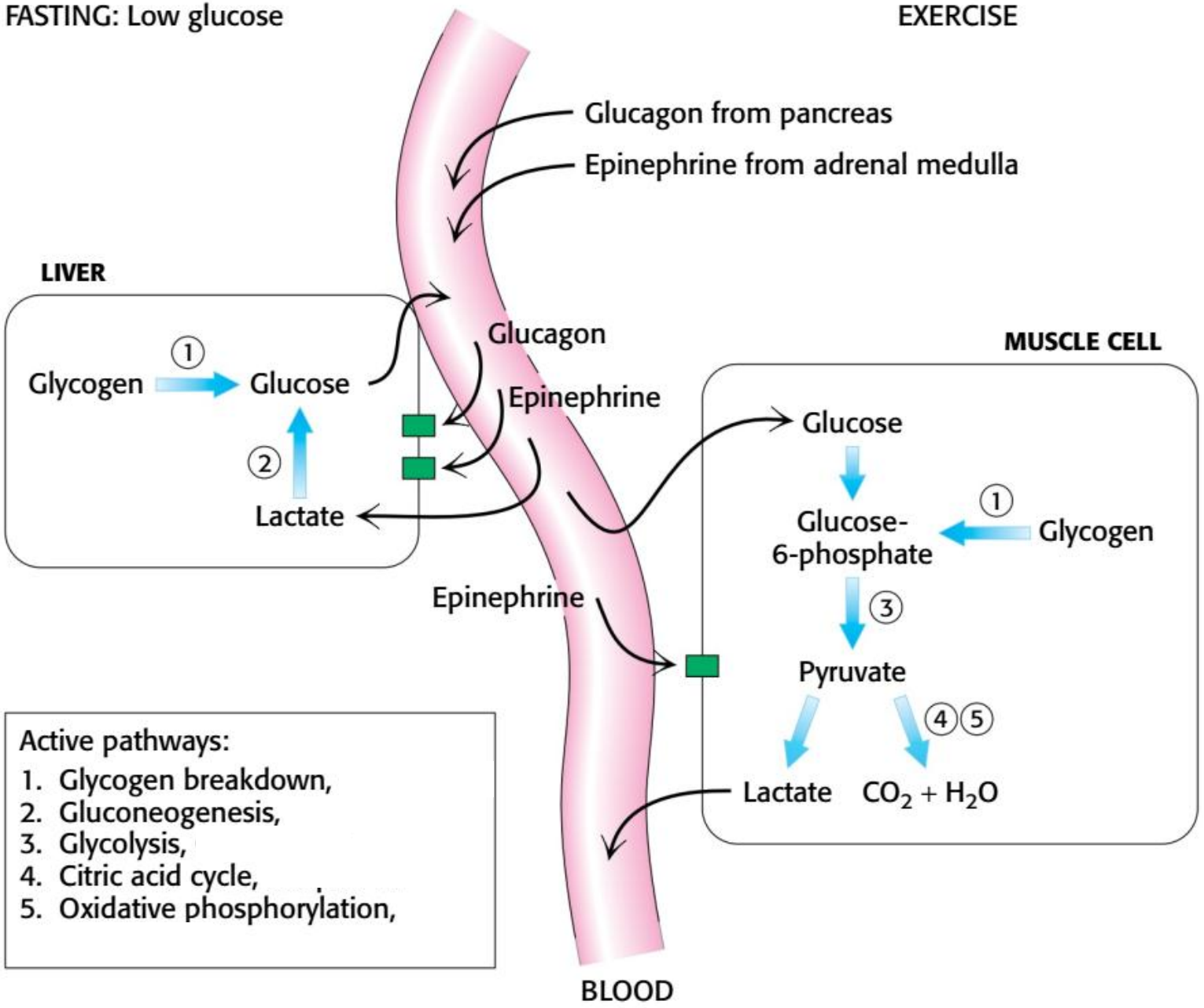
Glucagon

- Epinephrine (肾上腺素)

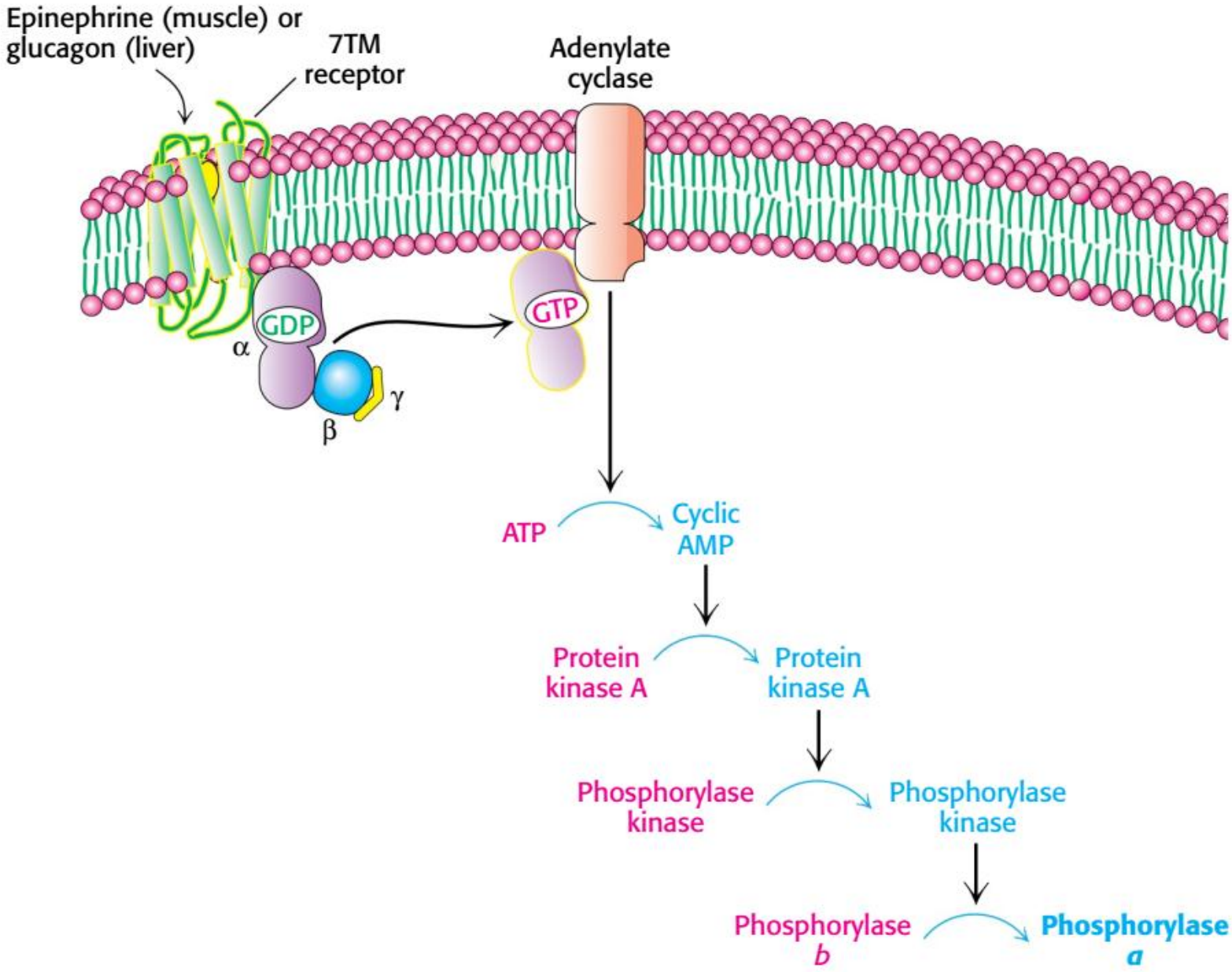


Epinephrine

• Hormonal control of glycogen breakdown



• Regulatory cascade for glycogen breakdown



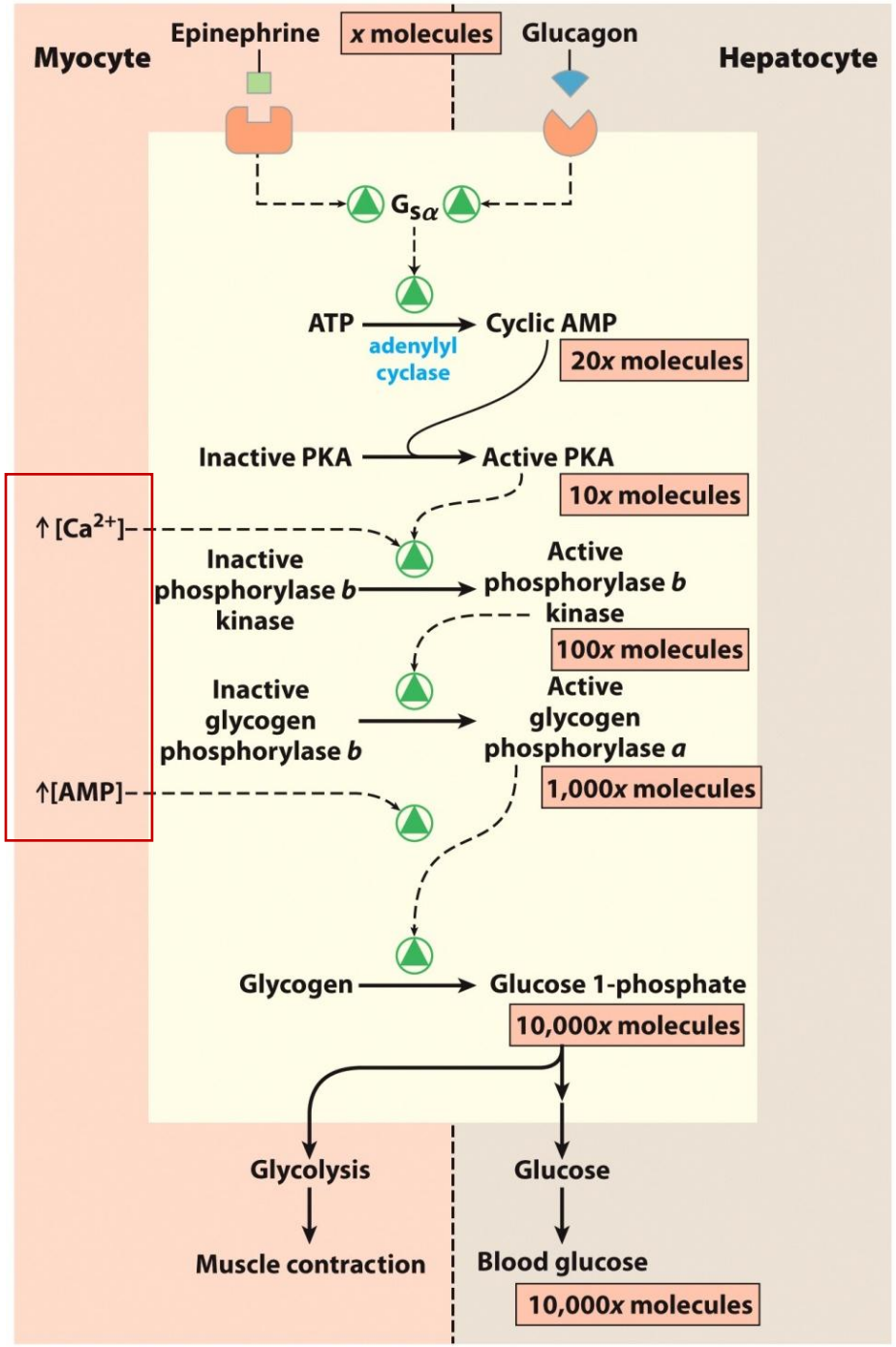


Figure 15-37

Cascade mechanism of epinephrine and glucagon action

• Termination of glycogen breakdown

- Secretion of the initiating hormone ceases.
- Phosphodiesterases (PDE) always present in the cell convert cAMP into AMP.
- Protein phosphatase 1 (PP1, also called phosphorylase a phosphatase) removes the phosphoryl groups from phosphorylase kinase, thereby inactivating the enzyme.
- PP1 also removes the phosphoryl group from glycogen phosphorylase, converting the enzyme into the usually inactive *b* form.
- PDE and PP1 can be activated by insulin.

• Glycogen phosphorylase of liver as a glucose sensor

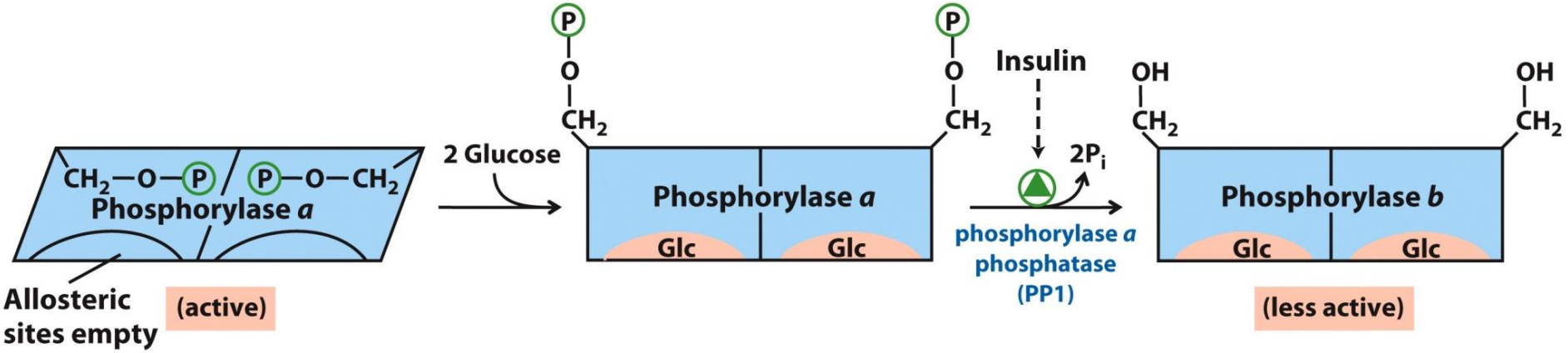
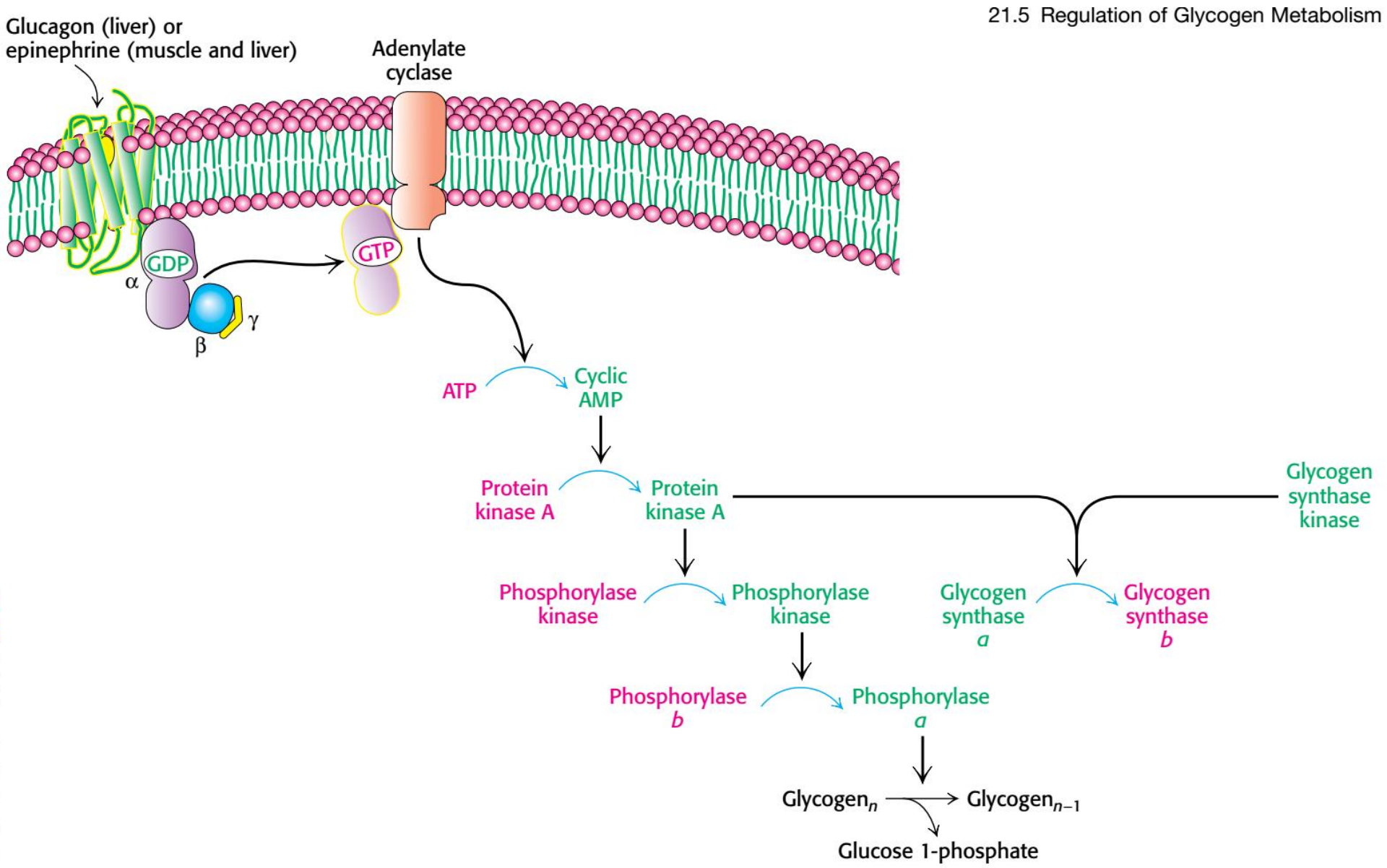


Figure 15-38

• Regulation of glycogen synthase



• Regulation of glycogen synthase

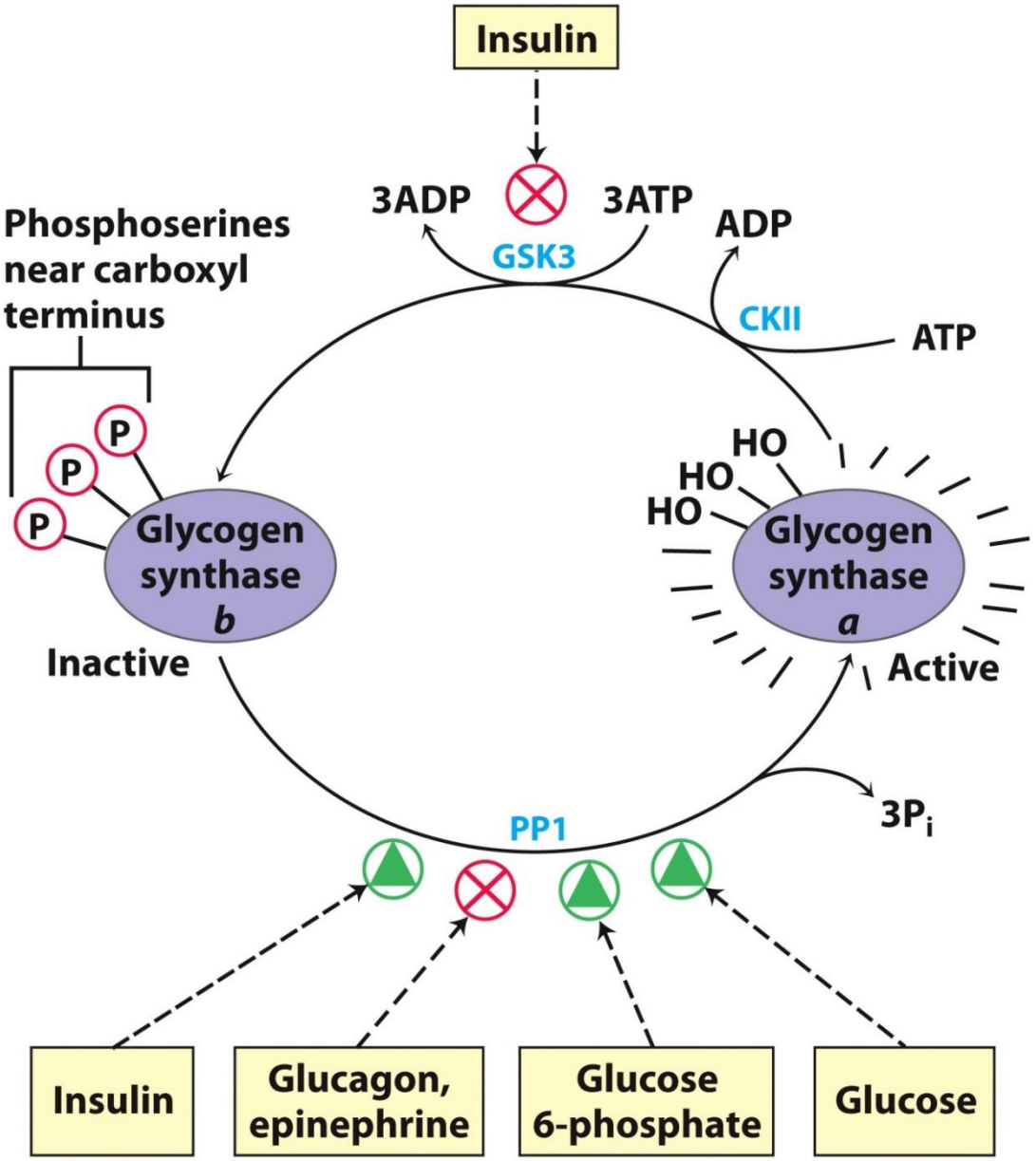


Figure 15-39

glycogen synthase kinase 3 (**GSK3**)

Casein kinase II **(CK II)**

Glycogen synthase is **G-6-P** sensor

• Glycogen Synthase Kinase 3 (GSK3)

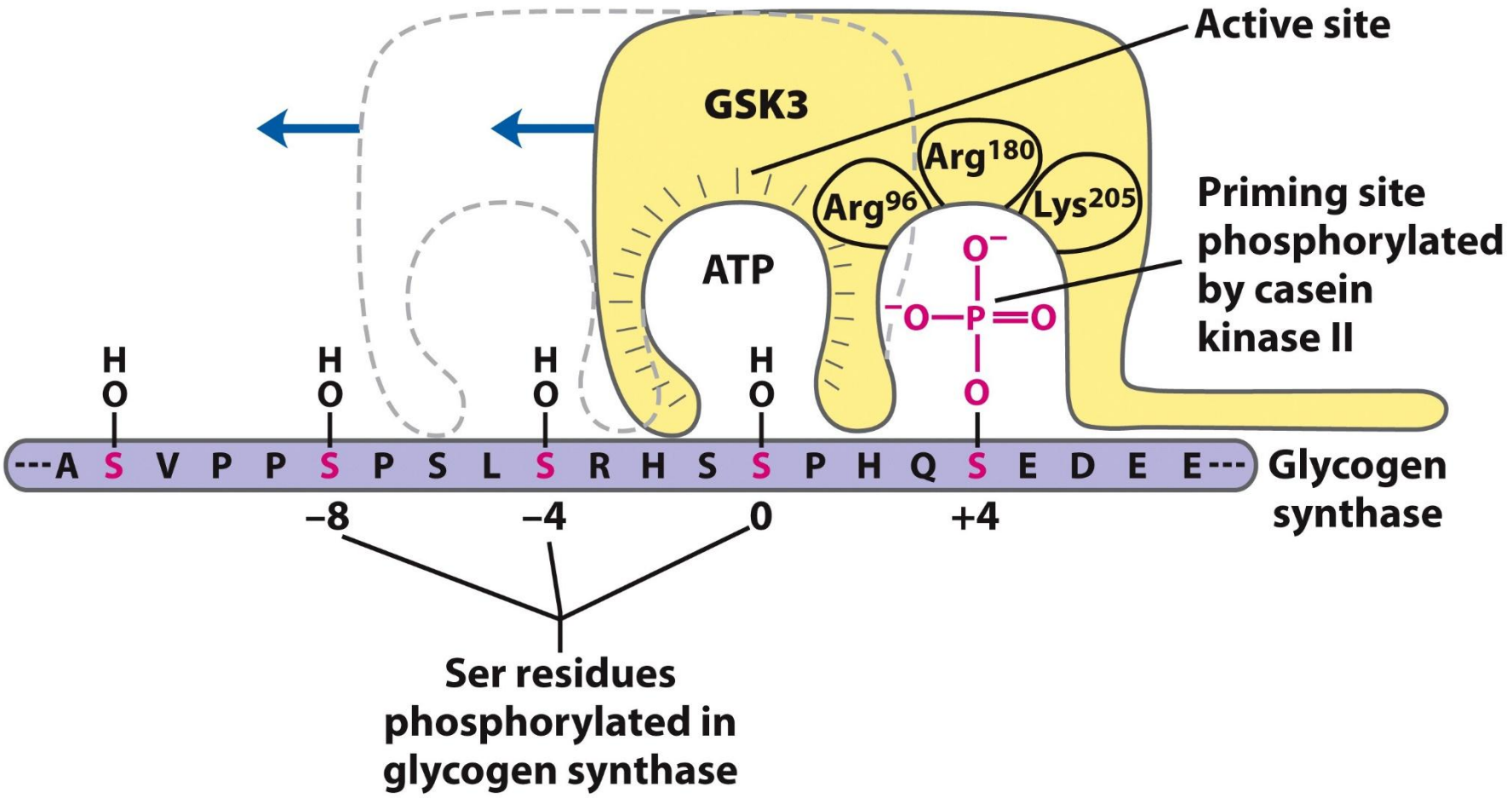


Figure 15-40a

Priming of GSK3 phosphorylation of glycogen synthase

• Glycogen Synthase Kinase 3 (GSK3)

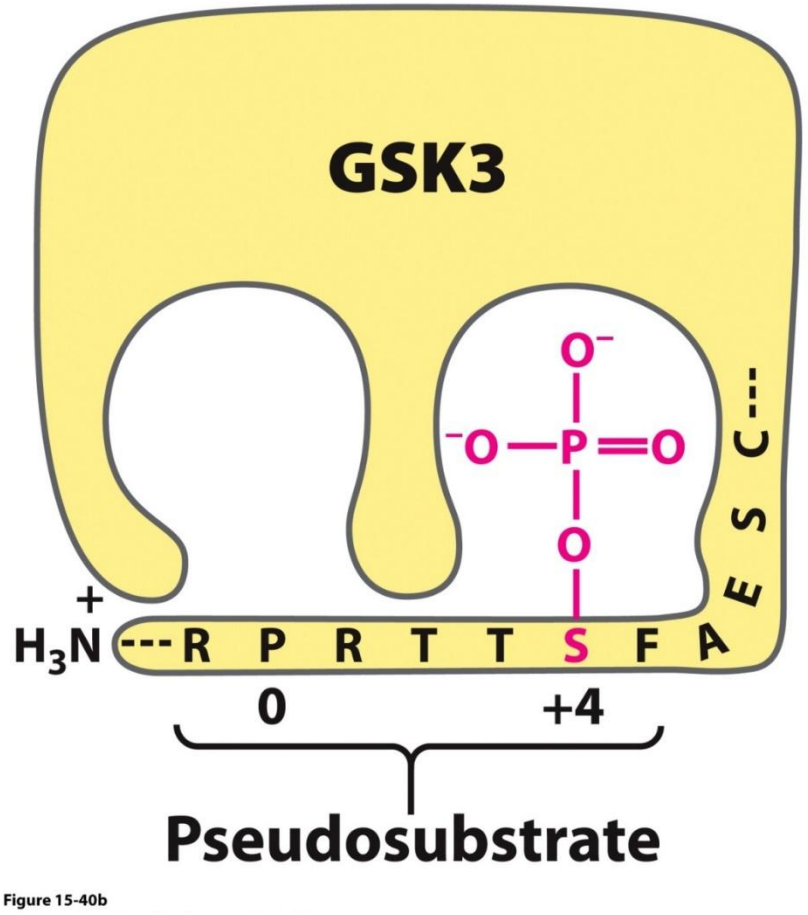


Figure 15-40b

PKB mediated phosphorylation

Autoinhibitory mechanism of GSK3 based on the formation of a intramolecular "pseudosubstrate" region

• The path from insulin to GSK3

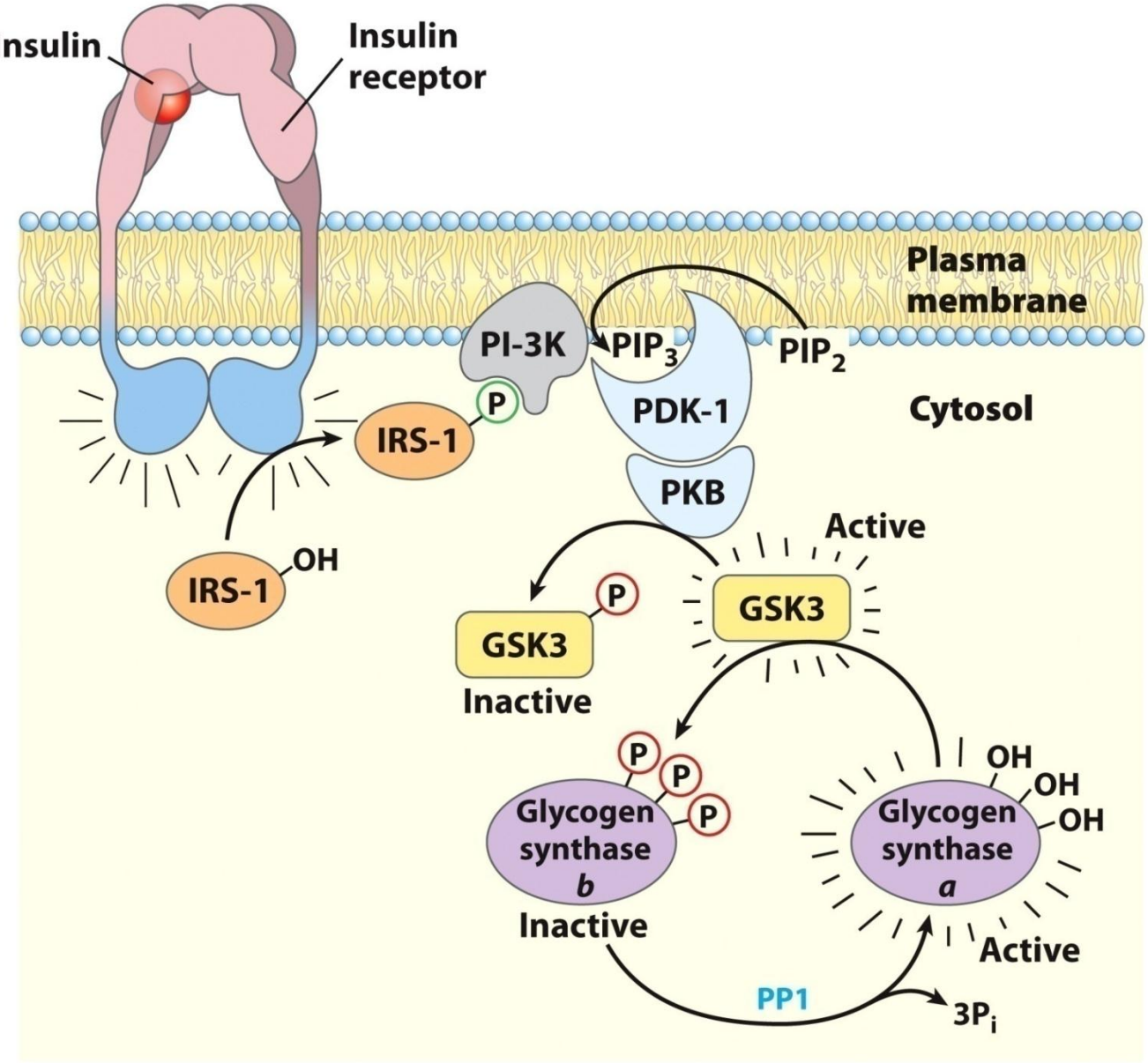


Figure 15-41

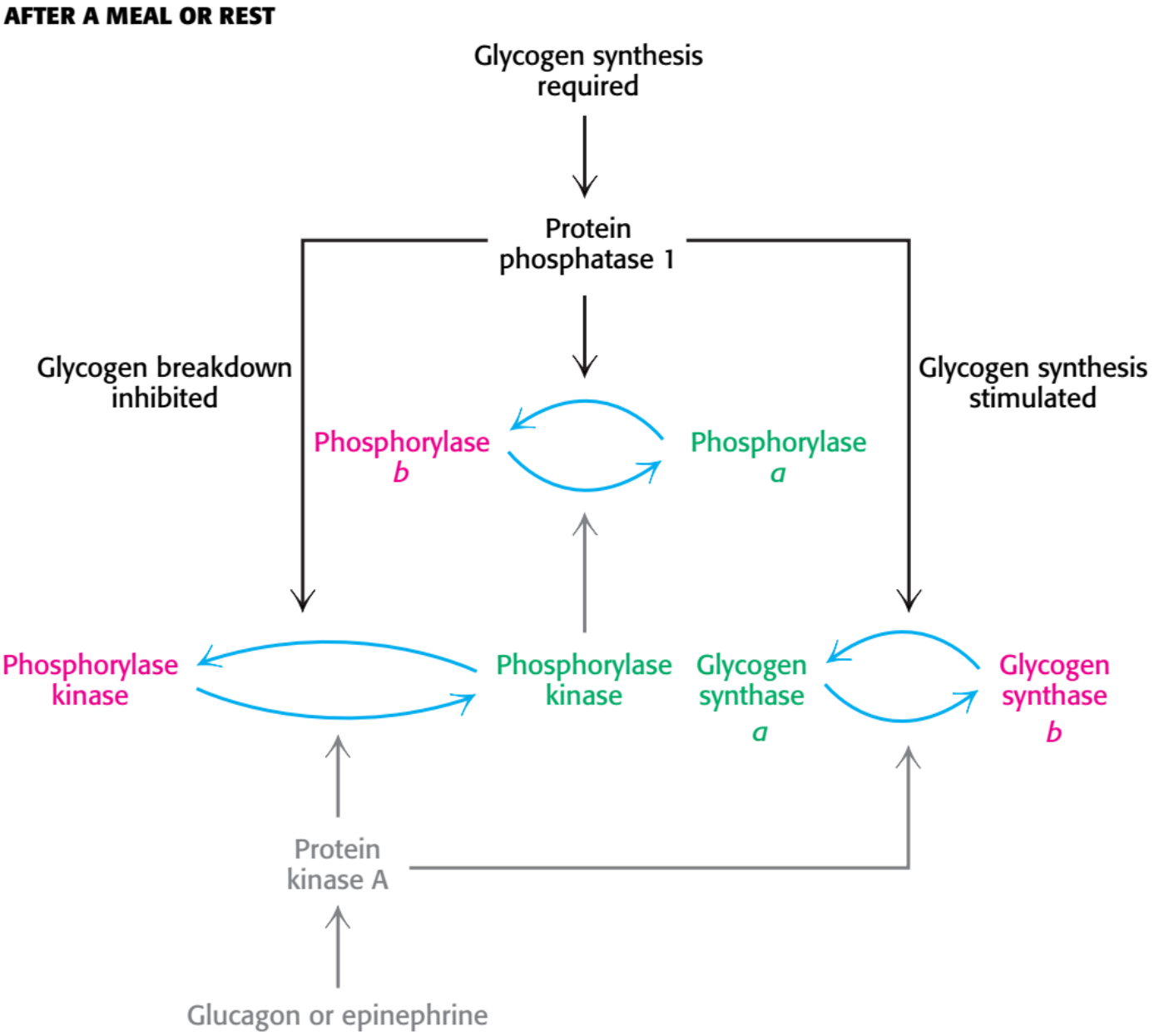
insulin receptor substrate-1(**IRS-1**)

phosphatidylinositol 4,5-bisphosphate (**PIP2**)

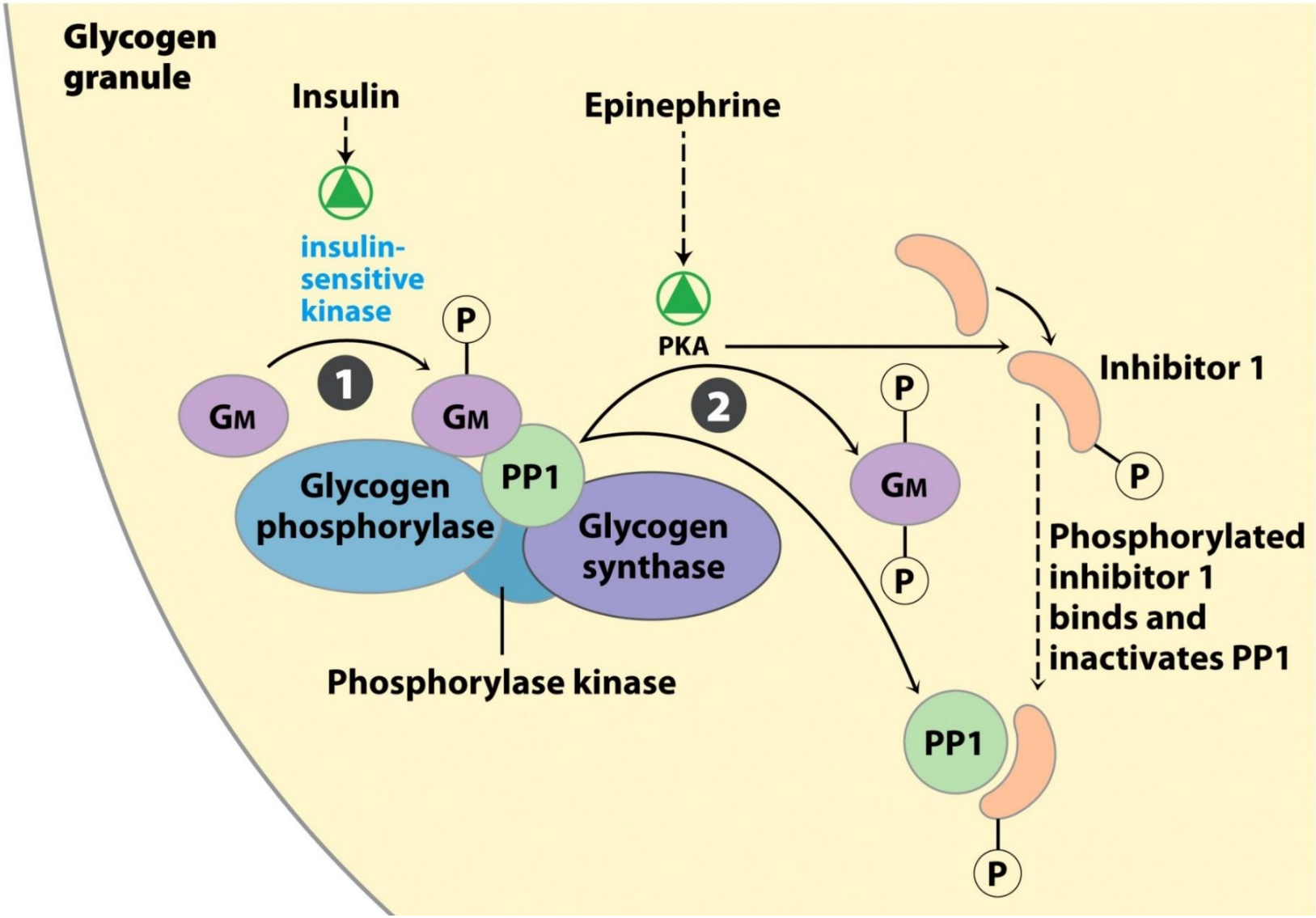
phosphatidylinositol 3-kinase (**PI-3K**)

phosphatidylinositol 3,4 ,5-trisphosphate (**PIP3**)

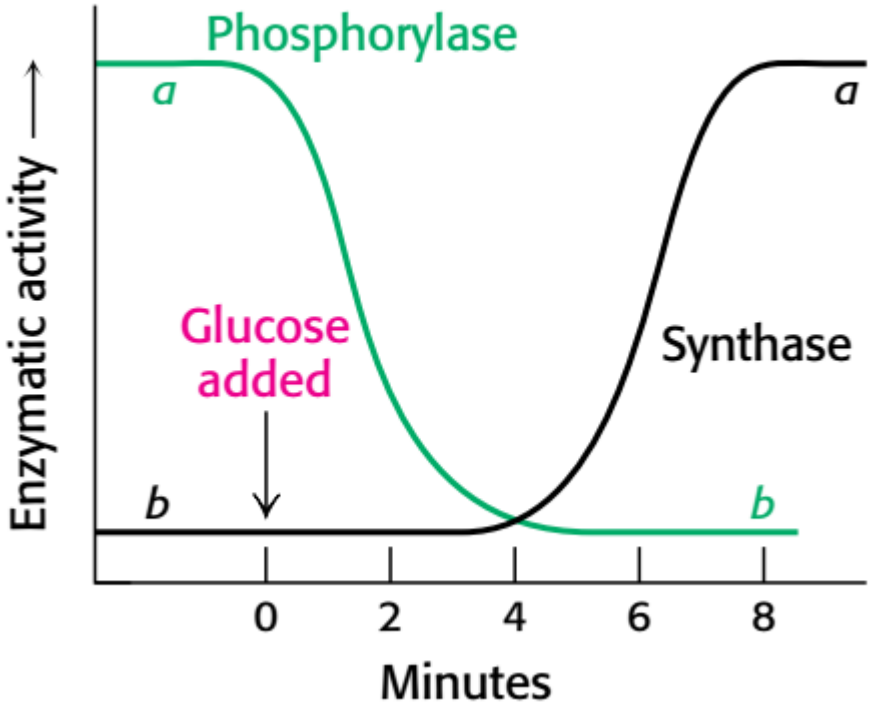
• Regulation of glycogen synthesis by PP1



- Glycogen-targeting protein G_M

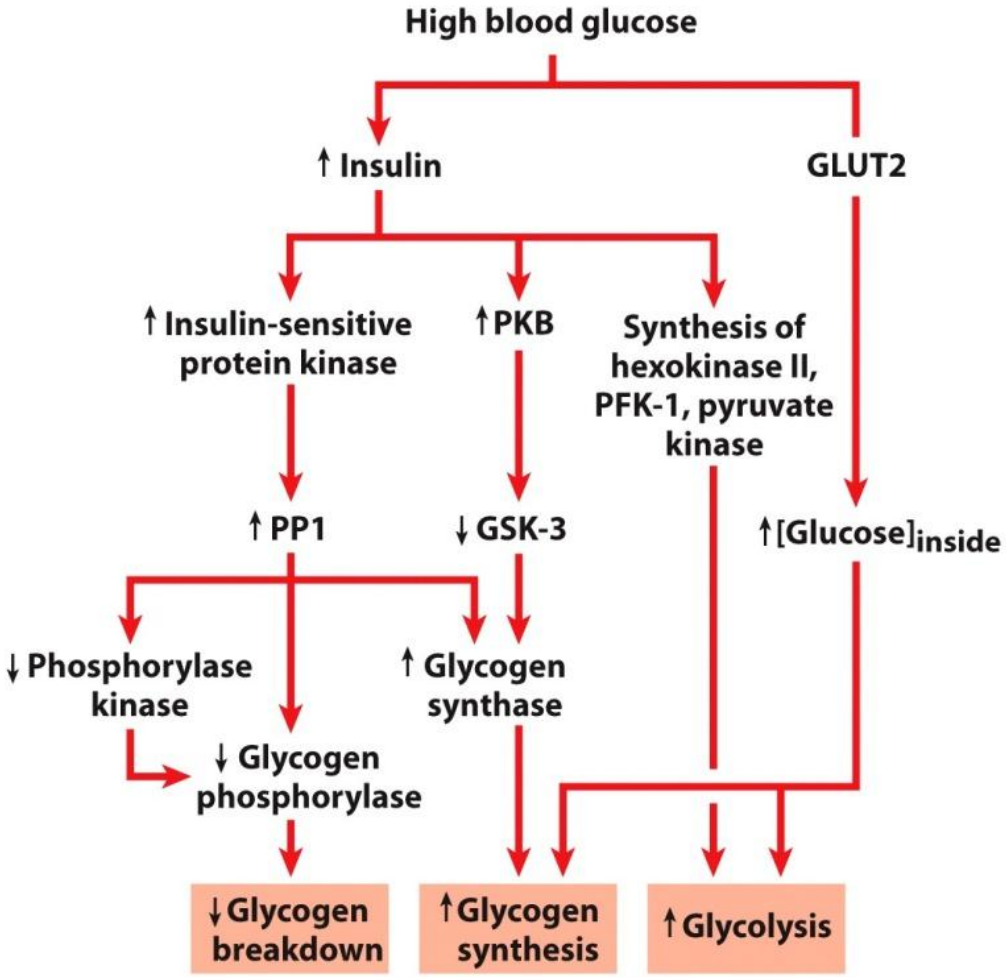


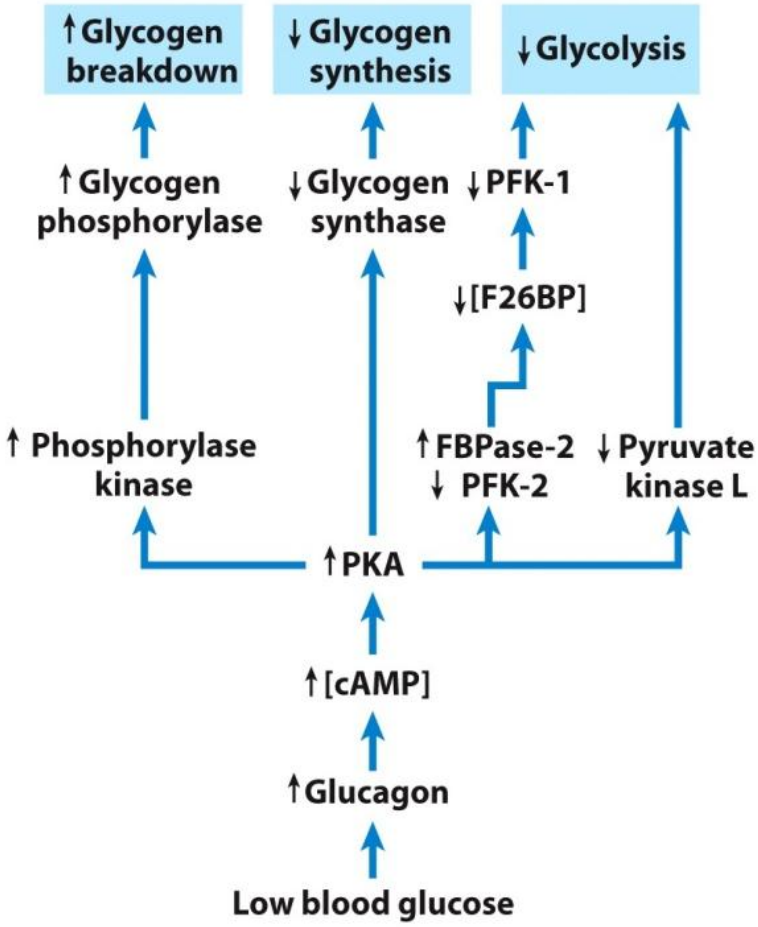
• Blood glucose regulates liver-glycogen metabolism



[Data from W. Stalmans, H. De Wulf, L. Hue, and H.-G. Hers. *Eur. J. Biochem.* 41:117–134, 1974.]

• Regulation of carbohydrate metabolism in the liver





• Regulation of carbohydrate metabolism

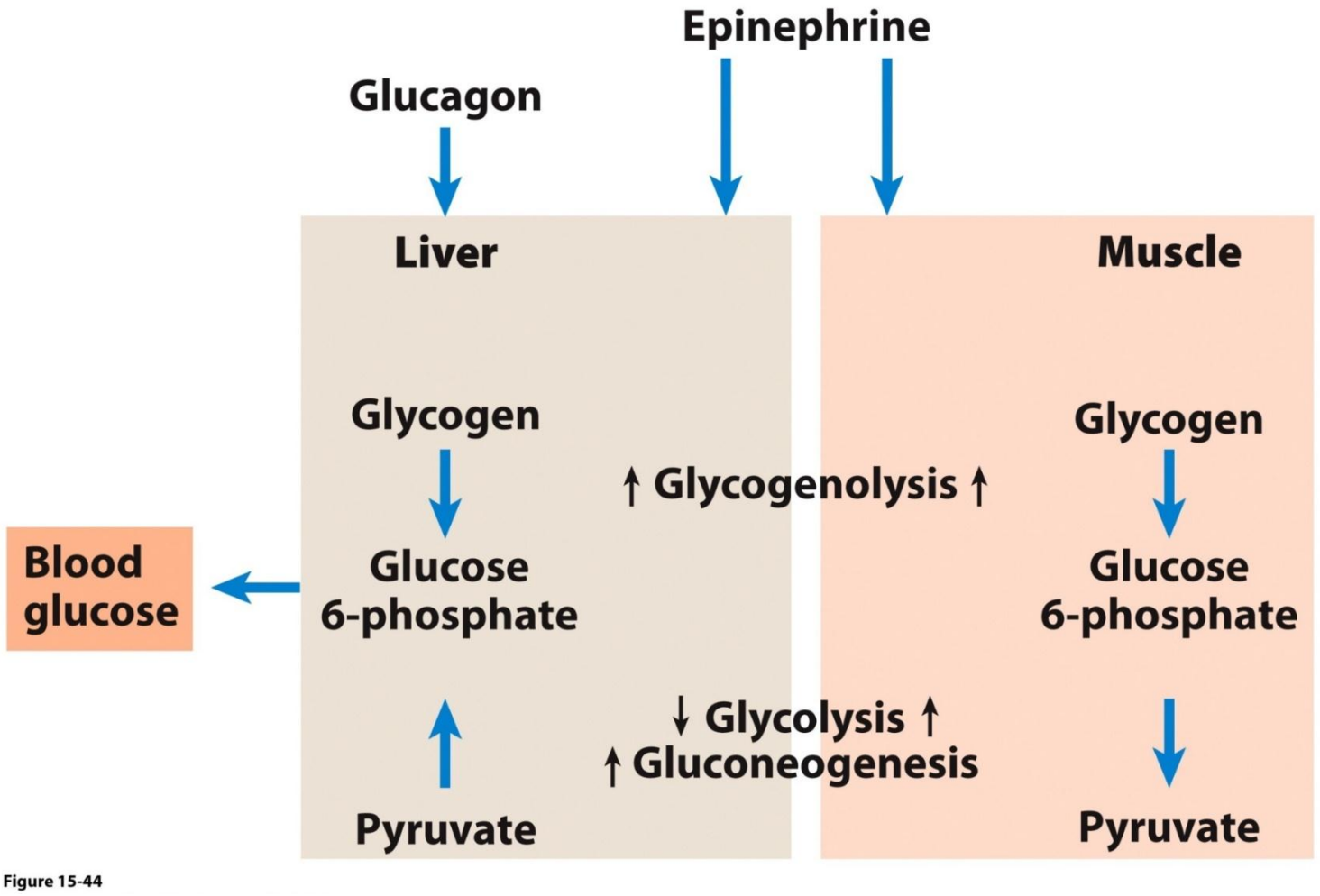


Figure 15-44

Difference in the regulation of carbohydrate metabolism in liver and muscle

• SUMMARY 15.5

- Glycogen phosphorylase is activated in response to glucagon or epinephrine, which raise [cAMP] and activate PKA. PKA phosphorylates and activates phosphorylase kinase, which converts glycogen phosphorylase b to its active a form. Phosphoprotein phosphatase 1 (PP1) reverses the phosphorylation of glycogen phosphorylase a, inactivating it. Glucose binds to the liver isozyme of glycogen phosphorylase a, favoring its dephosphorylation and inactivation.
- Glycogen synthase *a* is inactivated by phosphorylation catalyzed by GSK3. Insulin blocks GSK3. PP1, which is activated by insulin, reverses the inhibition by dephosphorylating glycogen synthase *b*.
- Insulin increases glucose uptake into myocytes and adipocytes by triggering movement of the glucose transporter GLUT4 to the plasma membrane.

• SUMMARY 15.5

- Insulin stimulates the synthesis of hexokinases II and IV, PFK-1, pyruvate kinase, and several enzymes involved in lipid synthesis. Insulin stimulates glycogen synthesis in muscle and liver.

- In liver, glucagon stimulates glycogen breakdown and gluconeogenesis while blocking glycolysis, thereby sparing glucose for export to the brain and other tissues.

- In muscle, epinephrine stimulates glycogen breakdown and glycolysis, providing ATP to support contraction.

单选题 1分

设置

Which enzyme is not required for glycogen breakdown?

A Glycogen phosphorylase

B Branching enzyme

C Debranching enzyme

D Phosphoglucomutase

提交

单选题 1分

设置

What is the glucose donor in the biosysthesis of glycogen?

A glucose

B glucose 1-phosphate

C glucose 6-phsphate

D UDP-Glucose

E UTP-Glucose

提交

主观题 10分

设置

Please explain the process of glycogenolysis

正常使用主观题需2.0以上版本雨课堂

作答