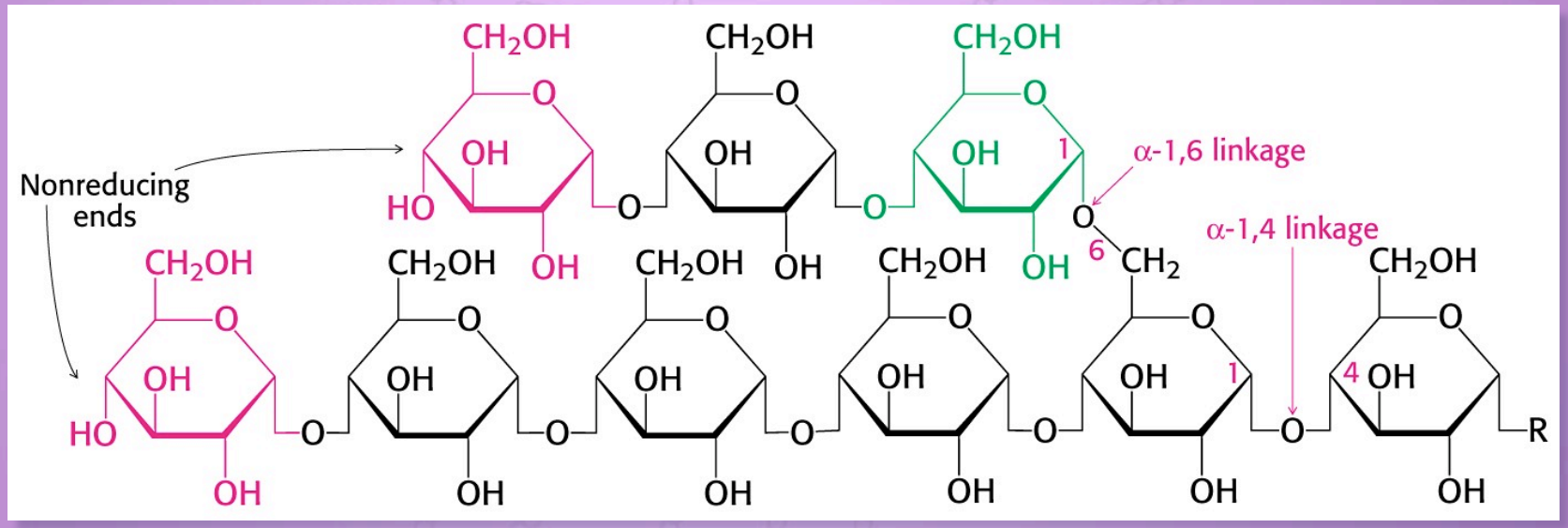
# Chapter 21 - Glycogen Metabolism

Chem 454: Biochemistry II
University of Wisconsin-Eau Claire

# Introduction

## Glycogen

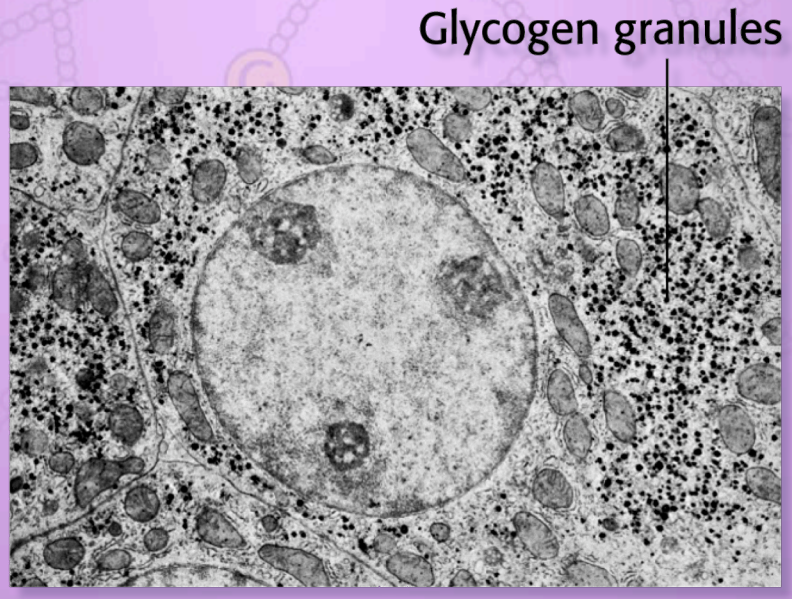
- A storage form of glucose



# Introduction

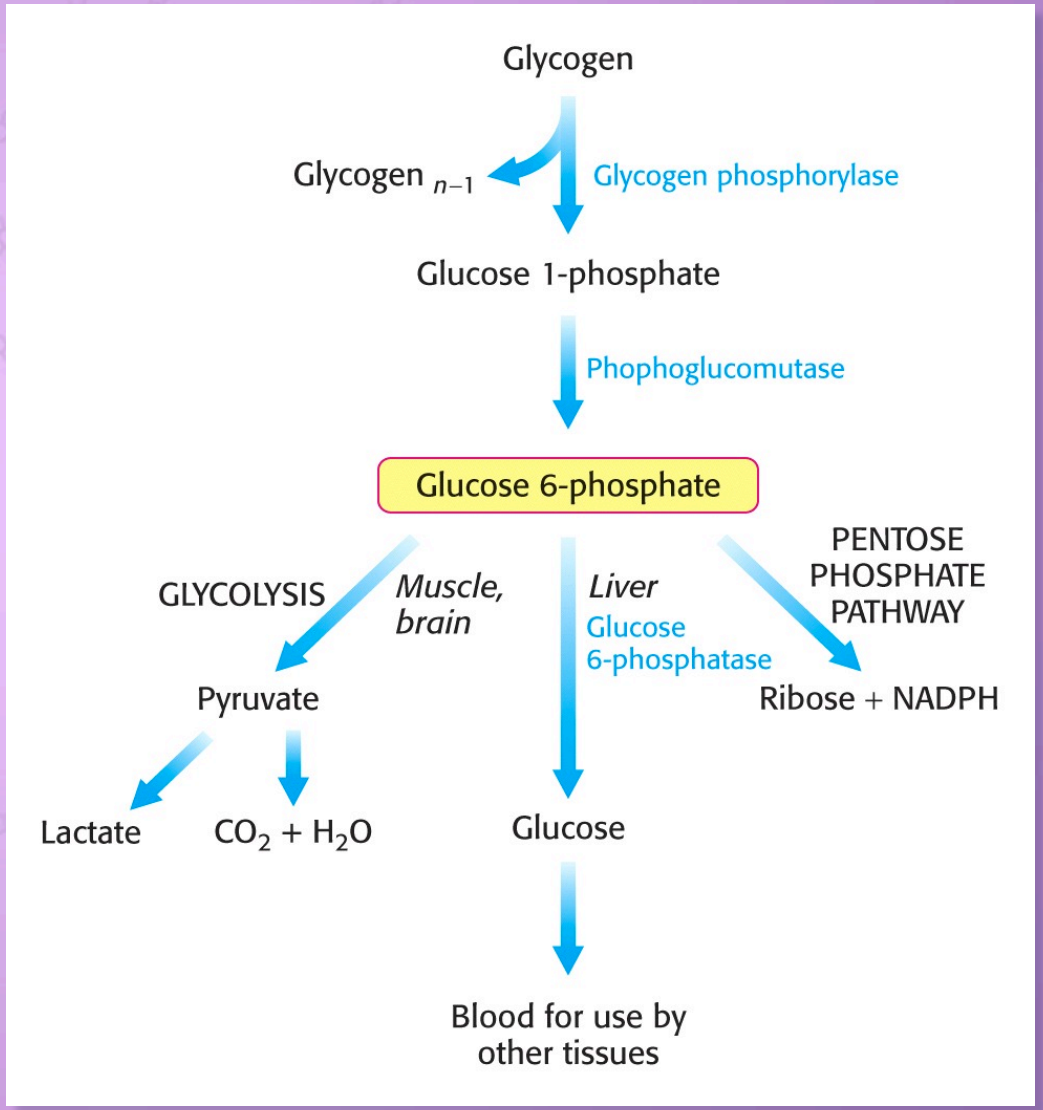
Glycogen is stored primarily in the liver and skeletal muscles.

- Liver - used for maintaining blood glucose levels
- Muscles - used to meet energy needs of the muscles



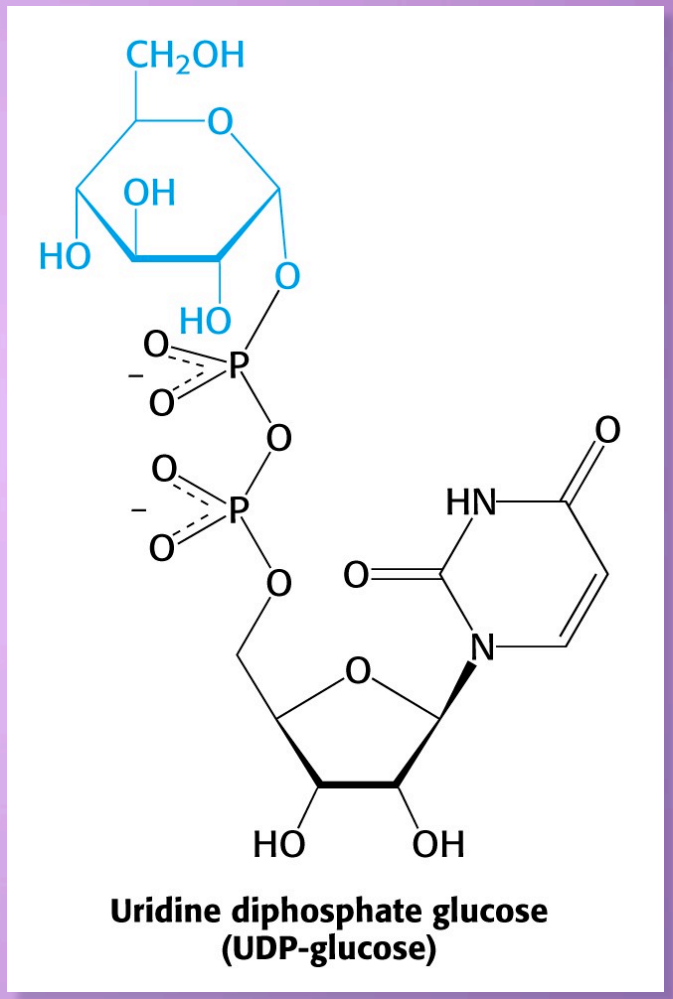
# Introduction

Glycogen degradation occurs in three steps



# Introduction

- Glycogen synthesis uses activated precursor UDP-glucose




**Uridine diphosphate glucose (UDP-glucose)**

# Introduction

Regulation of glycogen metabolism is complex.

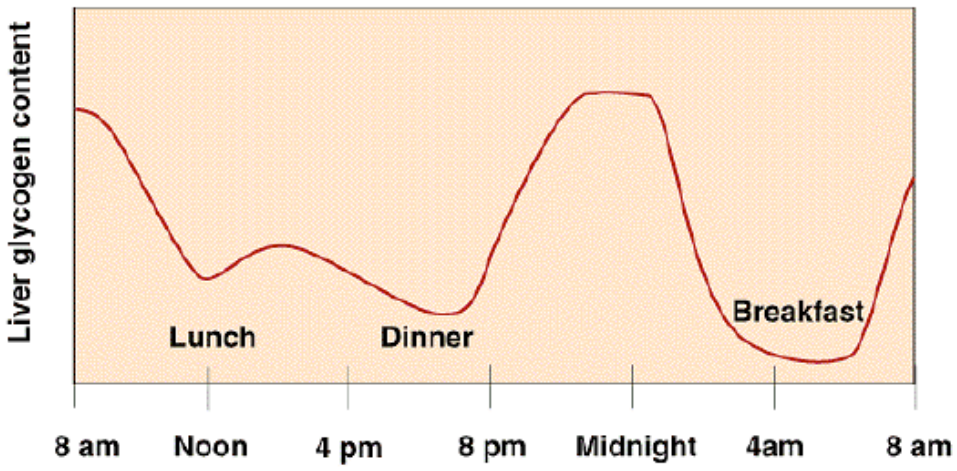
- Allosteric regulation to meet the needs of the cell
- Hormonal regulation to meet the needs of the organsim

# The Big Picture

## Glycogenolysis

- Glycogen breakdown serves different purposes in liver and muscle:
  - Muscle—ATP production within the tissue during activity
  - Liver—furnish glucose to other tissues (supply for ~24 hours)
- Glucagon (acting in liver) and epinephrine (acting in muscle) trigger glycogen breakdown by initiating a G protein-dependent signal transduction pathway that results in phosphorylation and activation of glycogen phosphorylase

Variation in glycogen levels between meals and during night



# Fuel Reserves

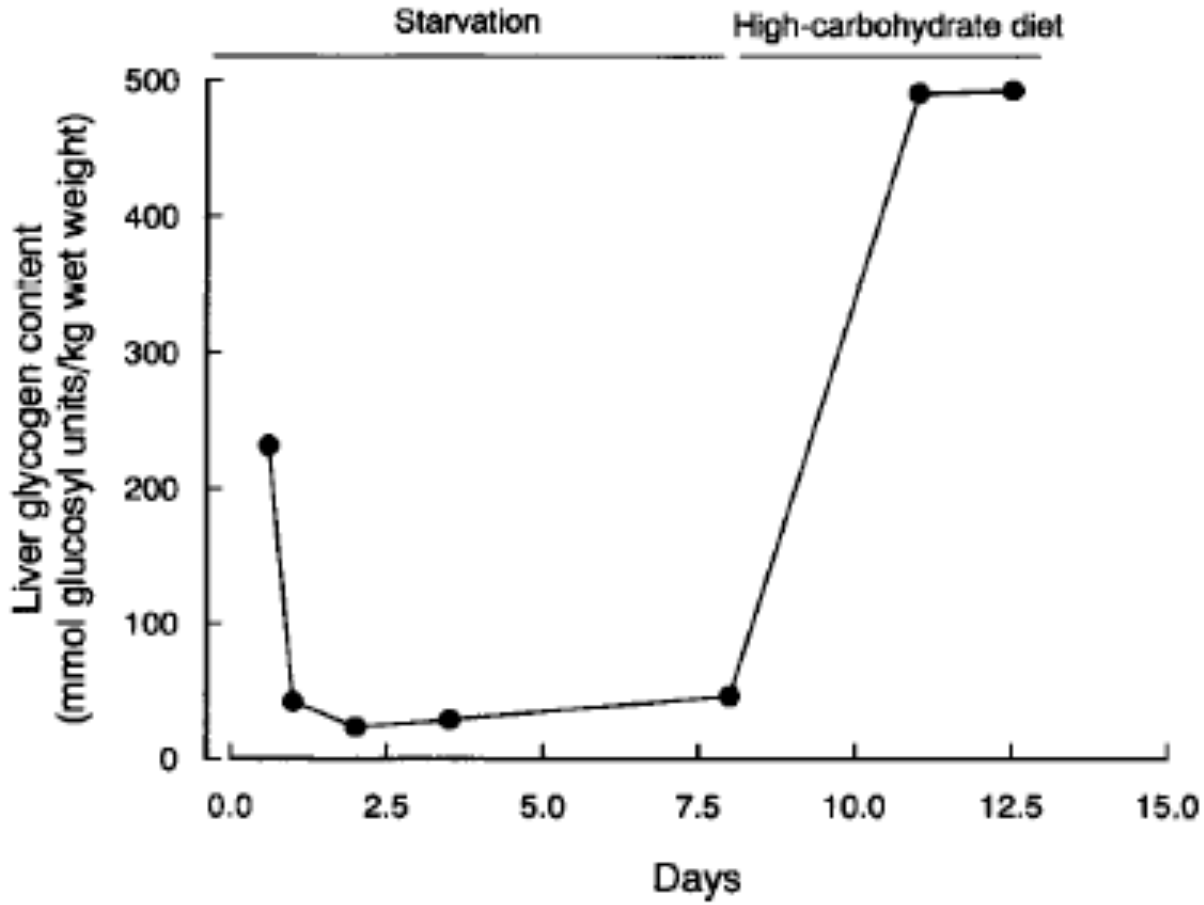
## Fuel supplies in extreme situations--starvation

| Fuel | Tissue | Fuel Reserves (g) | Fuel Reserves (kcal) |
|---|---|---|---|
| Glycogen | Liver | 70 | 280 |
| Glycogen | Muscle | 120 | 480 |
| Fat | Adipose | 15,000 | 135,000 |
| Protein | Muscle | 6,000 | 24,000 |

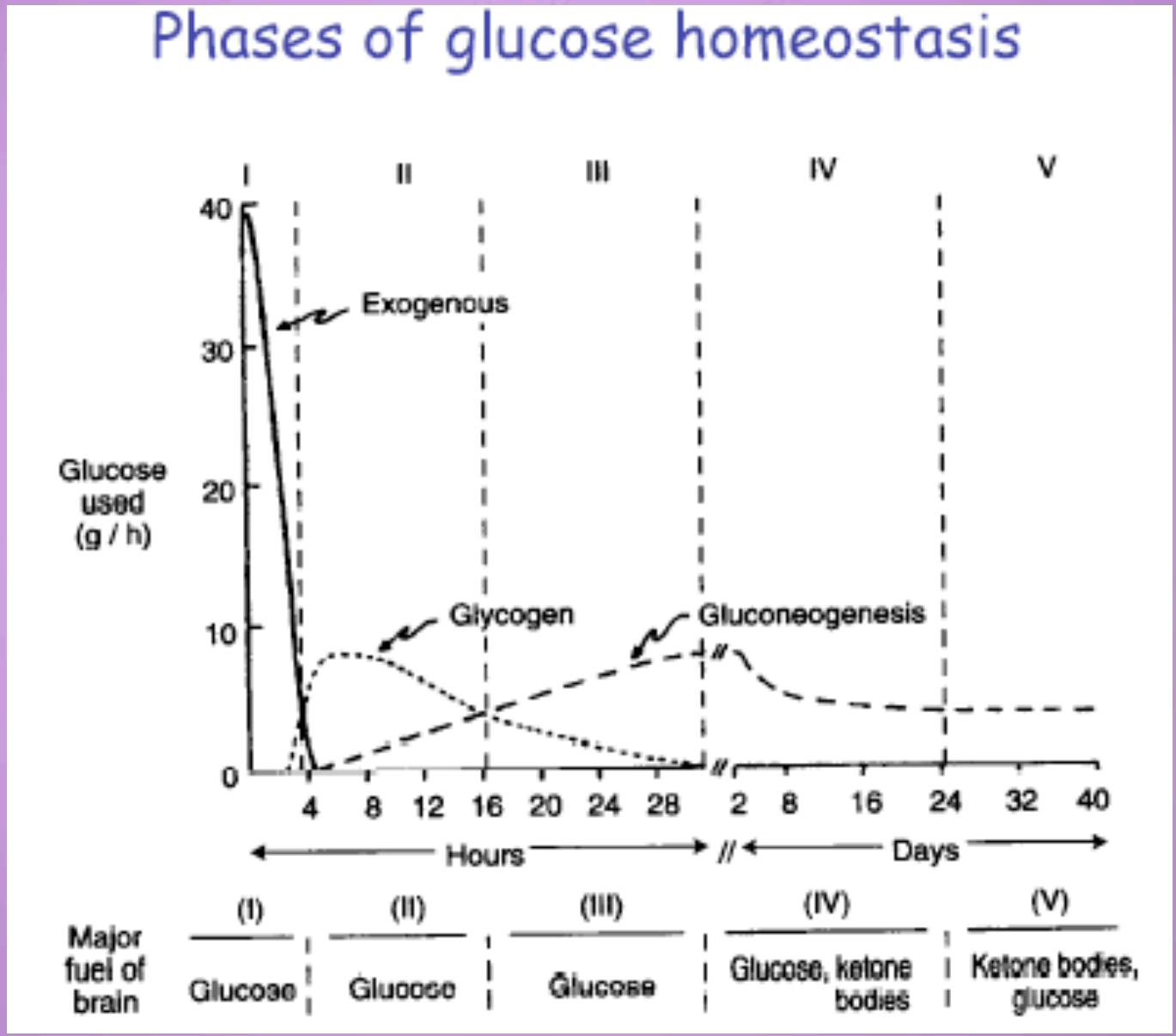
Energy use in order of preference:
(1) Glucose from food
(2) Glucose from glycogen
(3) Glucose from gluconeogenesis
(4) Fatty acids from stored fat
(5) Amino acids from protein

# Fuel Reserves

## Liver glycogen is depleted in a day



# Glucose Homeostasis



# Glucose Homeostasis: Integrated metabolic regulation

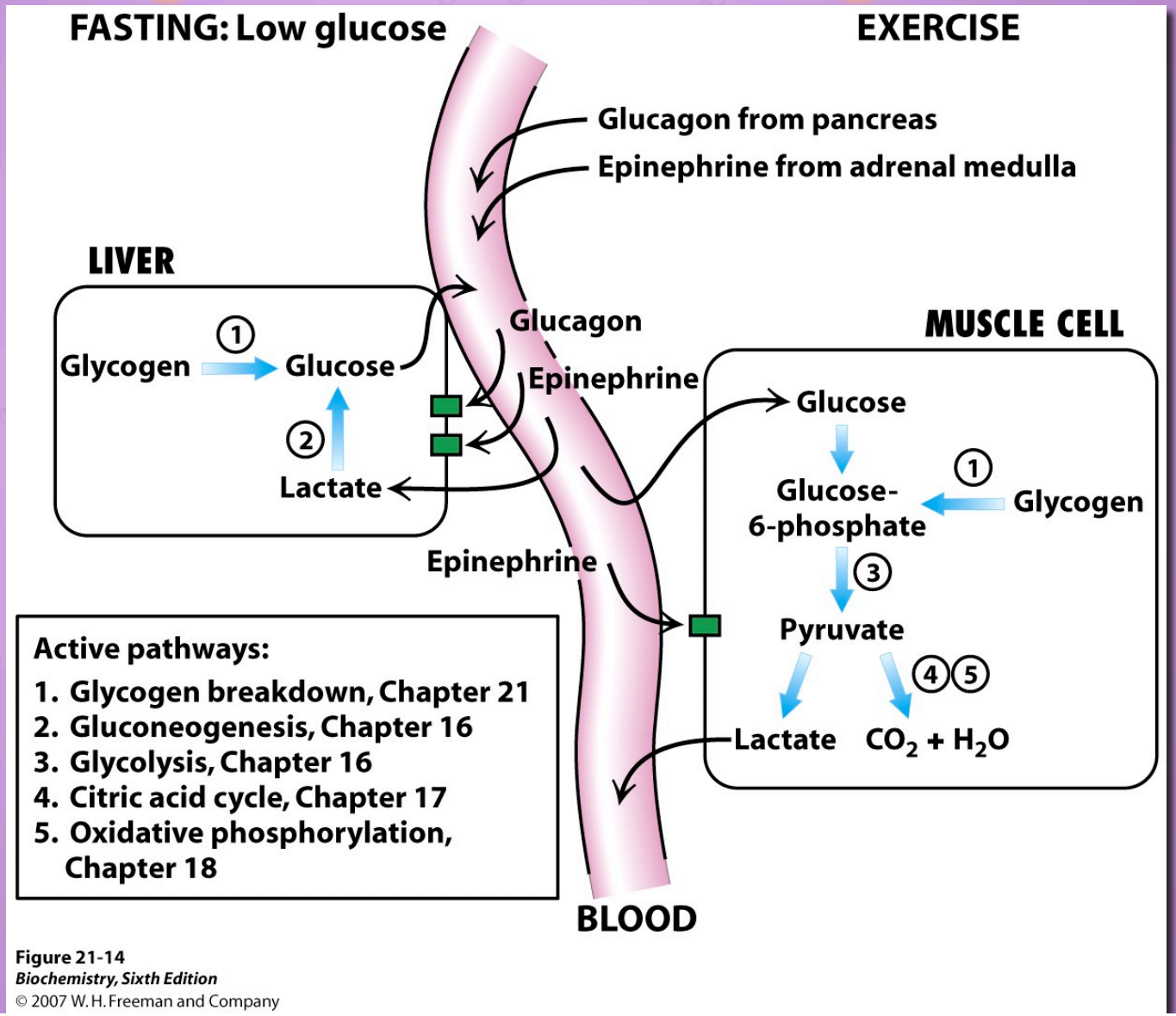


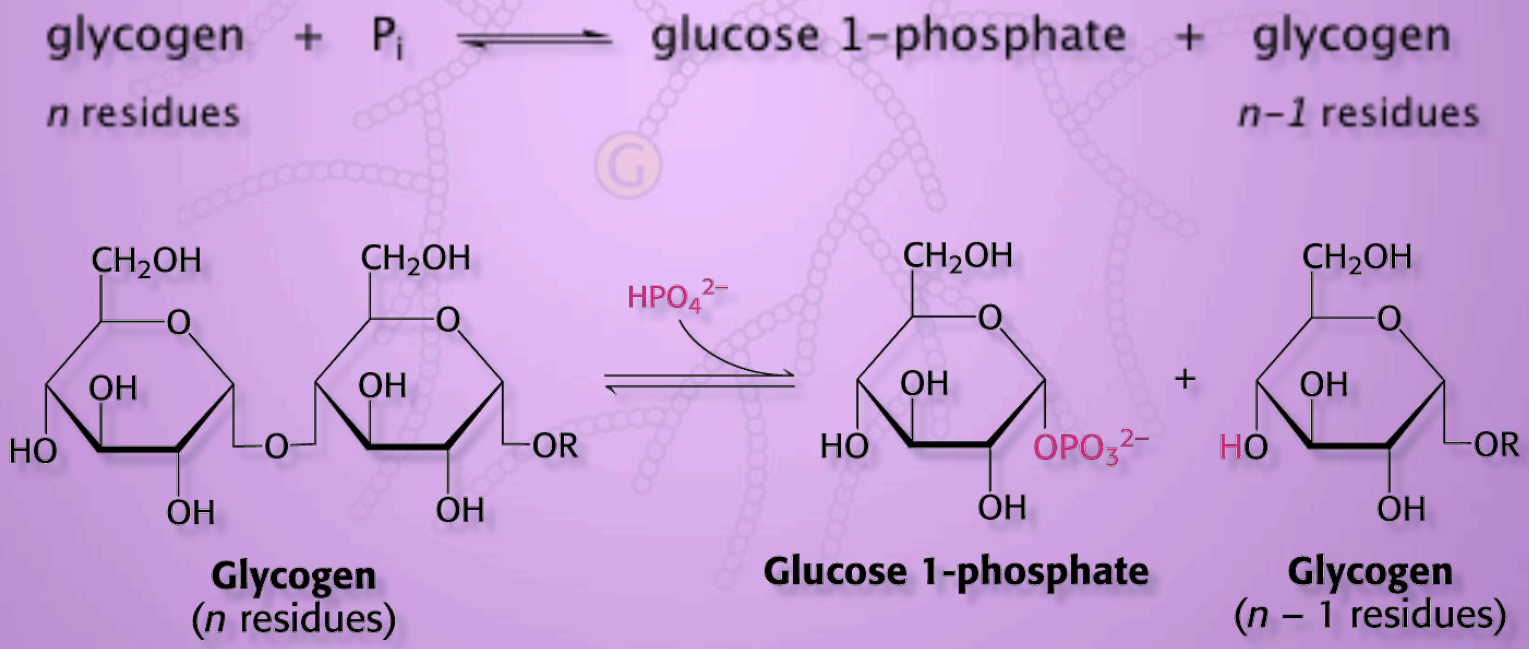

**Figure 21-14**
***Biochemistry, Sixth Edition***

# 1. Details, Details: Glycogen Breakdown

- Requires three enzymes and produces glucose 6-phosphate
  - Glycogen Phosphorylase
  - Debranching Enzyme
  - Phosphoglucomutase
- In the liver, an additional enzyme produces free glucose
  - Glucose 6-phosphatase

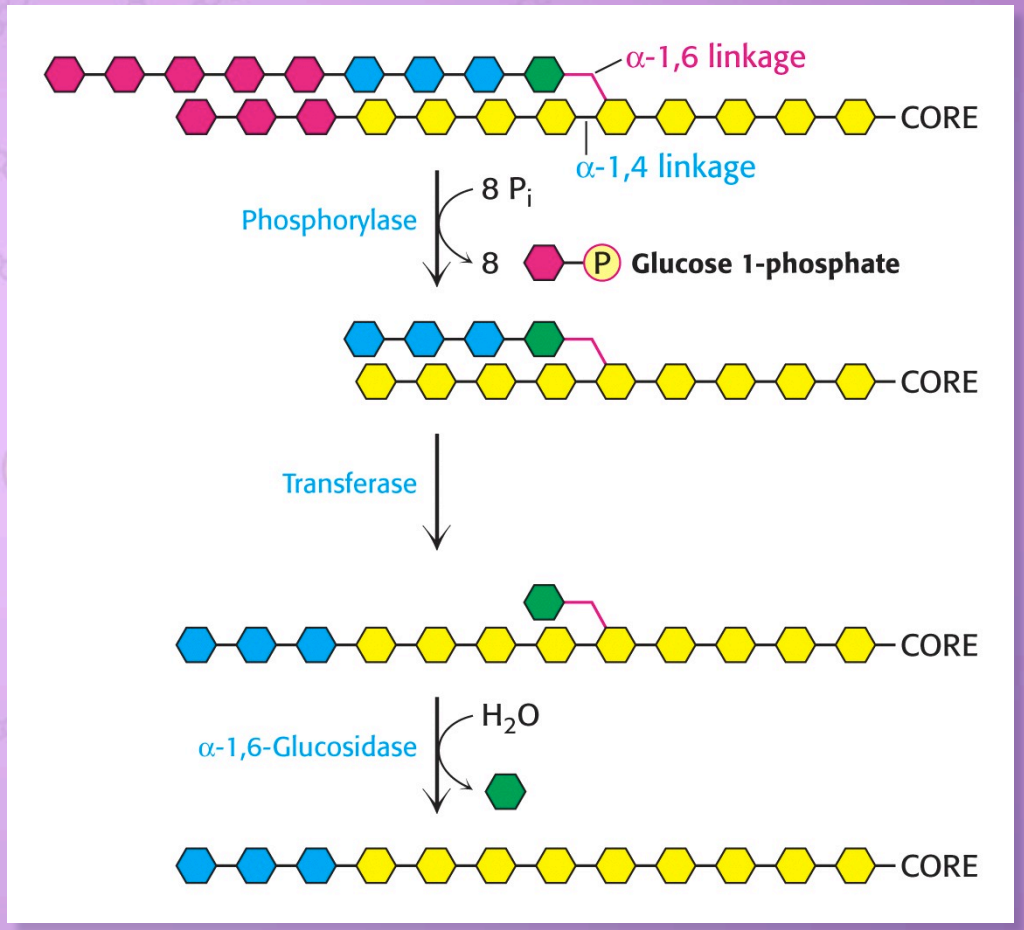
# 1.1 Phosphorylase

Cleavage uses orthophosphate in phosphorolysis reactions



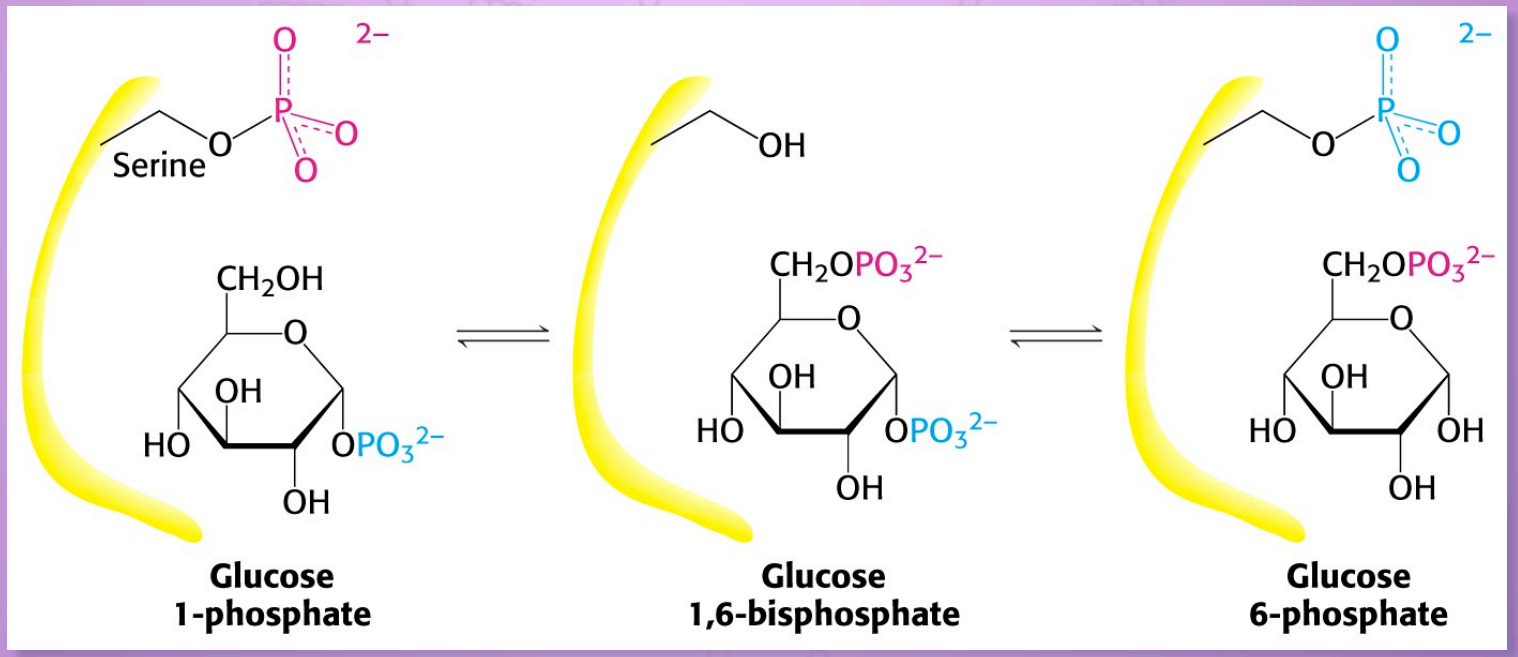
# 1.2 Debranching Enzyme

Two enzymes activities are needed to deal with the α–1,6 branch points



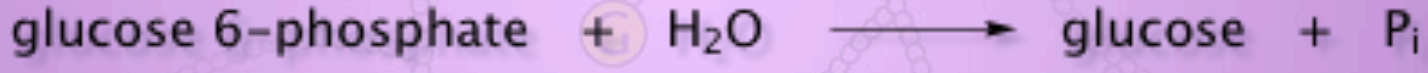
# 1.3 Phosphoglucomutase

Mechanism is like that of phosphoglycerate mutase

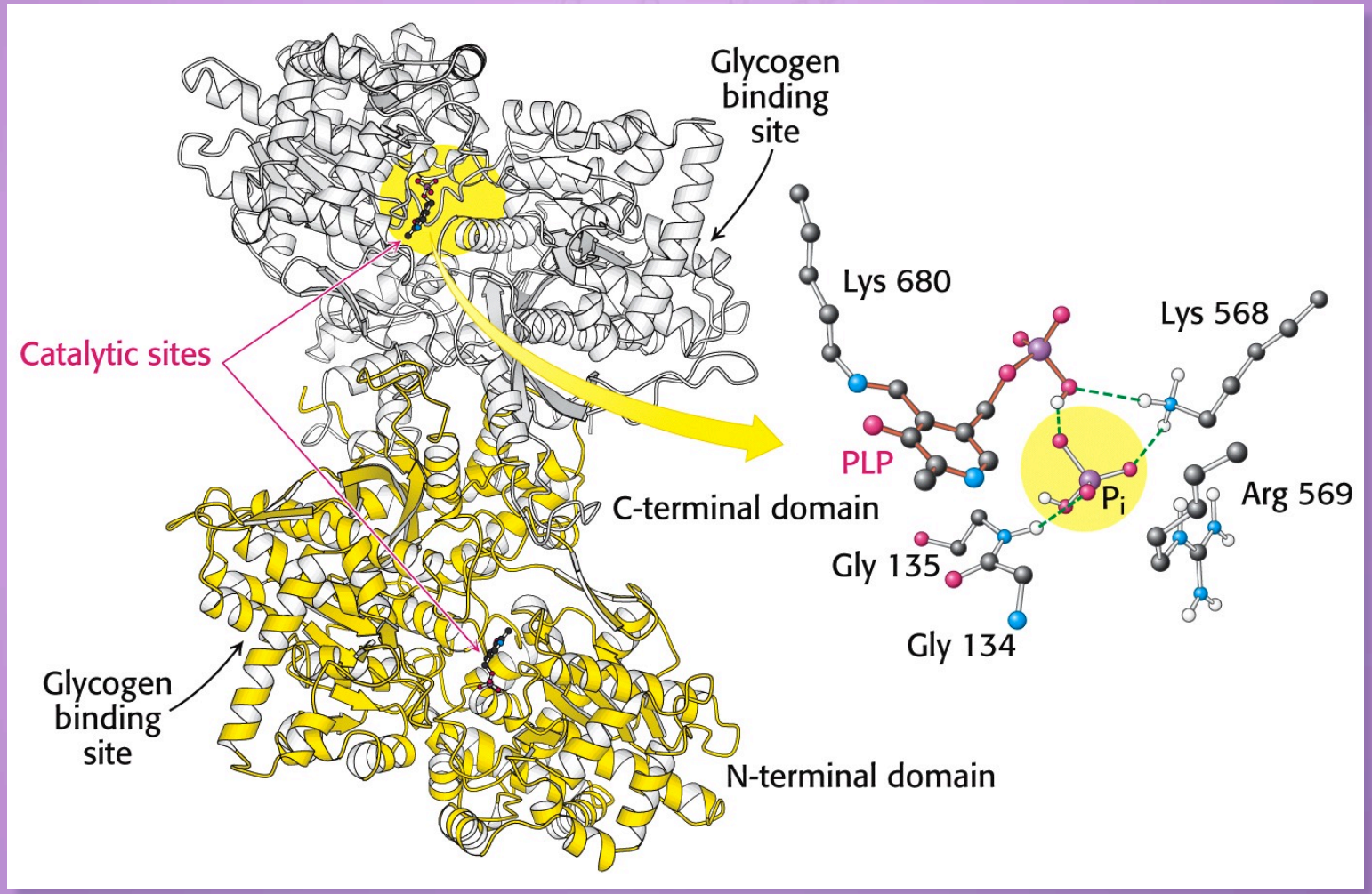


# 1.4 Glucose 6-phosphatase

Enzyme is found primarily in the liver and is used to release glucose into the bloodstream

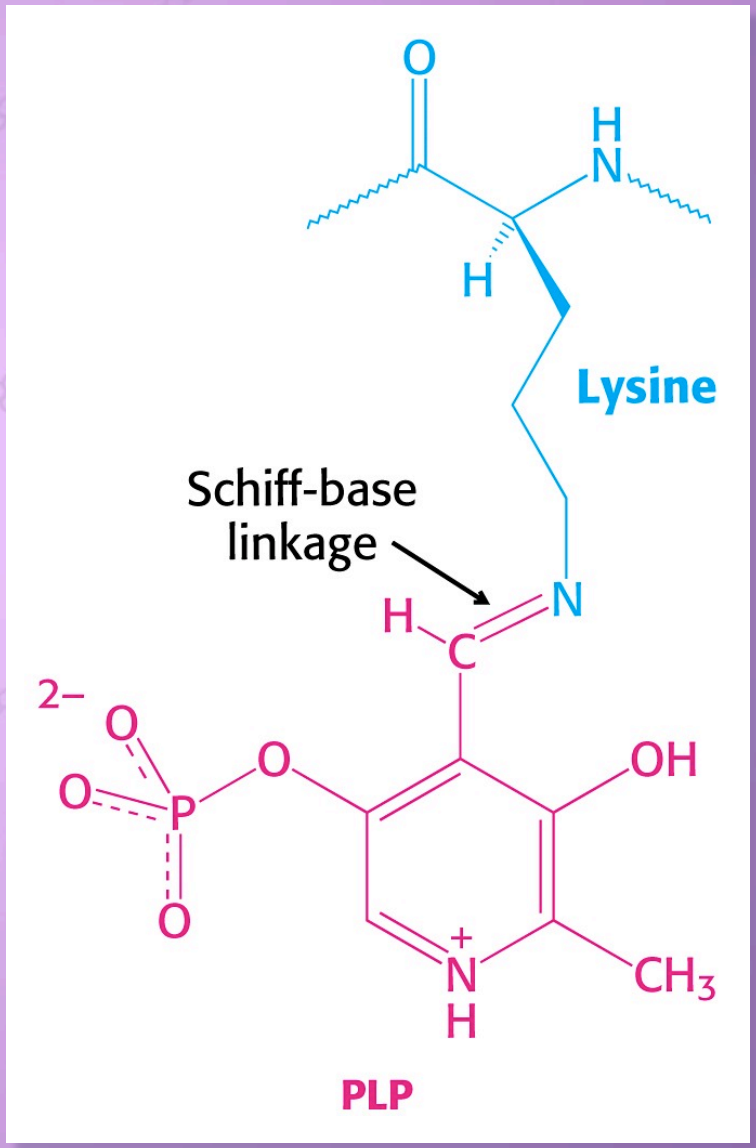


# 1.5 Mechanism for Phosphorolysis

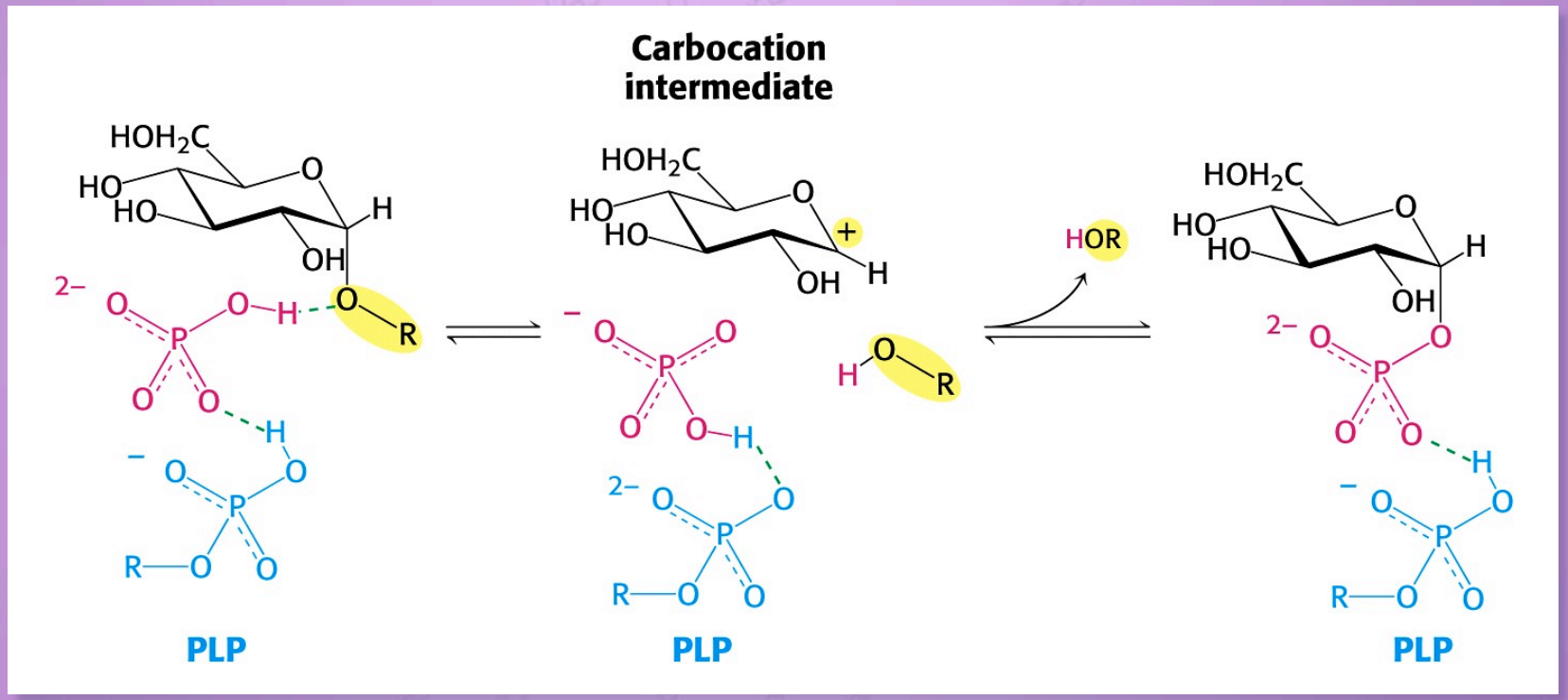


# 1.5 Mechanism for Phosphorolysis

Pyridoxyl phosphate coenzyme



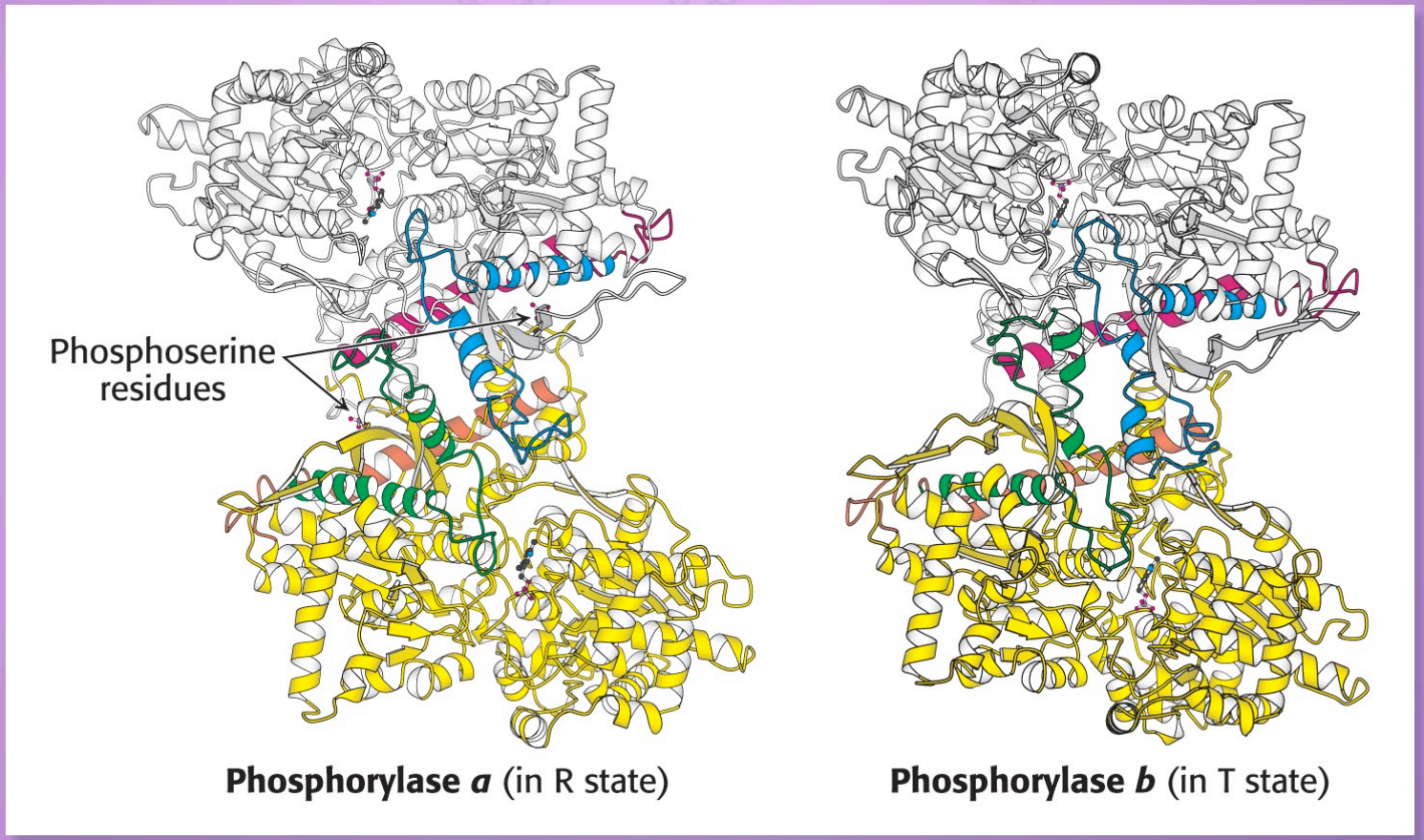
# 1.5 Mechanism for Phosphorolysis



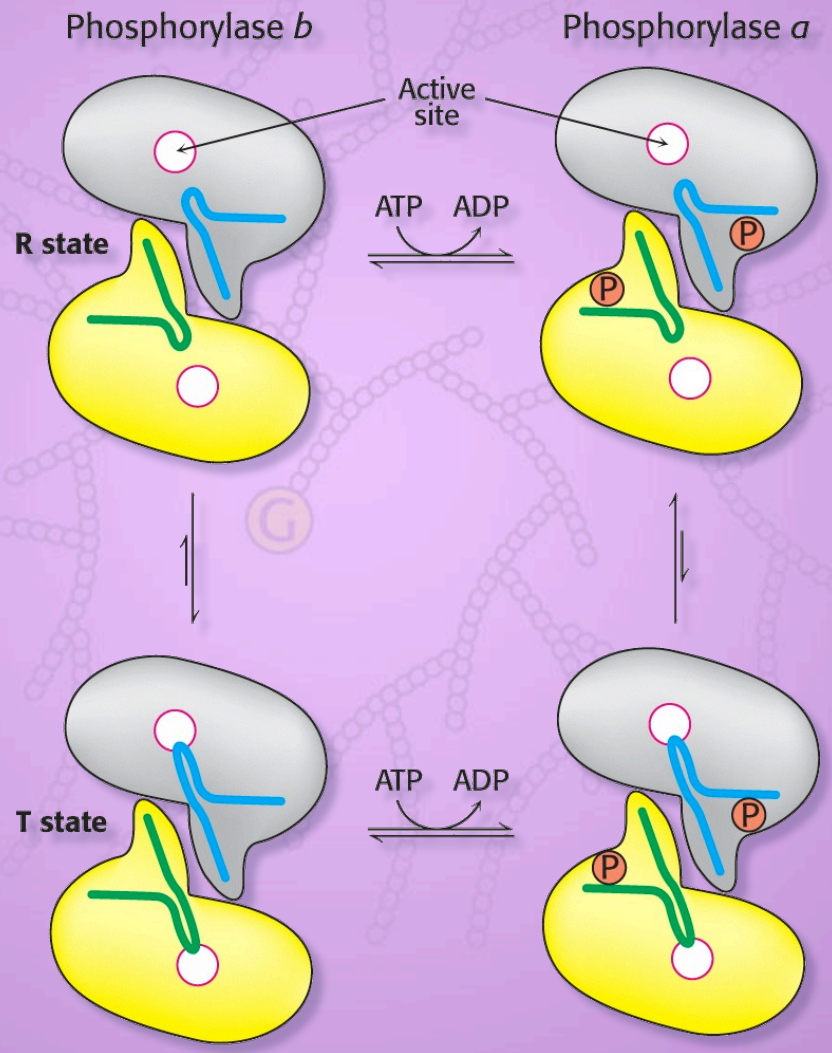
# 2. Regulation of Phosphorylase

- Phosphorylase is regulated by several allosteric effectors that signal the energy state of the cell
- It is also regulated by reversible phosphorylation in response to the hormones insulin, epinephrine, and glucagon

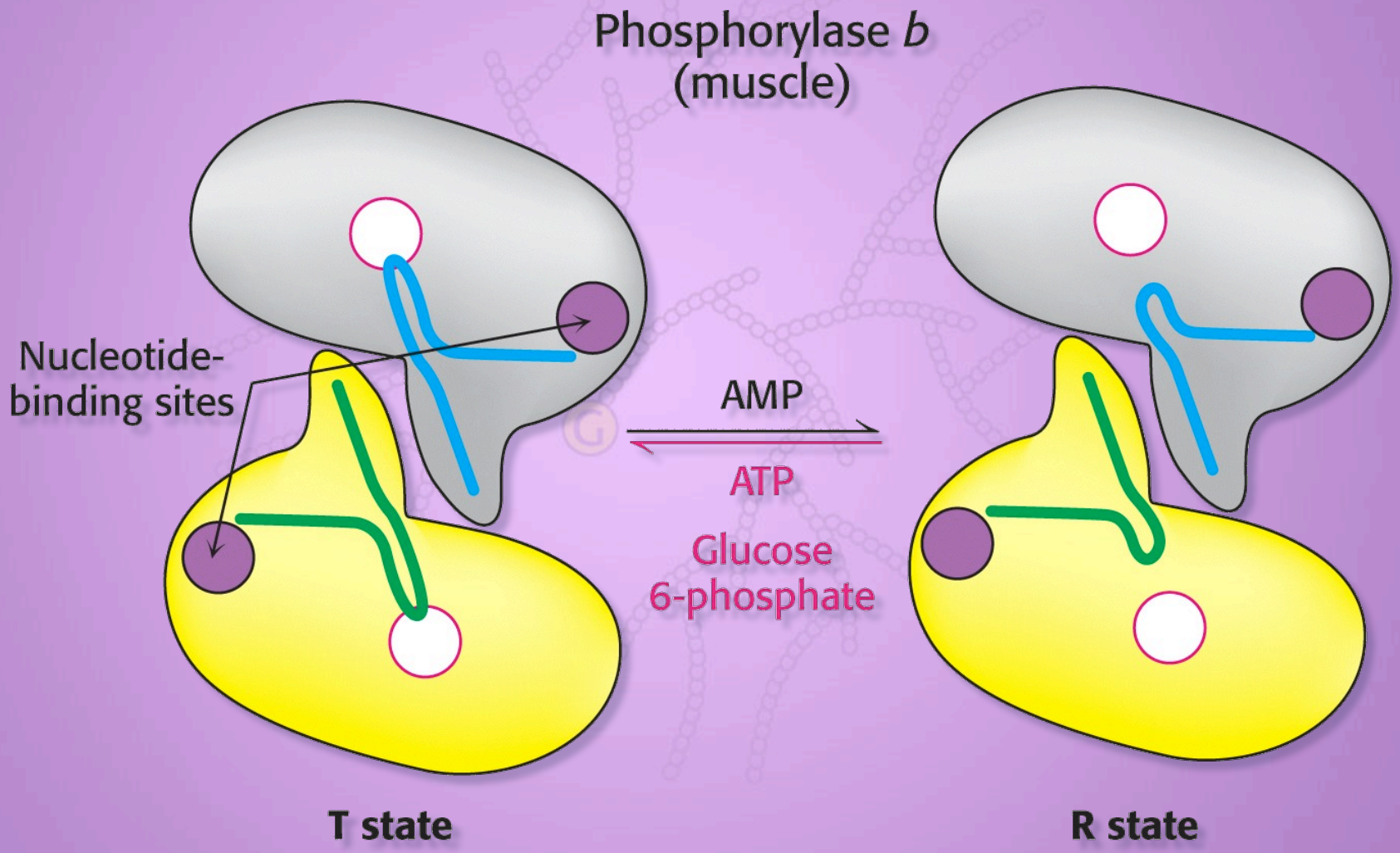
# 2.1 Muscle Phosphorylase



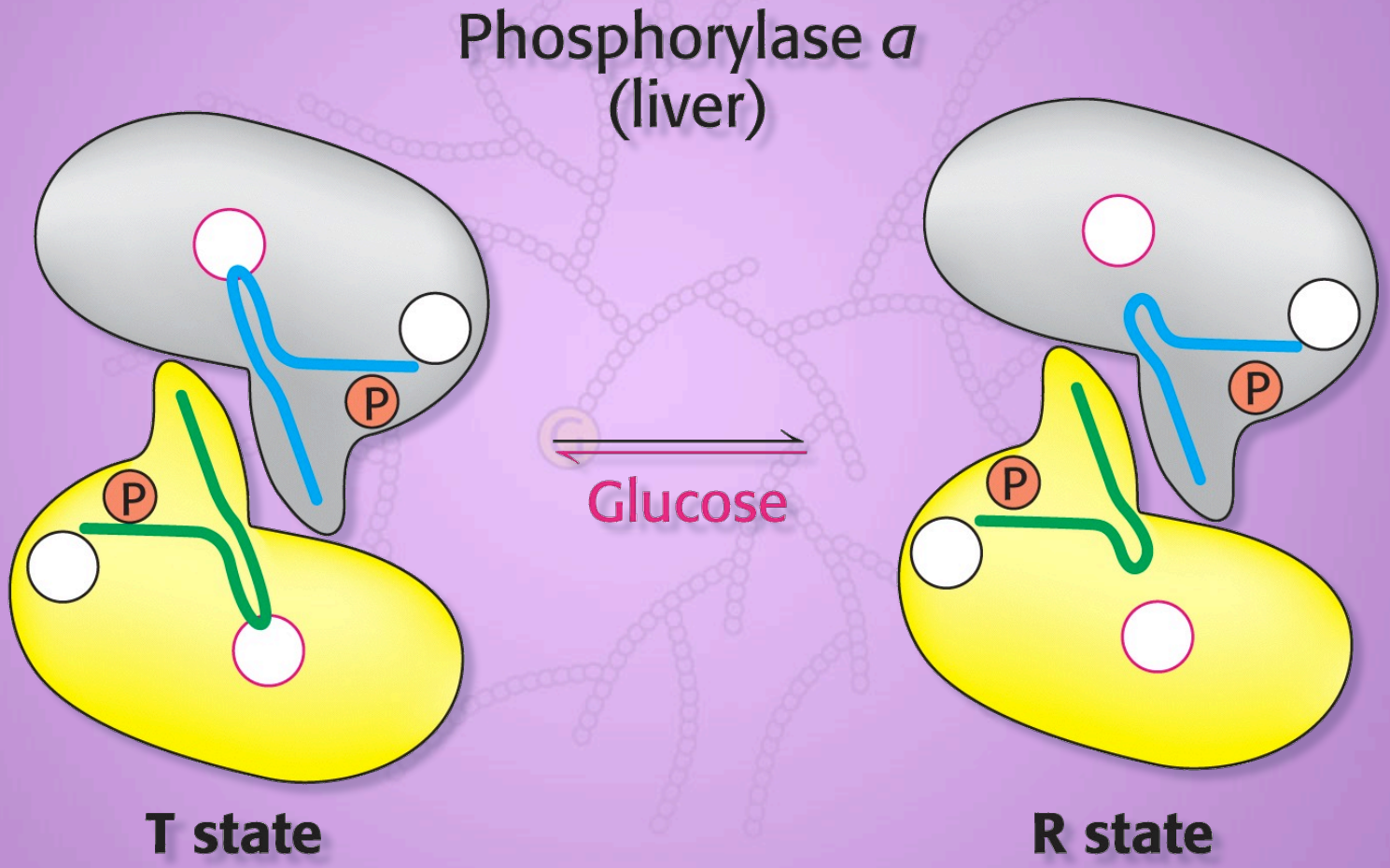
# 2.1 Muscle Phosphorylase



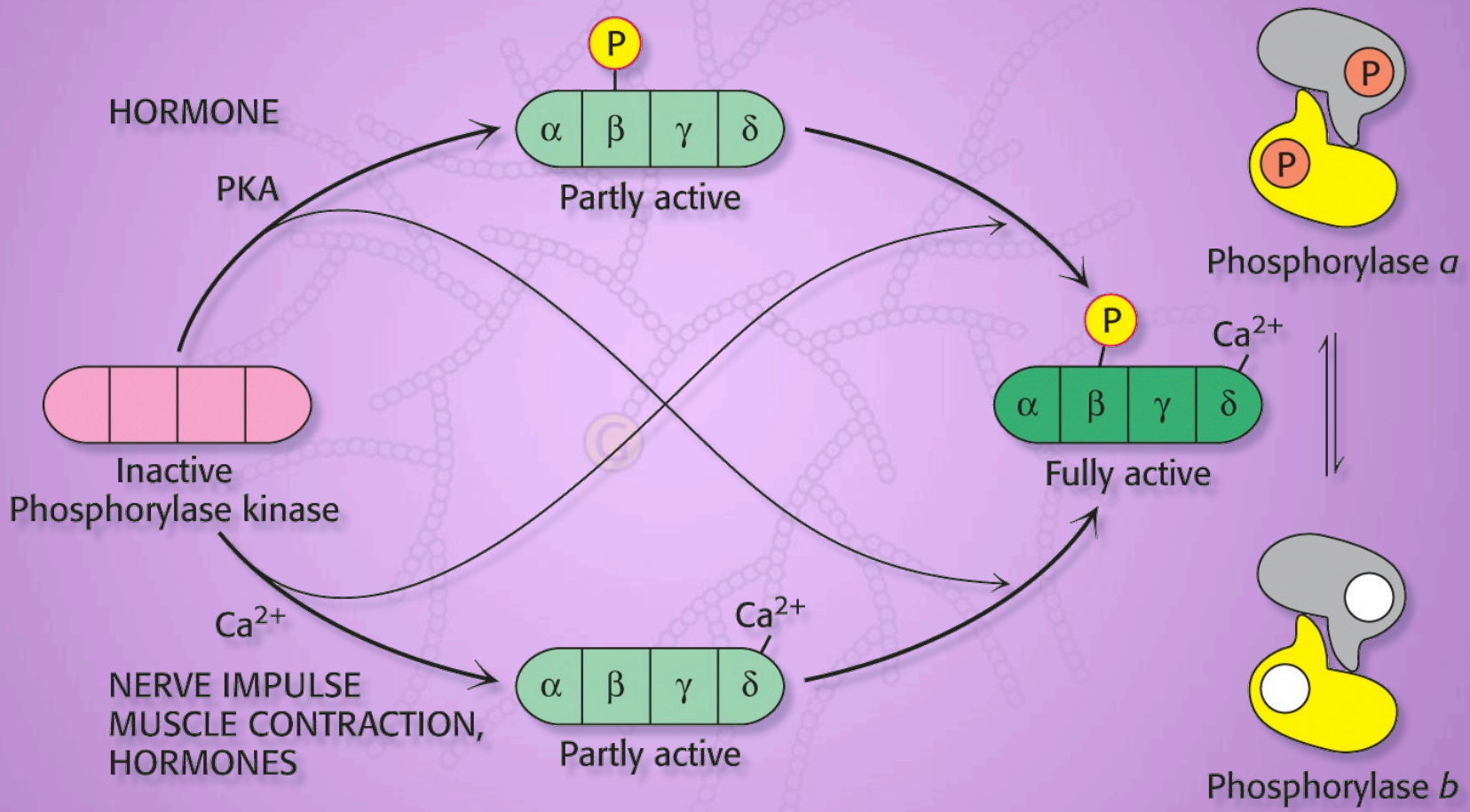
# 2.1 Muscle Phosphorylase



# 2.2 Liver Phosphorylase



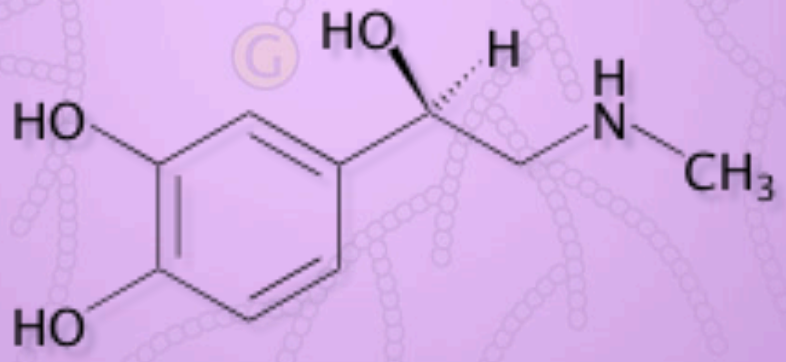
# 2.3 Phosphorylase Kinase



# 3. Epinephrine and Glucagon

Epinephrine and glucagon signal the need for glycogen breakdown

- Epinephrine stimulates glycogen breakdown to a greater extent in the muscle than the liver.

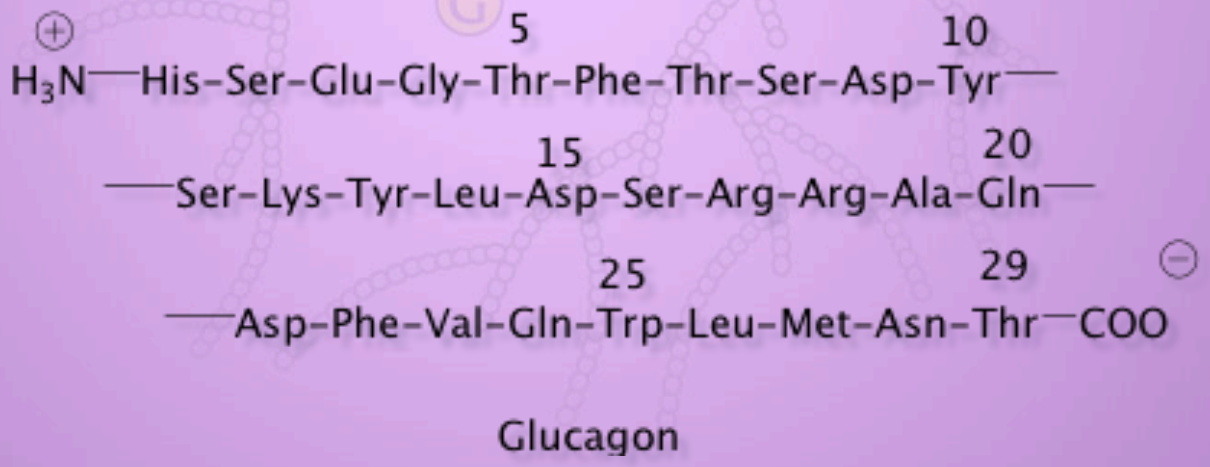



Epinephrine

# 3. Epinephrine and Glucagon

Epinephrine and glucagon signal the need for glycogen breakdown

- Glucagon is a peptide hormone that is secreted by the α-cells of the pancreases when blood glucose levels are low




Glucagon

# 3.1 G-protein Signal Transduction

## Epinephrine binds to a 7TM receptor

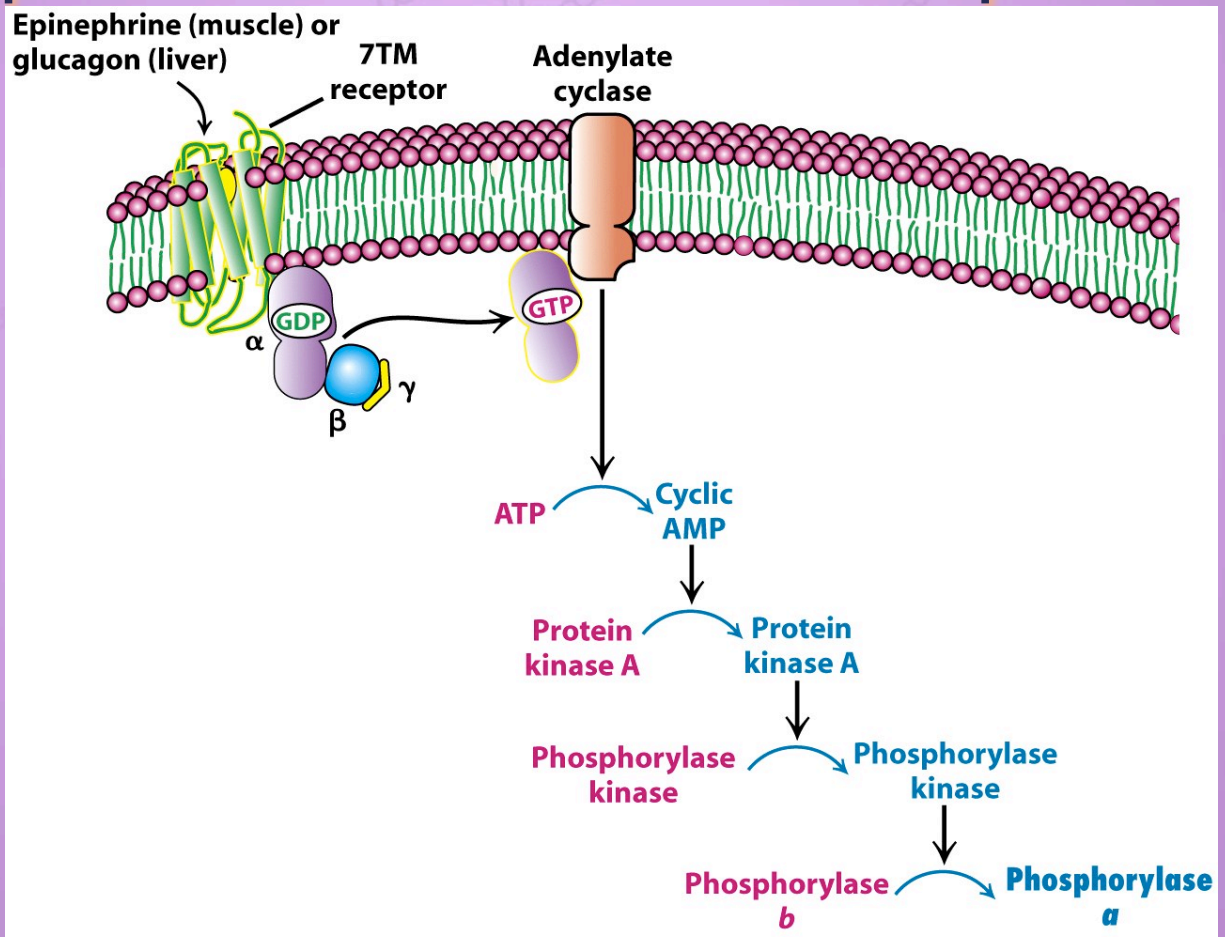
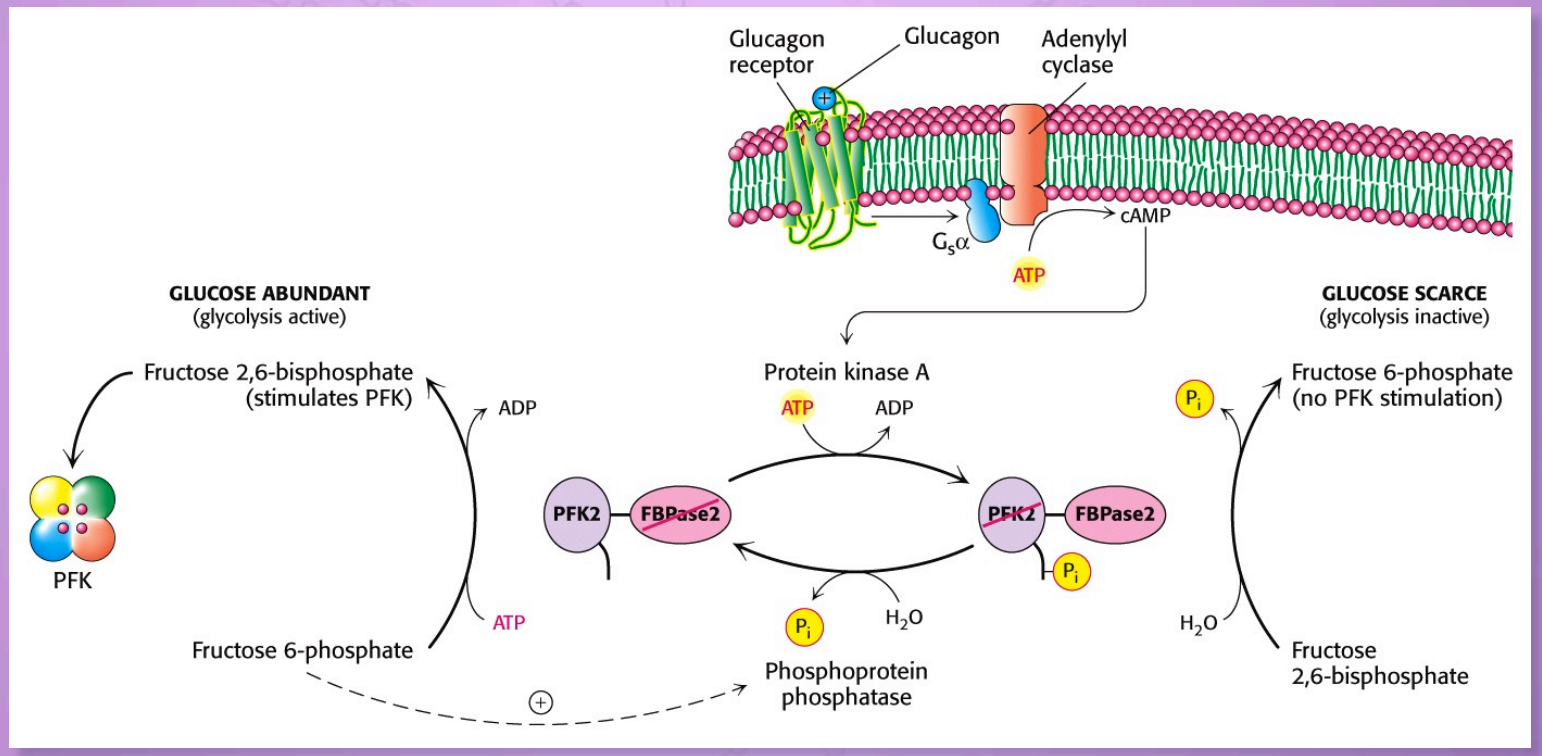



**Figure 21-15**
***Biochemistry, Sixth Edition***

# 3.1 G-protein Signal Transduction

## Glucagon also binds to a 7TM receptor

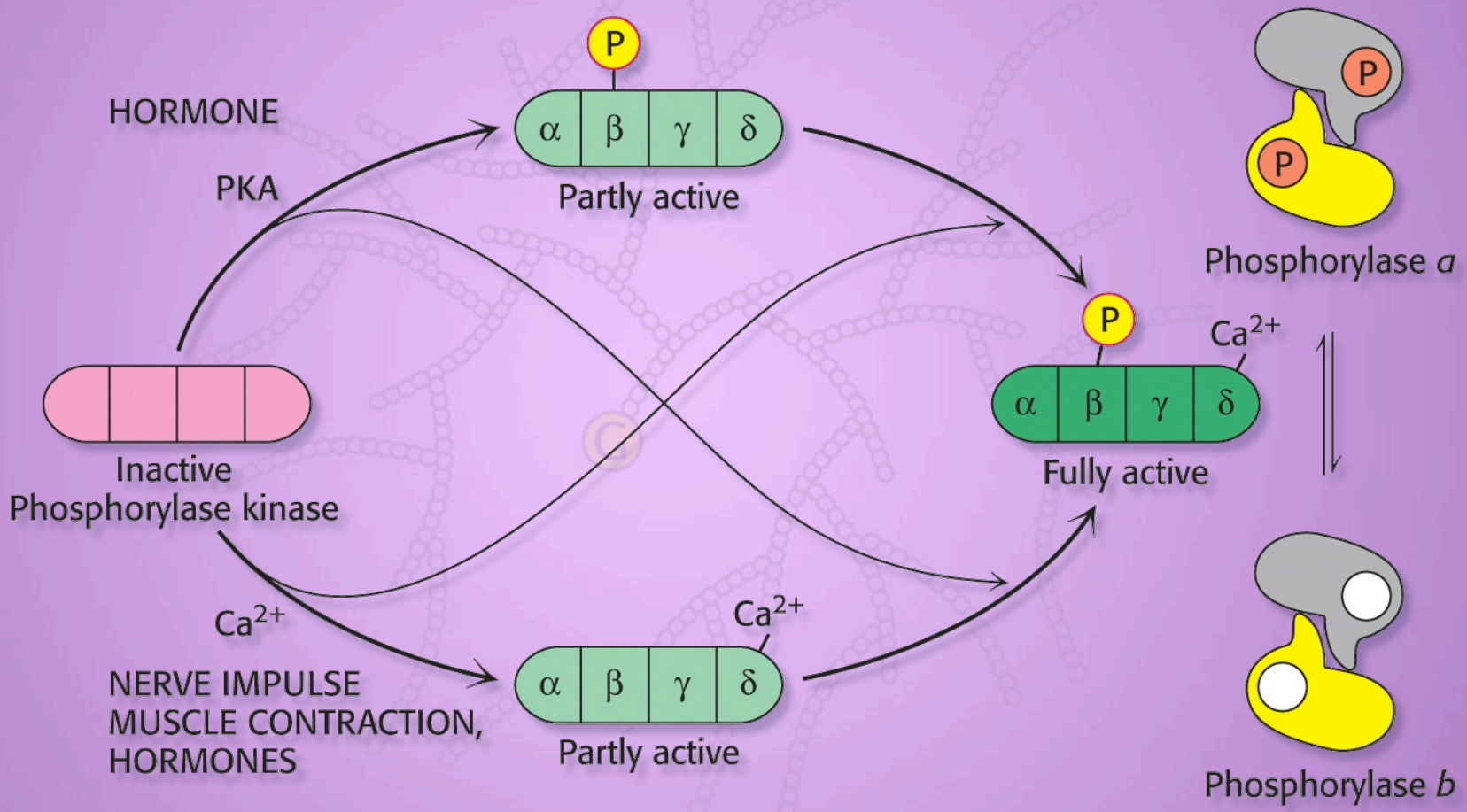


# 3.1 α-Adrenergic Receptors in Liver

In the liver, epinephrine also binds to α-adrenergic receptors, which activate the phosphoinositide signal transduction pathway

- Release of inositol 1,4,5-trisphosphate by phospholipase C induces the release of $Ca^{2+}$ from the ER.
- Binding of $Ca^{2+}$ to calmodulin partially activates phosphorylase kinase

# 3.1 α-Adrenergic Receptors in Liver



# 3.2 Turning It Off

Glycogen breakdown can also be rapidly turned off.

- GTPase activity of the G-proteins
- cAMP phosphodiesterase
- Protein kinase A also phophorylates the α-subunit of phosphorylase kinase. This makes it more susceptible to dephosphorylation (inactivation) by protein phosphatase 1 (PP1)

# 4. Glycogen Synthesis *vs* Degradation

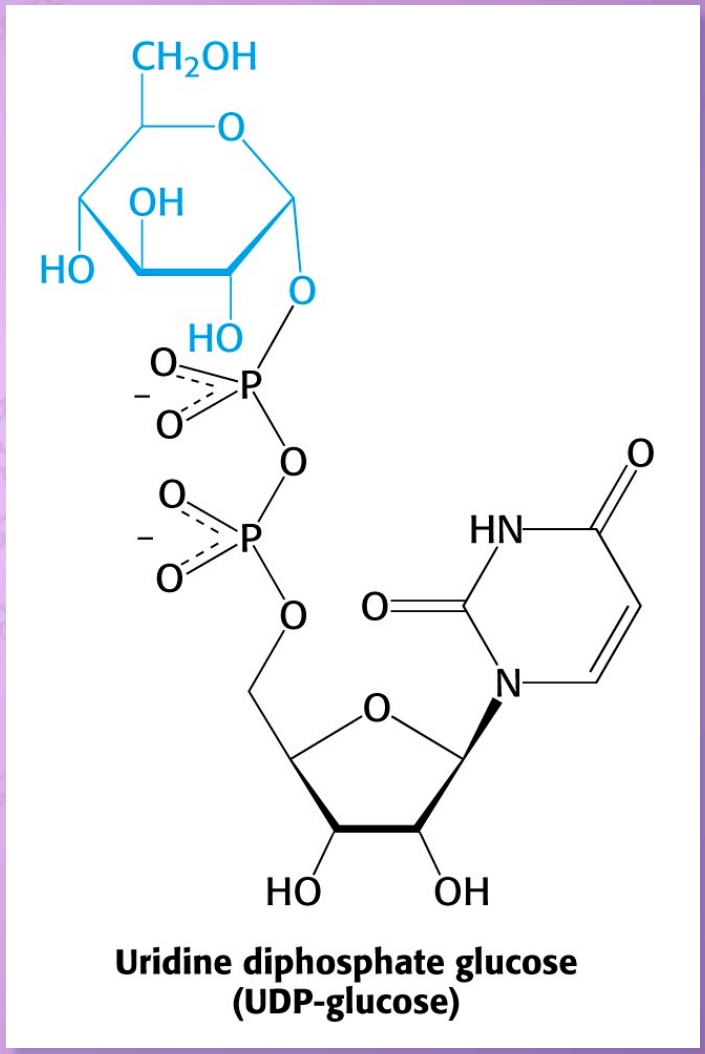
Different pathways are used for the synthesis and degradation.

$$\text{Glycogen}_{n+1} + P_i \longrightarrow \text{Glycogen}_n + \text{Glucose 1-phosphate}$$

$$\text{Glycogen}_n + \text{UDP-Glucose} \longrightarrow \text{Glycogen}_{n+1} + \text{UDP}$$

# 4.1 UDP-Glucose

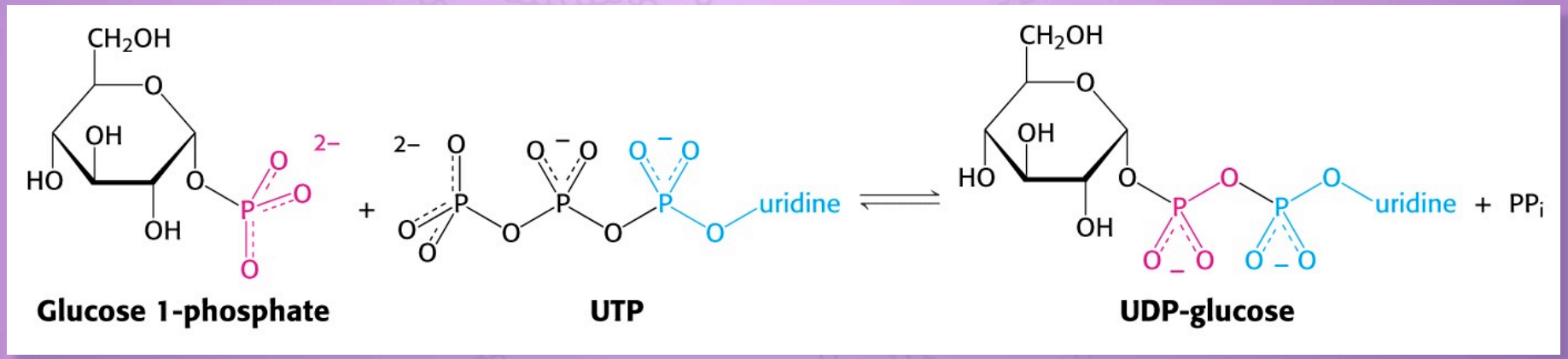
UDP-Glucose is an activated form of glucose




**Uridine diphosphate glucose (UDP-glucose)**

# 4.1 Glycogen Synthesis

## UDP-Glucose is an activated form of glucose



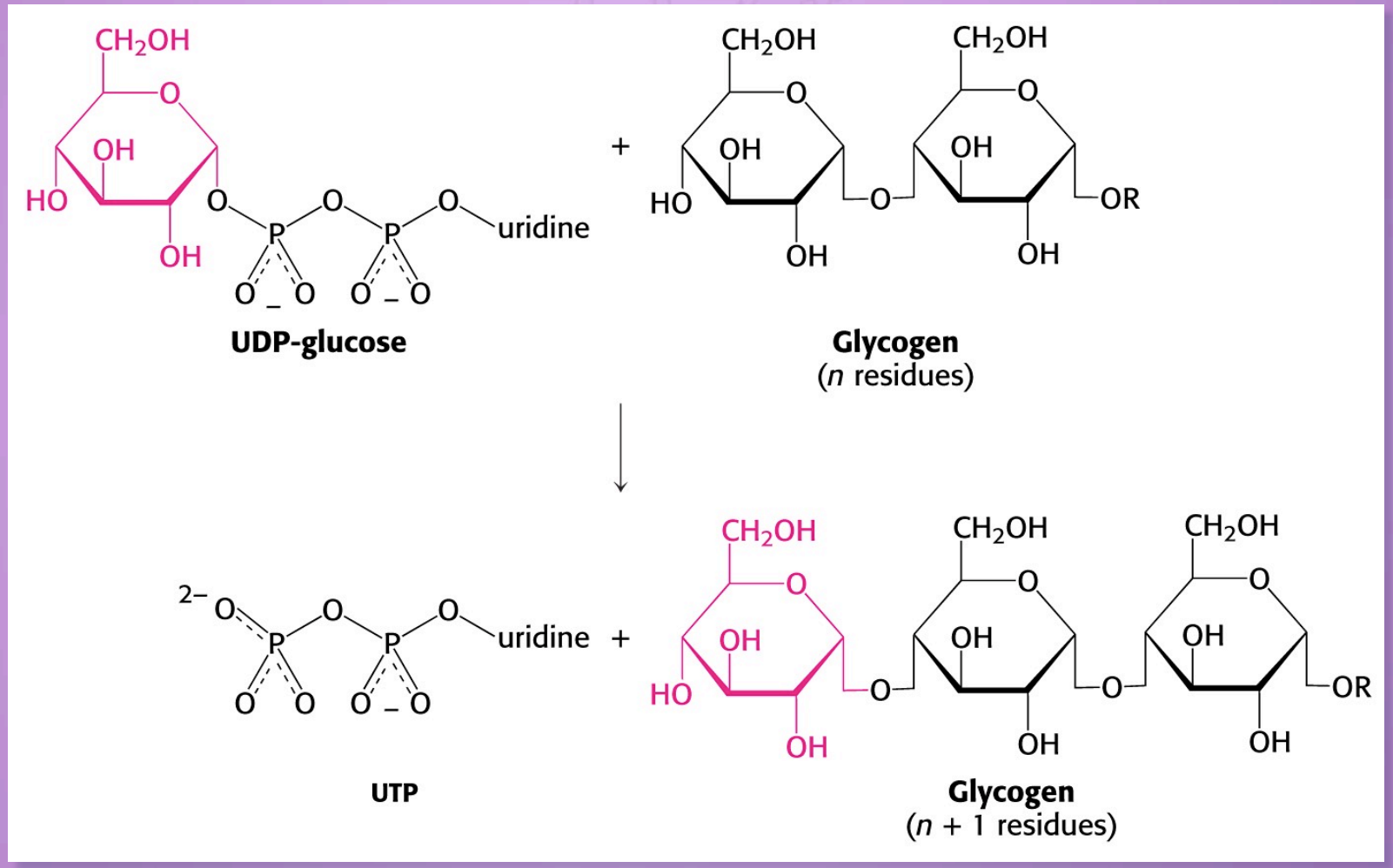

Glucose 1-phosphate + UTP $\rightleftharpoons$ UDB-Glucose + $PP_i$

$PP_i + H_2O \longrightarrow 2\ P_i$

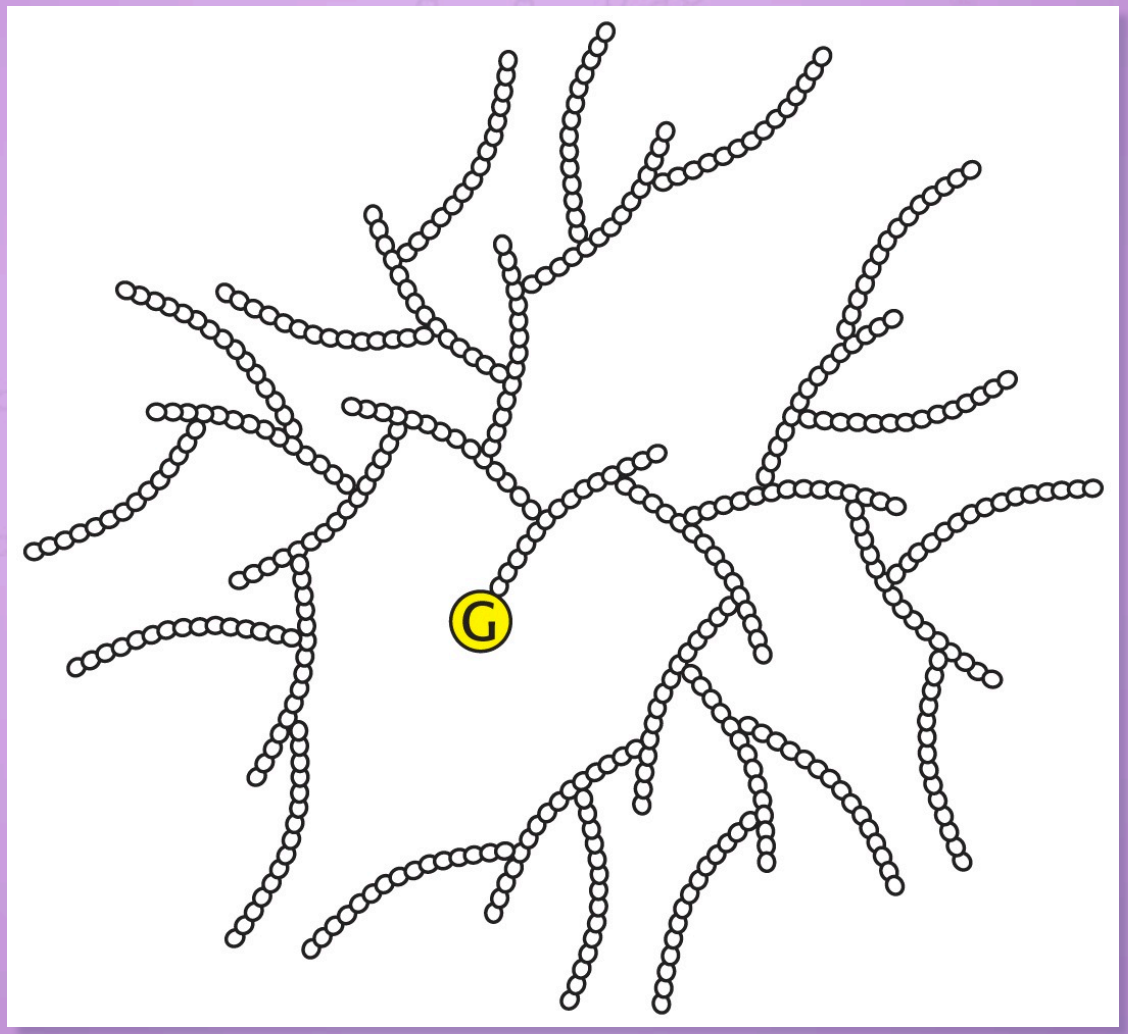
---

Glucose 1-phosphate + UTP + $H_2O \longrightarrow Glycogen_{n+1}$ + UDP + 2 $P_i$

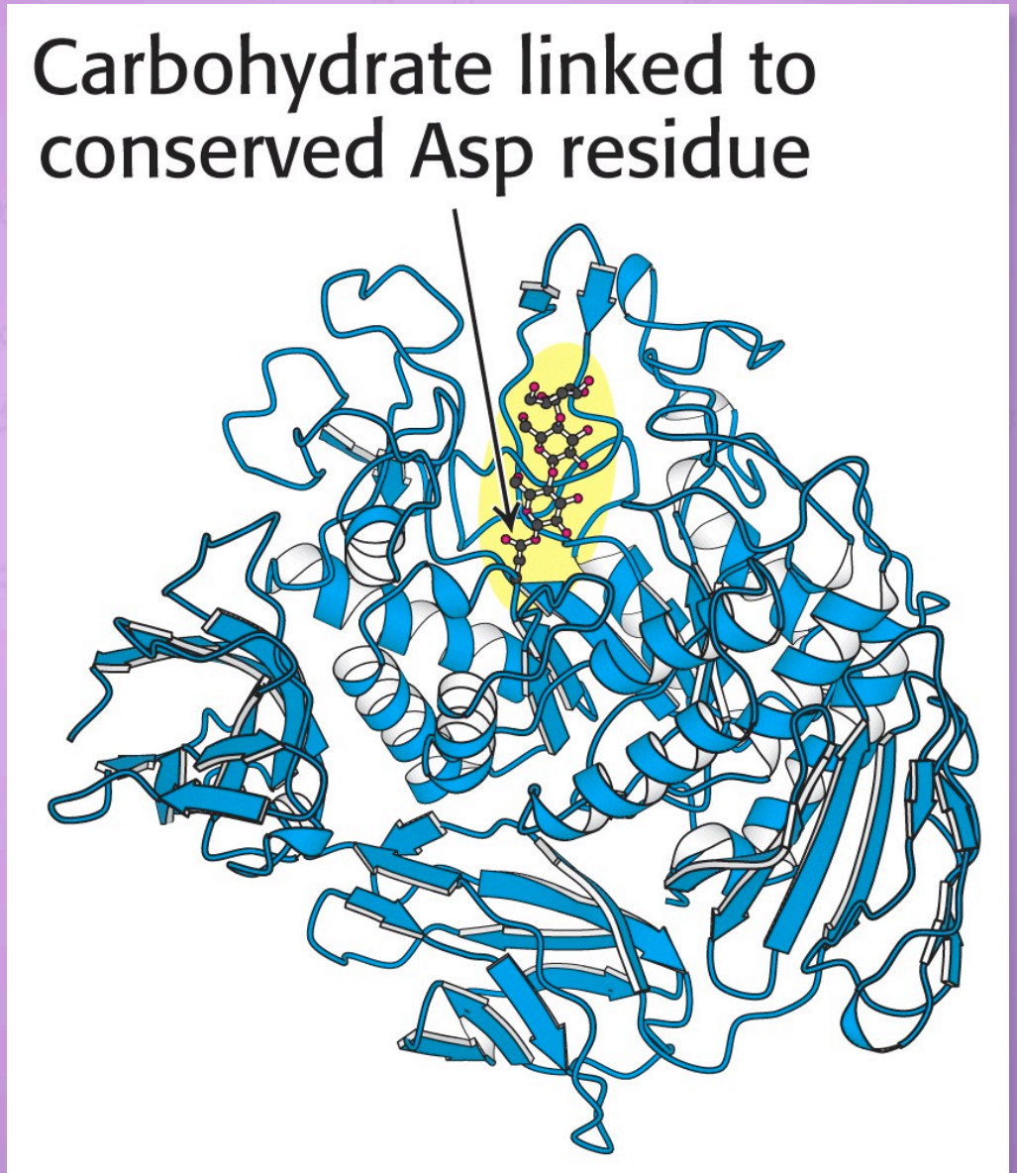
# 4.2 Glycogen Synthase



# 4.3 Branching Enzyme



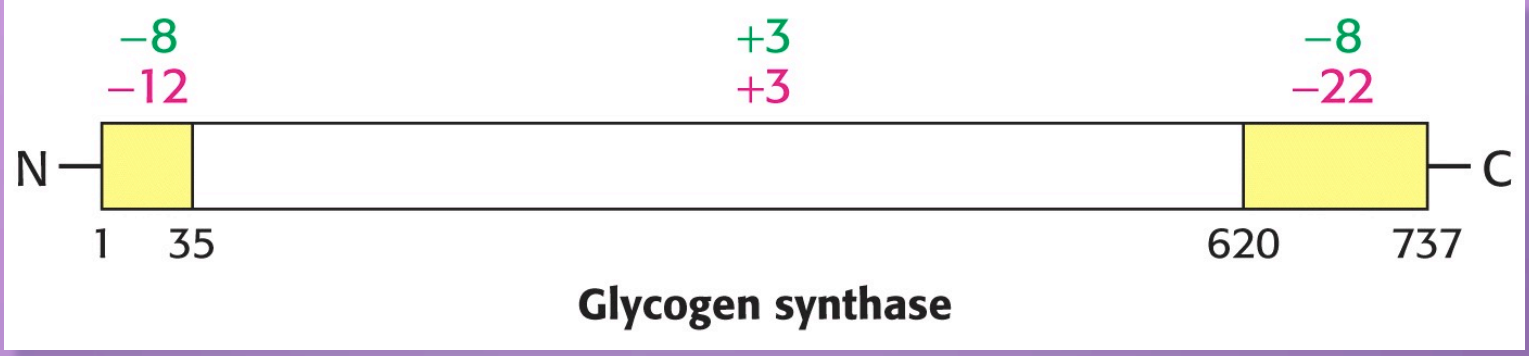
# 4.3 Branching Enzyme



# 4.4 Regulation of Glycogen Synthase

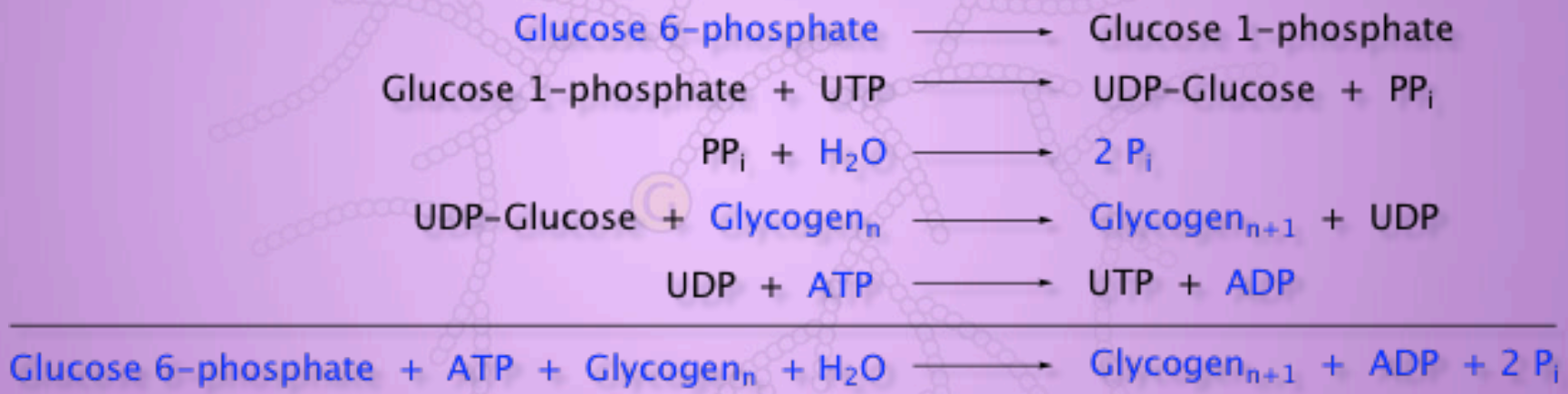
Glycogen Synthase is also regulated by phosphorylation

- Protein kinase A catalyses the phosphorylation
- Glycogen synthase a is the more active, dephosphorylated form
- Glycogen synthase b is the less active, phosphorylated form



# 4.5 Glycogen is an Efficient Storage Form of Glucose

Only 1 equivalent of ATP is used for storing each glucose unit



# 5. Reciprocal Regulation of Synthesis *vs* Breakdown

Regulation by hormone triggered c-AMP cascade:

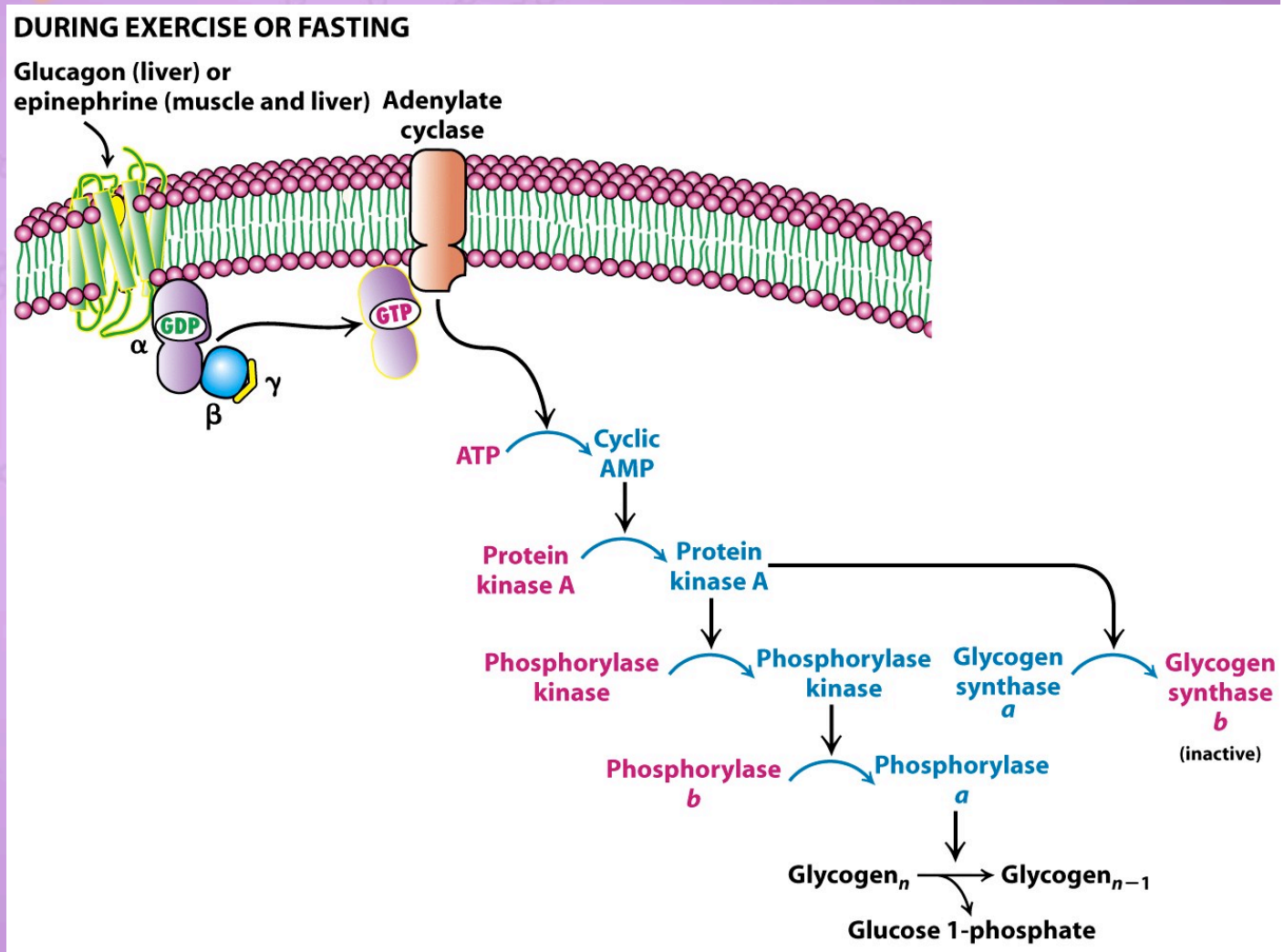



**Figure 21-17**
***Biochemistry, Sixth Edition***

# 5.1 Protein Phosphatase 1

## PP1 reverses regulatory effects of kinases

- PP1 dephosphorylates
  - glycogen phosphorylase
  - phosphorylase kinase
  - glycogen synthase

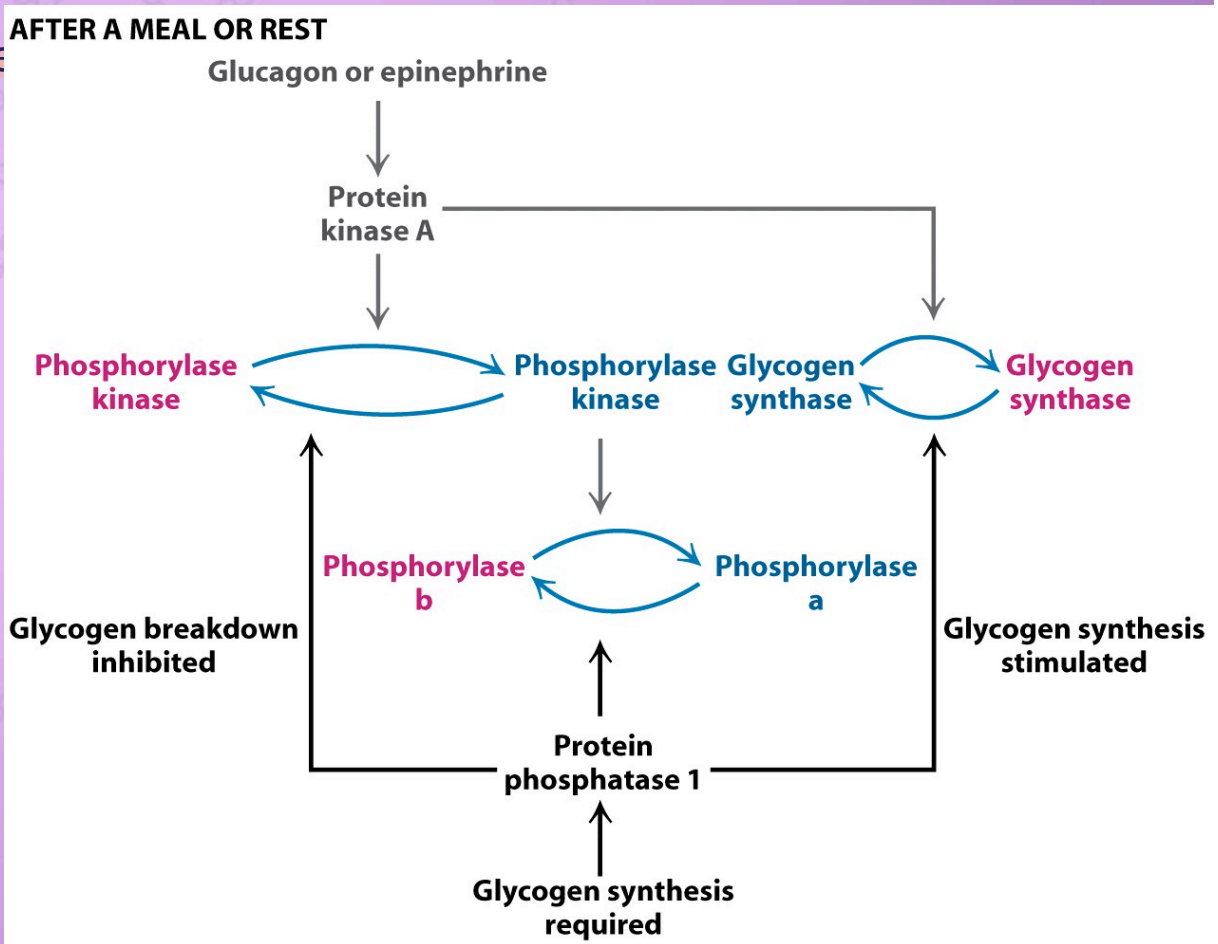



**Figure 21-18**
***Biochemistry, Sixth Edition***

# 5.1 Protein Phosphatase 1

## PP1 is inactivated by the hormone-triggered c-AMP cascade

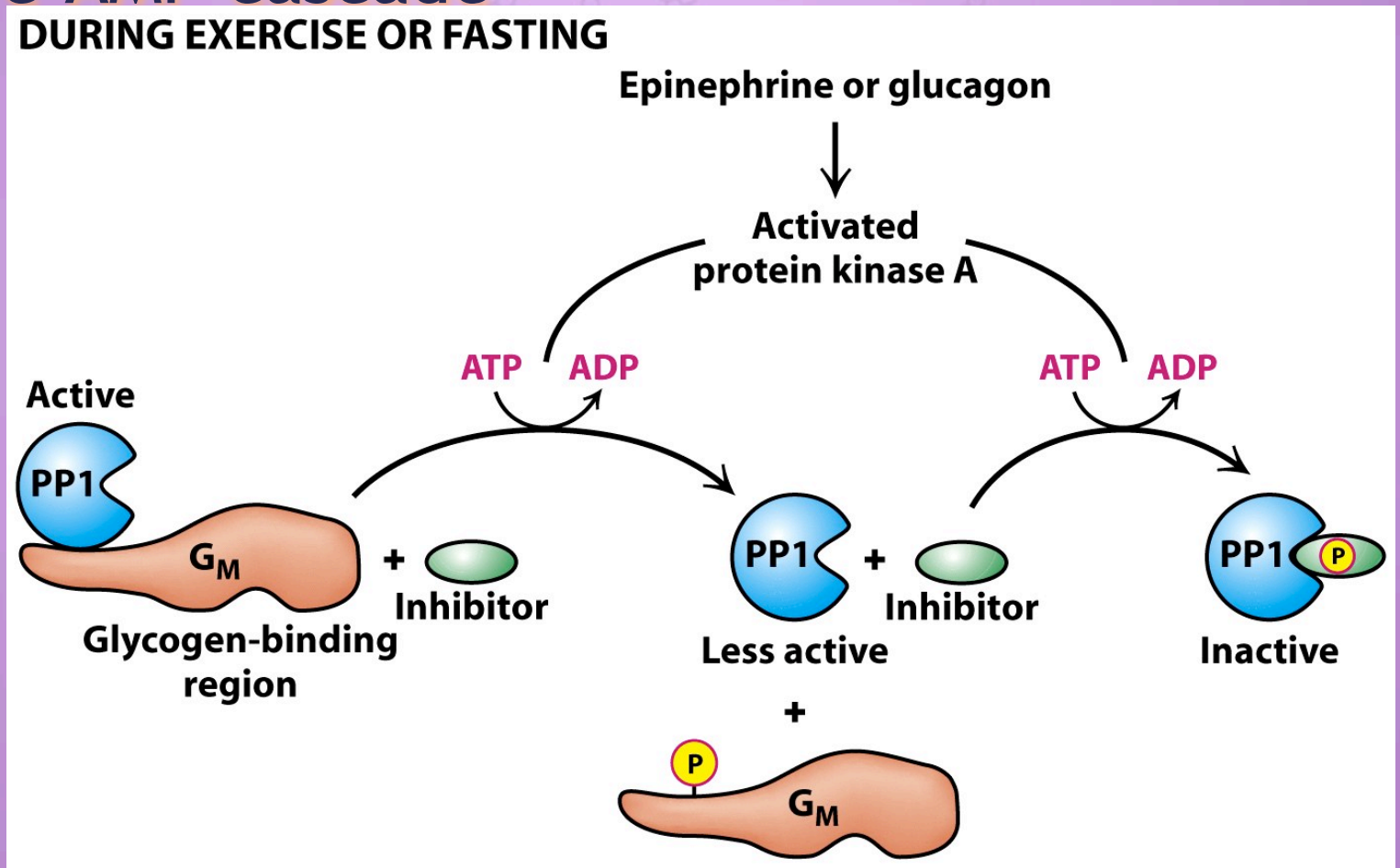





Figure 21-19
*Biochemistry, Sixth Edition*

# 5.2 Insulin Activation

## The insulin-triggered tyrosine kinase cascade

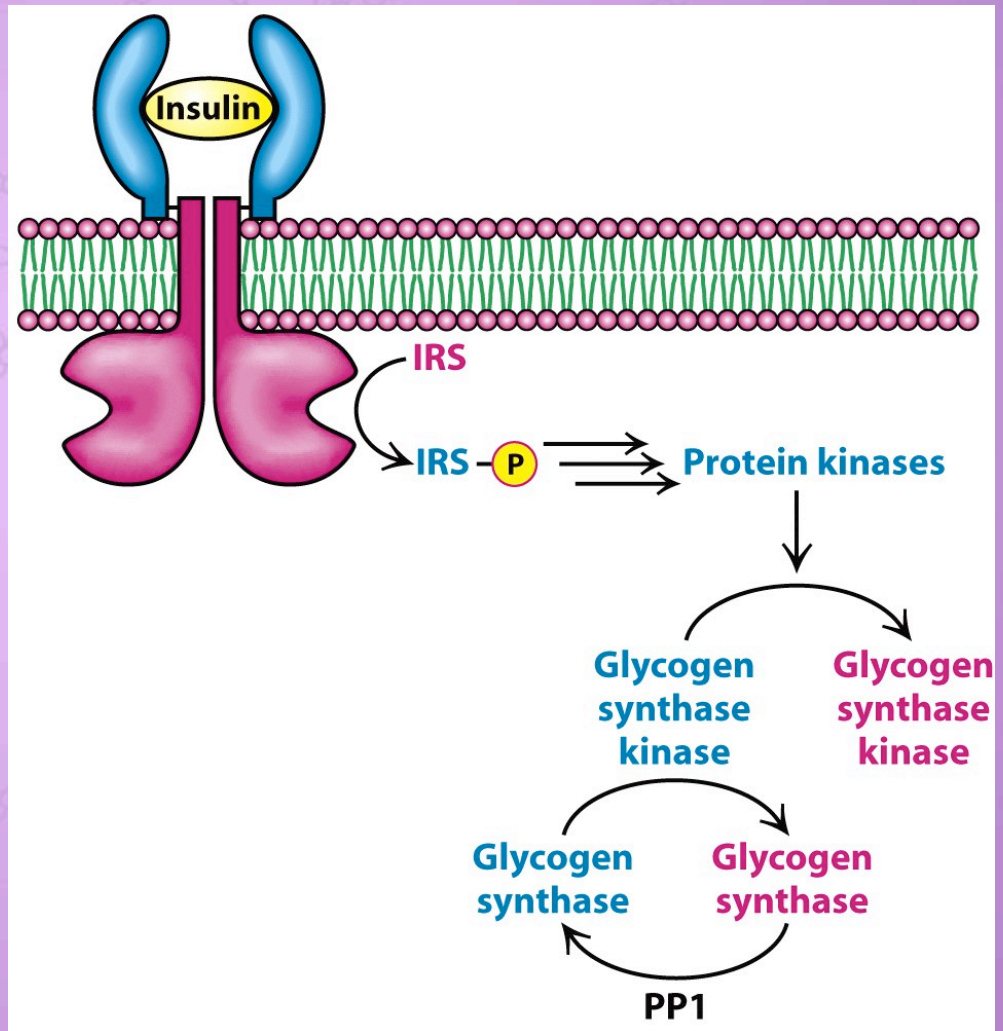
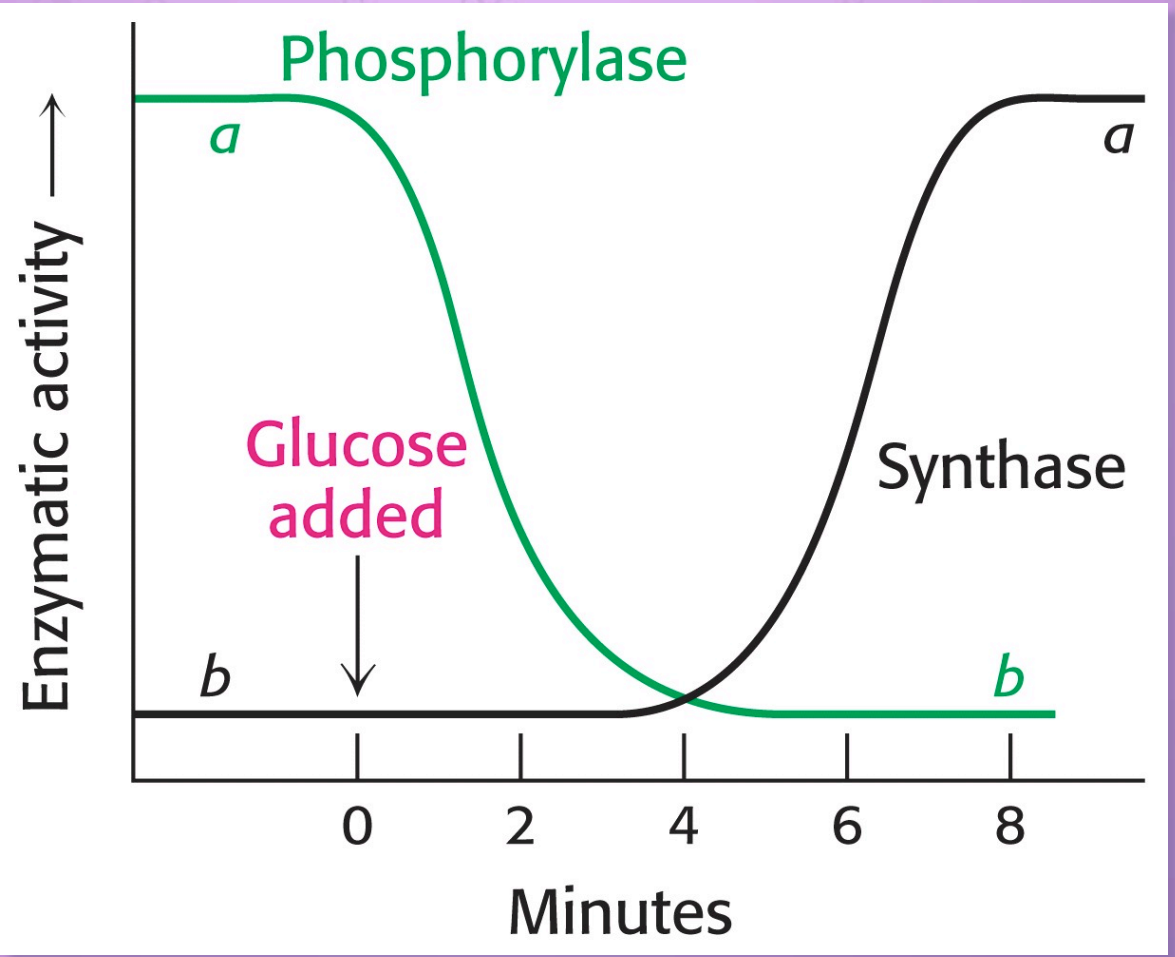



**Figure 21-20**
***Biochemistry, Sixth Edition***

# 5.3 Regulation by Blood Glucose

## Blood glucose levels regulate glycogen metabolism in the liver



# 5.3 Regulation by Blood Glucose

## Glucose allosterically converts phosphorylase a from the R-state to the T-State

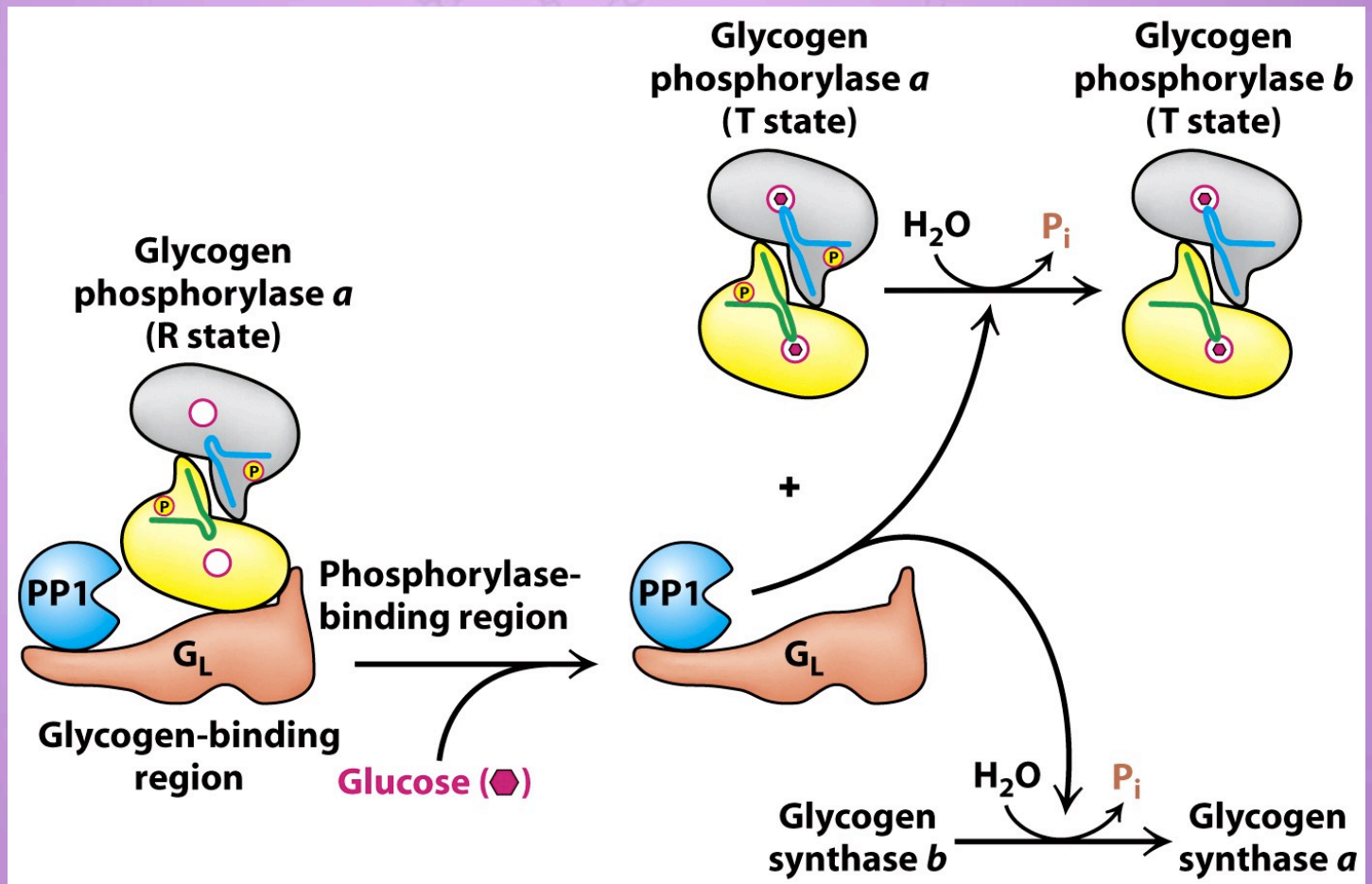



Figure 21-22
*Biochemistry, Sixth Edition*

# Diseases of Glycogen

**TABLE 21.1 Glycogen-storage diseases**

| Type | Defective enzyme | Organ affected | Glycogen in the affected organ | Clinical features |
|---|---|---|---|---|
| I Von Gierke disease | Glucose 6-phosphatase or transport system | Liver and kidney | Increased amount; normal structure. | Massive enlargement of the liver. Failure to thrive. Severe hypoglycemia, ketosis, hyperuricemia, hyperlipemia. |
| II Pompe disease | α-1,4-Glucosidase (lysosomal) | All organs | Massive increase in amount; normal structure. | Cardiorespiratory failure causes death, usually before age 2. |
| III Cori disease | Amylo-1,6-glucosidase (debranching enzyme) | Muscle and liver | Increased amount; short outer branches. | Like type I, but milder course. |
| IV Andersen disease | Branching enzyme (α-1,4 ⟶ α-1,6) | Liver and spleen | Normal amount; very long outer branches. | Progressive cirrhosis of the liver. Liver failure causes death, usually before age 2. |
| V McArdle disease | Phosphorylase | Muscle | Moderately increased amount; normal structure. | Limited ability to perform strenuous exercise because of painful muscle cramps. Otherwise patient is normal and well developed. |
| VI Hers disease | Phosphorylase | Liver | Increased amount. | Like type I, but milder course. |
| VII | Phosphofructokinase | Muscle | Increased amount; normal structure. | Like type V. |
| VIII | Phosphorylase kinase | Liver | Increased amount; normal structure. | Mild liver enlargement. Mild hypoglycemia. |

**Note: Types I through VII are inherited as autosomal recessives. Type VIII is sex linked.**

**Table 21-1**
***Biochemistry, Sixth Edition***