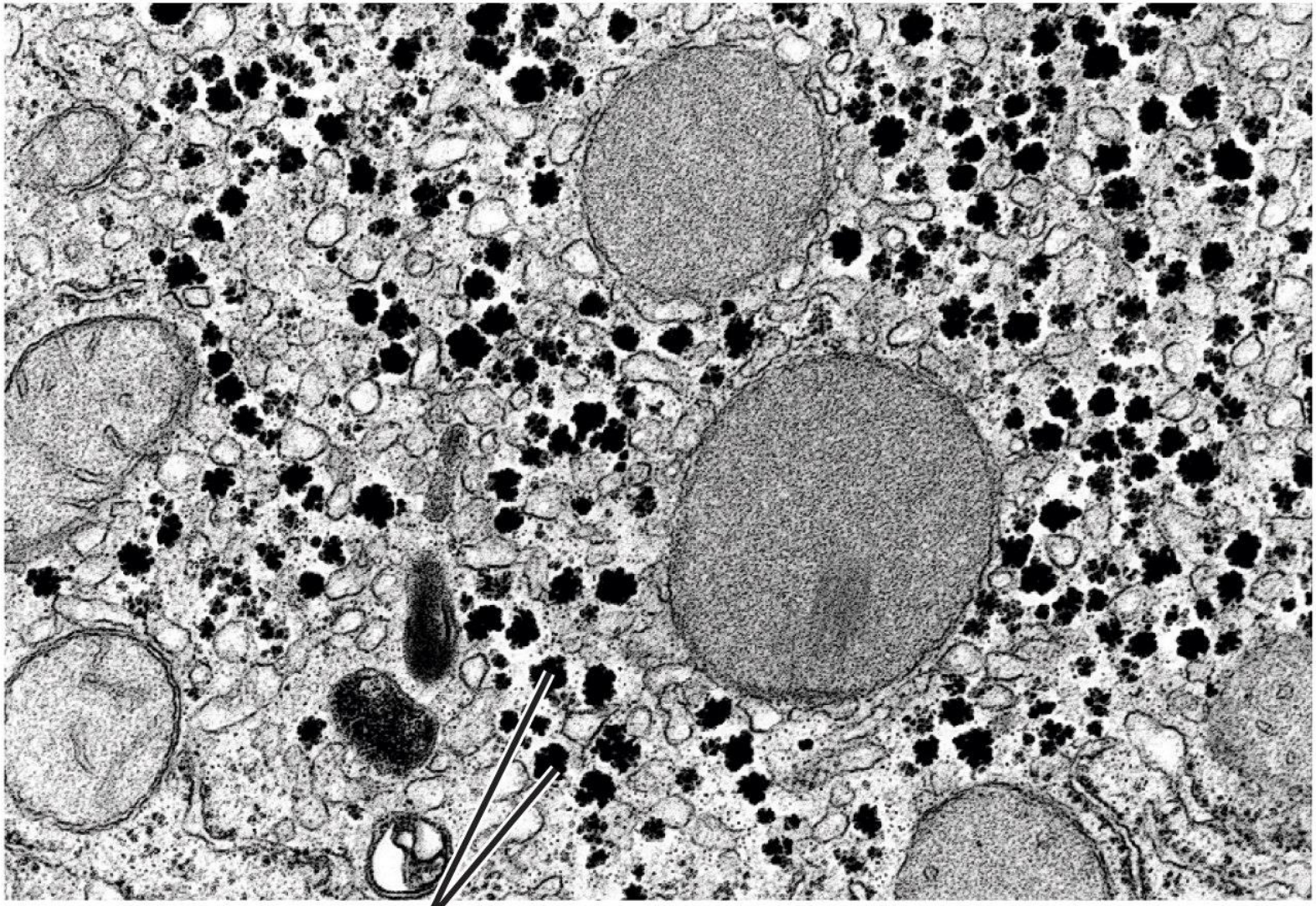
Glycogen Metabolism

Glycogenolysis: catabolism of glycogen

Glycogenesis: anabolism / biosynthesis of glycogen

- Glycogen represent a stored form of glucose & energy that is quickly mobilized by hormones.
- Total glucose in body fluids has an energy content of ~ 40 kcal
- Total body glycogen has an energy content of ~ 600 kcal.
- Stored in liver (5-6%) by weight & muscle (1-2%) by weight.
- Since muscle mass is >> liver mass, quantity of muscle glycogen is greater. Muscle = 40% of body weight.
- Stored in the cytosol in the form of glycogen granules which contain the enzyme that catalyzed glycogenolysis, glycogenesis, plus regulatory enzymes.



Glycogen granules

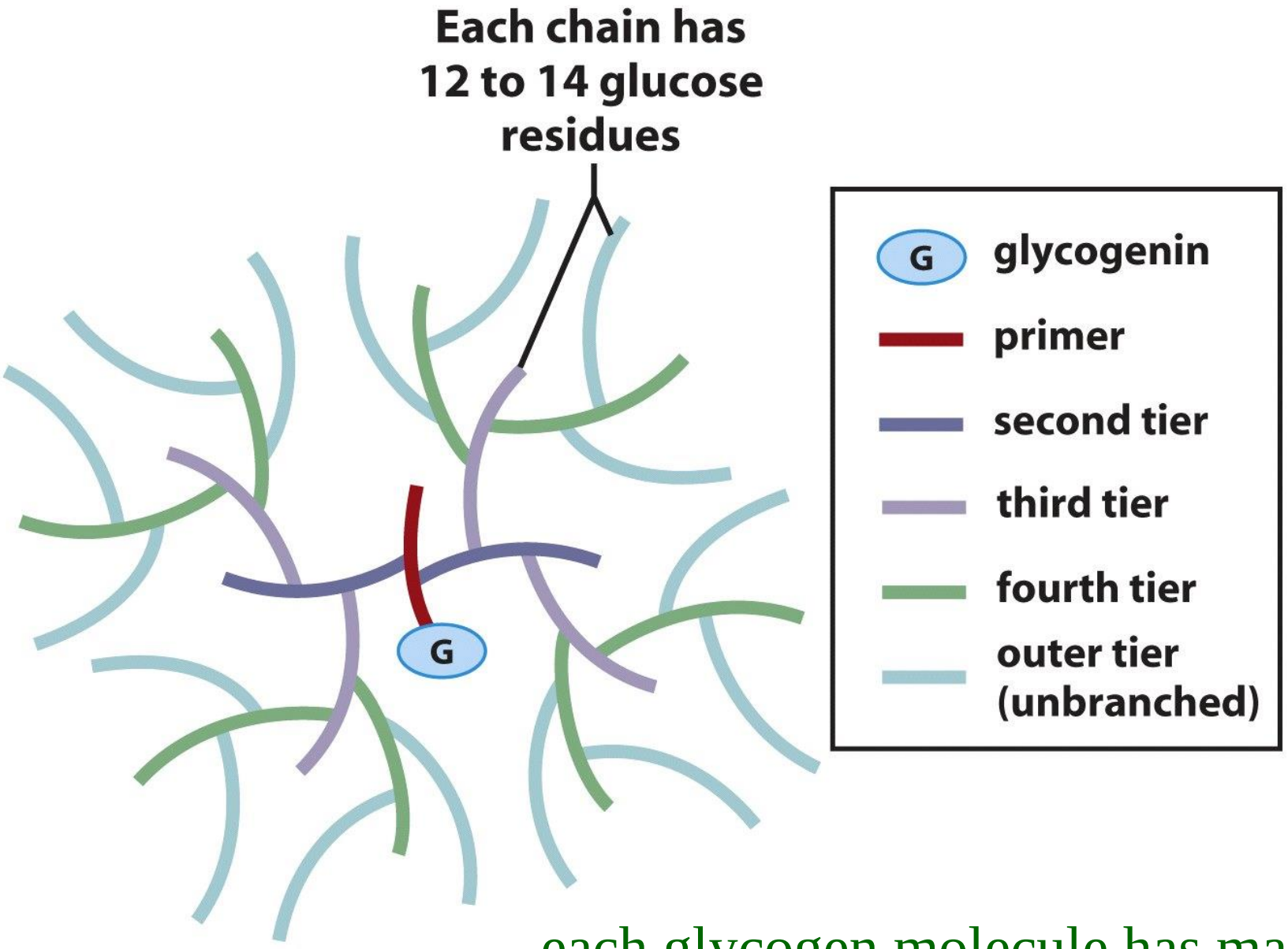
Granules contain enzymes that catalyze synthesis & degradation of glycogen & their regulatory enzymes

differ than multienzyme complex:

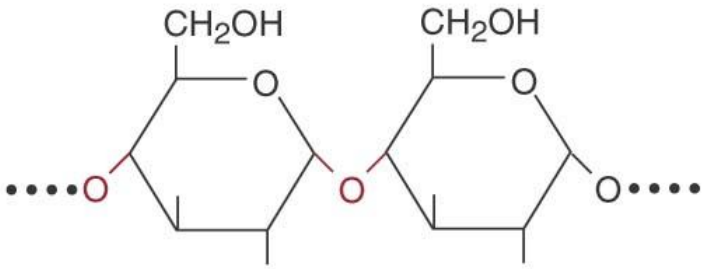
Bound enzymes are not present in defined ratios + granules are less organized than in complex.

Glycogen Metabolism:

1) Regulate blood glucose levels (reservoir of glucose)
2) Synthesis & degradation distinct pathways
3) Hormonal regulation is well understood
4) Enzymatic regulation by phosphorylation dephosphorylation.
5) Inherited enzyme defects impaired glycogen metabolism.

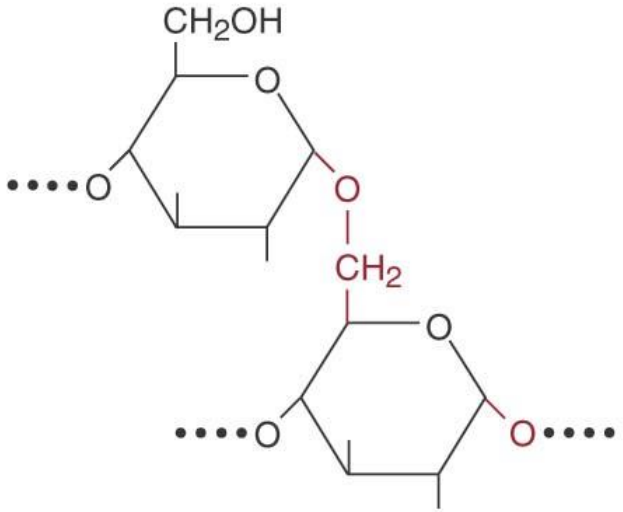


each glycogen molecule has many non-reducing ends



α-1,4-Glycosidic linkage

(a)



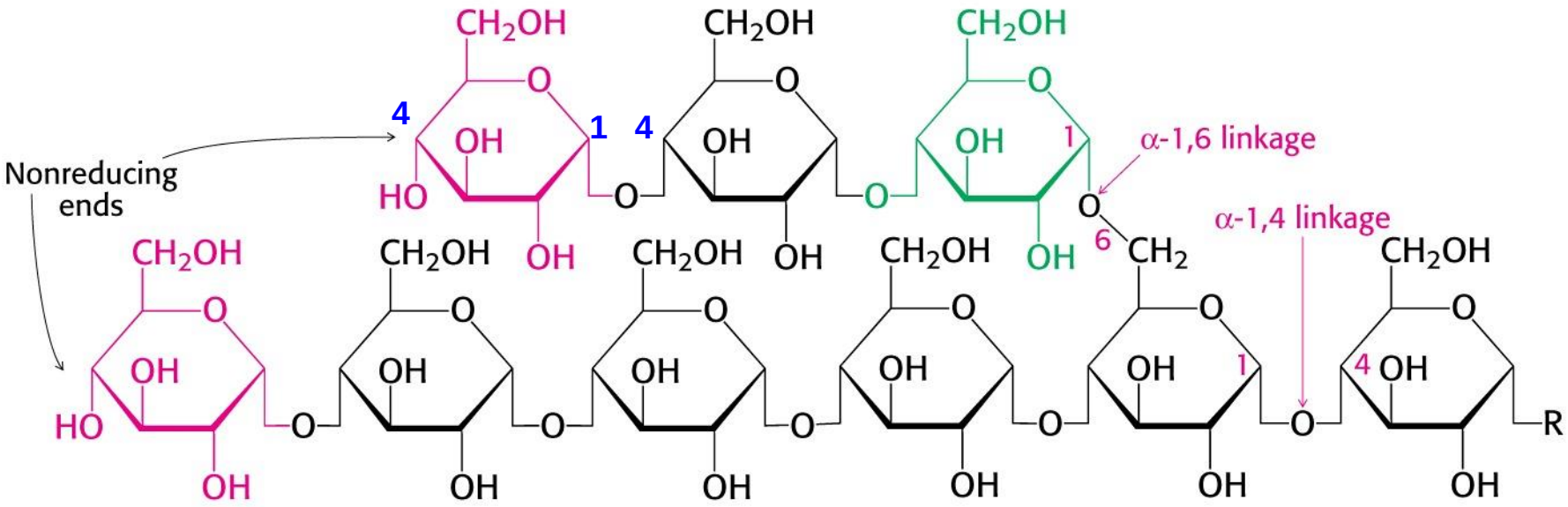
α-1,6-Glycosidic linkage

(b)

Figure 15.47. Two types of linkage between glucose molecules are present in glycogen.

Textbook of Biochemistry With Clinical Correlations, *Sixth Edition*, Edited by Thomas M. Devlin. Copyright © 2006 John Wiley & Sons, Inc.

Structure of Two Outer Branches of a Glycogen Particle

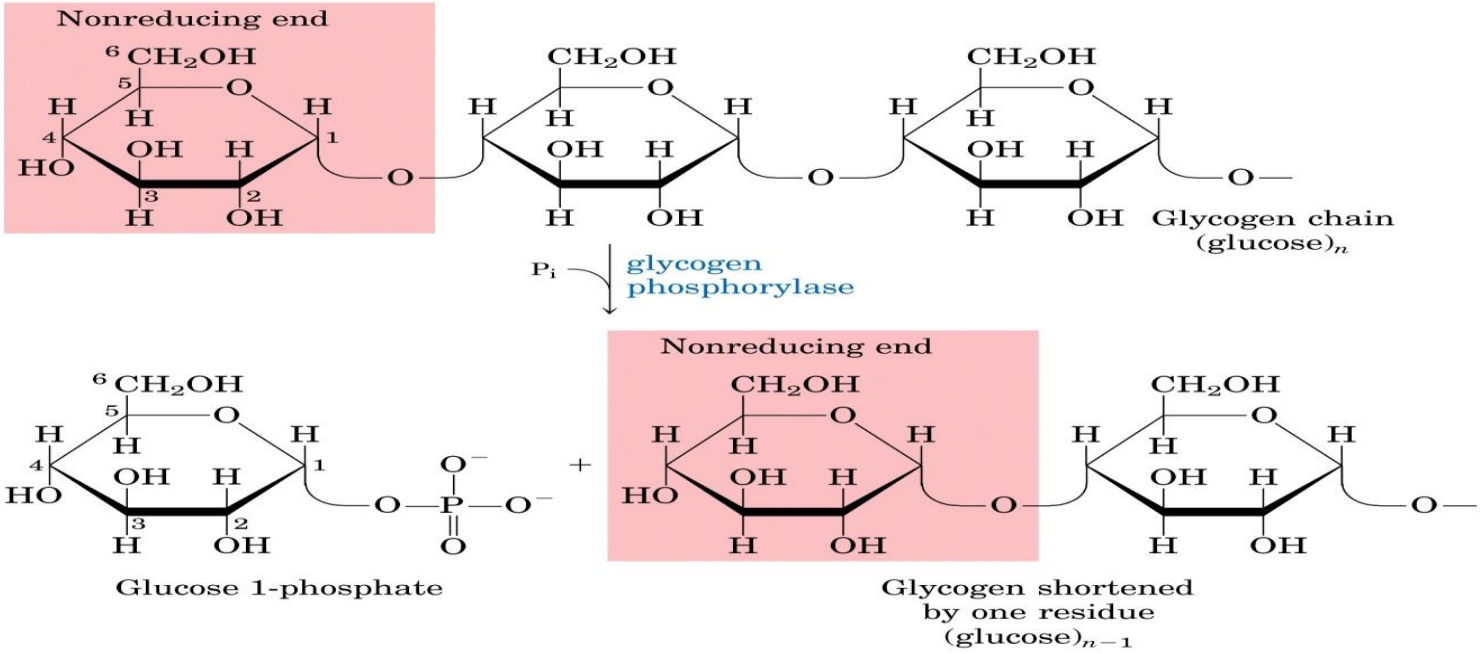


3 Enzymes of Glycogen Breakdown (Glycogenolysis)

- Glycogen Phosphorylase
- Glycogen Debranching Enzyme
- Phosphoglucomutase

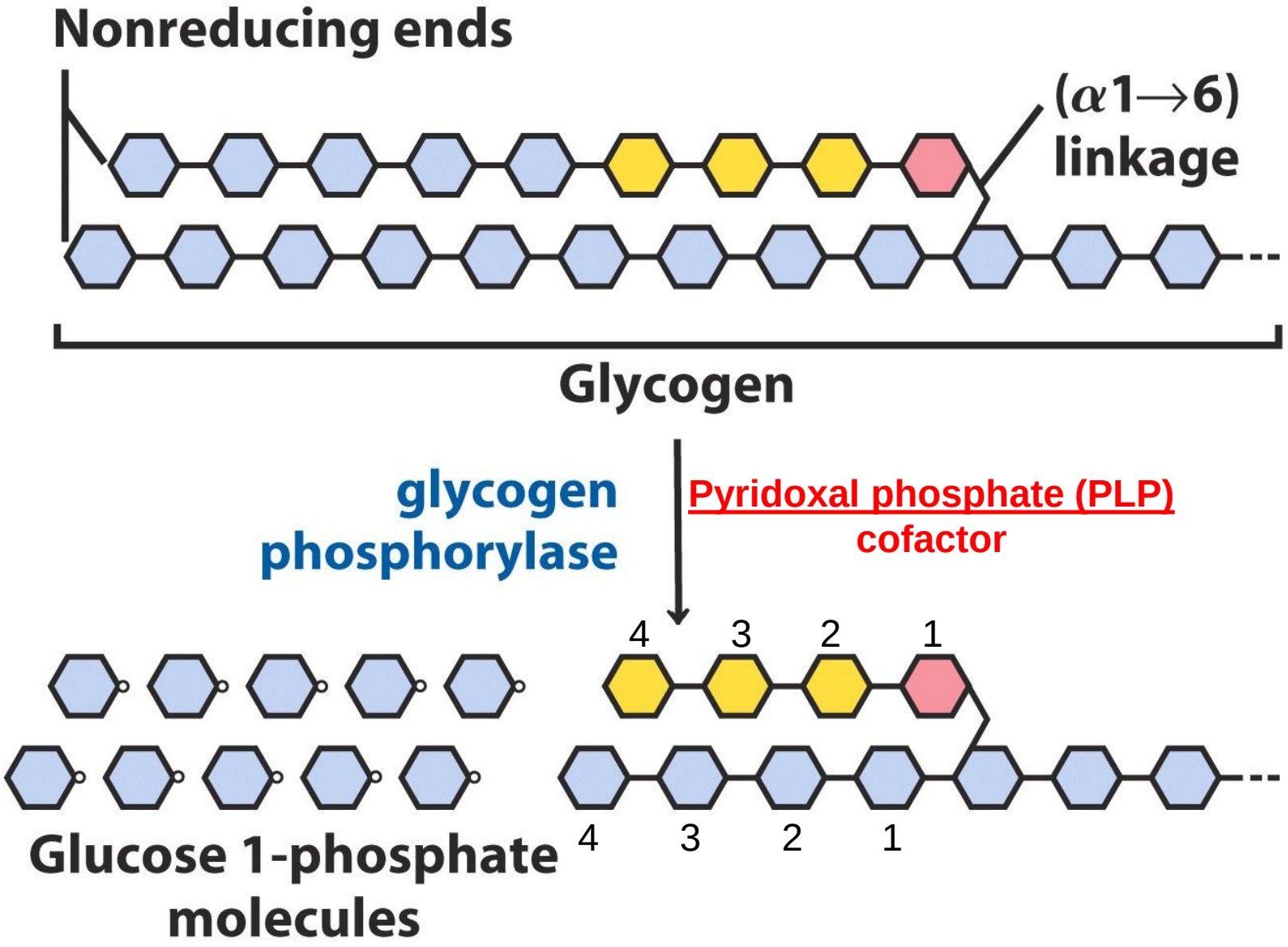
Glycogen phosphorylase:

An α-1,4 glycosidic bond linking 2 glucose residues by inorganic phosphate removing the terminal residues as glucose 1-phosphate.



Phosphorolysis not hydrolysis

- *Phosphorylase* stops cleaving α-1,4 linkages when it reaches a terminal residue 4 positions away from a branch point.
- Phosphorolytic cleavage is energetically advantageous:
  no need to phosphorylate glucose which needs ATP
  Phosphorylated glucose is trapped in the cell.


Nonreducing ends
(α1→6) linkage
Glycogen
glycogen phosphorylase
Pyridoxal phosphate (PLP) cofactor
4 3 2 1
4 3 2 1
Glucose 1-phosphate molecules

3 enzymes of glycogen breakdown (Glycogenolysis)

1) glycogen phosphorylase
2) glycogen debranching enzyme
3) Phosphoglucomutase

Further degradation occurs via the action of *debranching enzyme.*

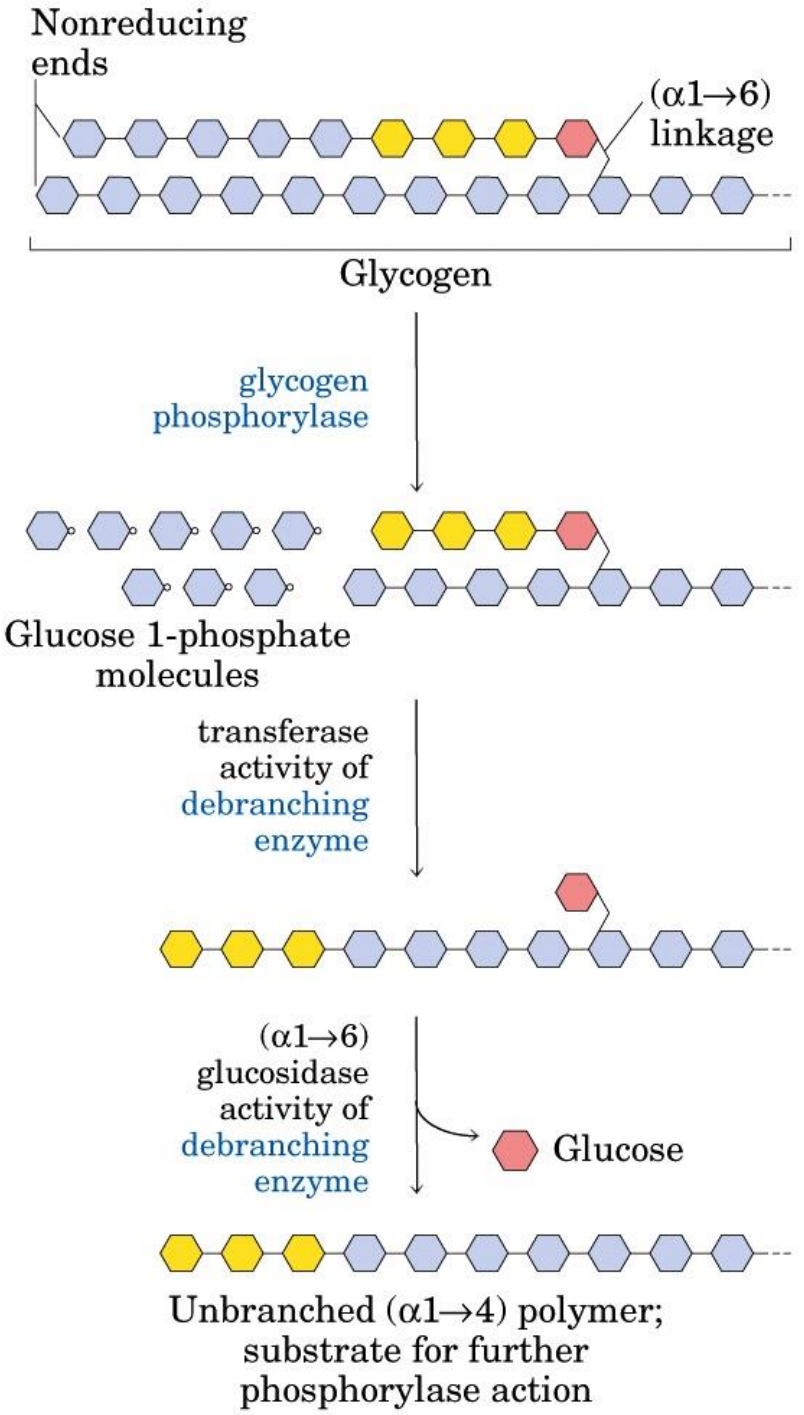
Debranching enzyme is bifunctional (it catalyzes 2 different reactions).

(1) <u>A transferase activity</u>
in which a block of 3 glycosyl residues are transferred from one outer branch to the other. The result is a longer amylose chain with only one glucosyl remaining in α-1,6 glycosidic linkage in the other chain.

(2) <u>α-1,6- glucosidase</u> :
Hydrolysis reaction of α-1,6- glucosidic bond releases glucose.

Thus, the sum of the transferase and the glucosidase activities of debranching enzyme convert a branched structure into a linear one. And yields mainly glucose 1-phosphate + some glucose (from the branch points).

The DEBRANCHING enzyme a single polypeptide 160kdal contain both active sites.



3 enzymes of glycogen breakdown (Glycogenolysis)

1) glycogen phosphorylase

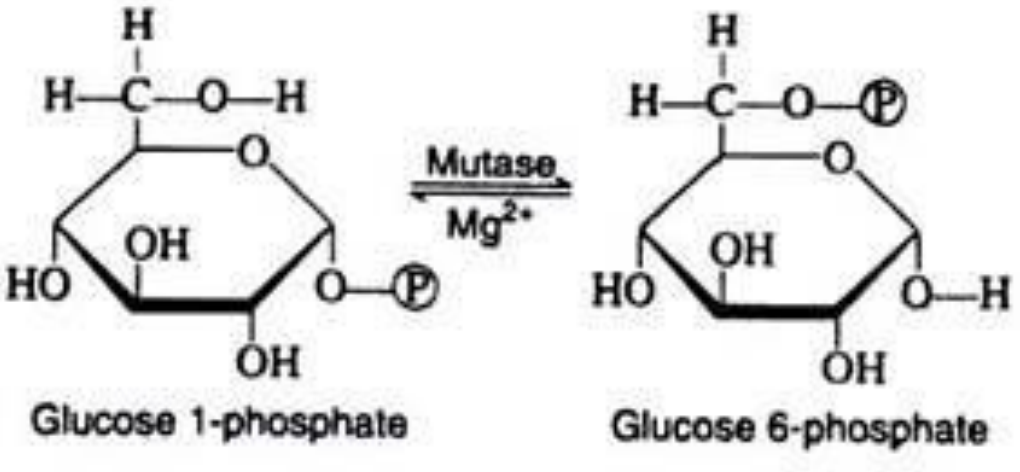
2) glycogen debranching enzyme

3) Phosphoglucomutase

Glu-1-P $\leftrightarrow$ Glu-6-P

Phosphoglucomutase:

converts glucose 1-phosphate to glucose 6-phosphate via shifting a phosphoryl group.



The glucose 6-phosphate can then enter the metabolic mainstream.

The Fate of Glucose 6-Phosphate

Tissues which have glucose 6-phosphatase.

can generate free glucose.

Liver, kidneys, intestine

HAVE THE ENZYME

The resulting free glucose is then transported into the bloodstream thereby providing a supply of glucose where needed.

Liver release glucose during muscular activity and after meals

Muscle, brain, adipose tissue,

DO NOT HAVE THE ENZYME

Thus glucose is effectively trapped within these cells where it is used as a fuel to generate ATP via Glycolysis and the Citric Acid Cycle and electron Transport chain

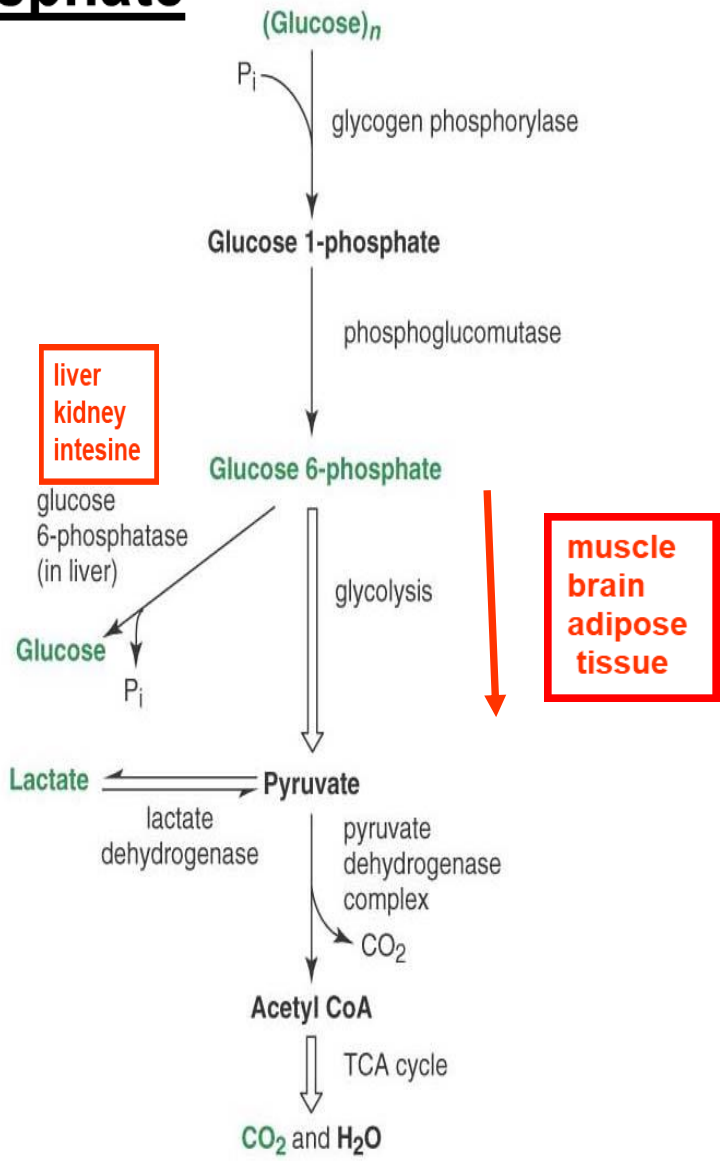


Figure 15.51. Glycogenolysis and the fate of glycogen degraded in liver versus its fate in peripheral tissues.

Textbook of Biochemistry With Clinical Correlations, Sixth Edition, Edited by Thomas M. Devlin. Copyright © 2006 John Wiley & Sons, Inc.

Glycogenesis

Glycogen synthesis occurs in virtually all animal tissues, but is most prominent in the liver and skeletal muscle.

1) The first reaction is catalyzed by *hexokinase (or glucokinase* in liver):

Glucose + ATP ⟶ Glucose 6-phosphate + ADP

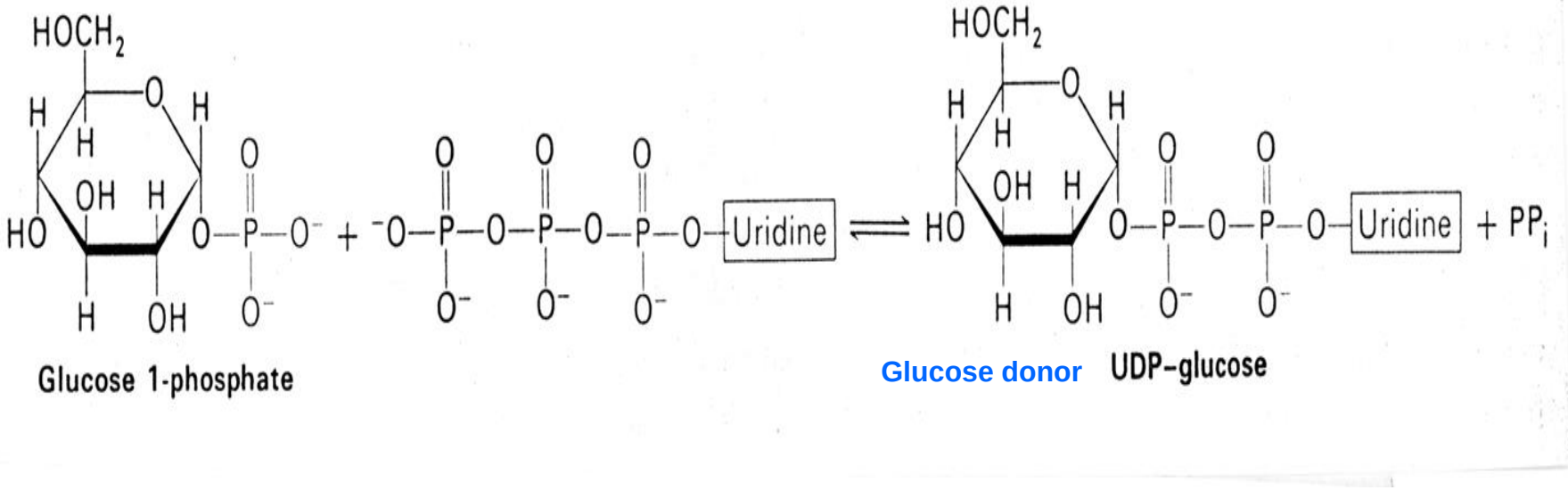
2) The second reaction is catalyzed by *phosphoglucomutase:*

Glucose 6 phosphate ⟶ Glucose 1-phosphate

3) *UDP-glucose pyrophosphorylase* or glucose 1 phosphate uridyl transferase catalyzes the formation of UDP-glucose which will serve as a glucose donor in subsequent reactions.

Thus, UDP glucose can be considered as an activated form of glucose.

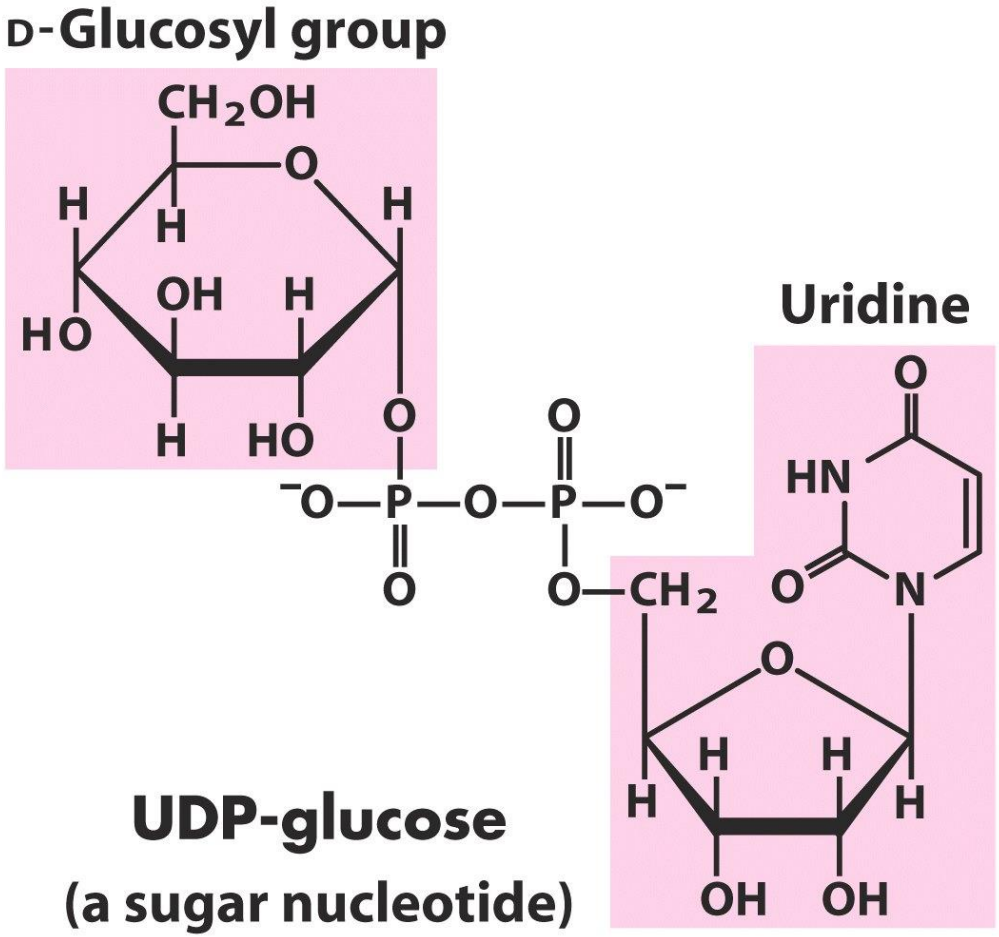
Glucose 1-phosphate + UTP ⟶ UDP-glucose + PPi



PPi is rapidly hydrolyzed to 2 Pi driving the above reaction to completion by pyrophosphate

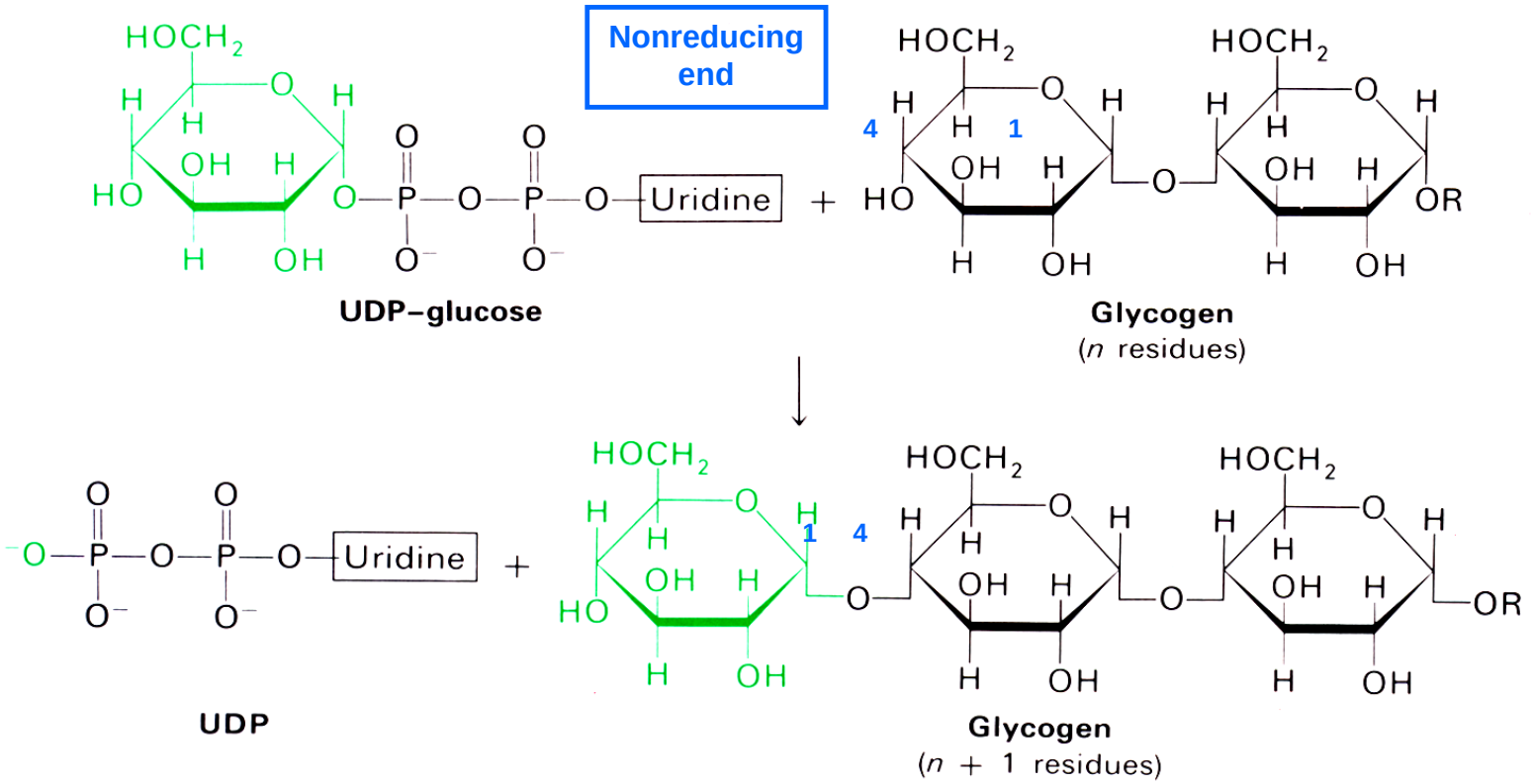
UDP Glucose is the Activated Precursor

uridine = uracil + ribose



4) *Glycogen synthase* catalyzes the transfer of glucose from UDP-glucose to a growing chain.

Glucosyl units are added to the non-reducing terminal residue of glycogen (i.e., to the hydroxyl group at the C-4 terminus) to form an α-1,4-glycosidic bond.



- **The reaction requires at least 4 residues of glucose as a primer.**
- **Thus a tetrasaccharide primer is elongated by one residue.**
- **This process is repeated many times to form a long, <u>unbranched</u> glycogen molecule.**

5) Glycogen synthase requires a primer. This priming function is carried out by *glycogenin*, a 37 kDa protein to which the first glucose residue is attached.

***Glycogenin* acts as a catalyst for synthesis of the nascent glycogen molecule by attaching a glucose to the hydroxyl group of a specific tyrosine residue within its structure.**

***Glycogenin* then autocatalyzes the addition of up to 8 glucose units in α-1,4 glycosidic linkages with UDP-glucose being the glucose donor.**

***Glycogen synthase* then takes over.**

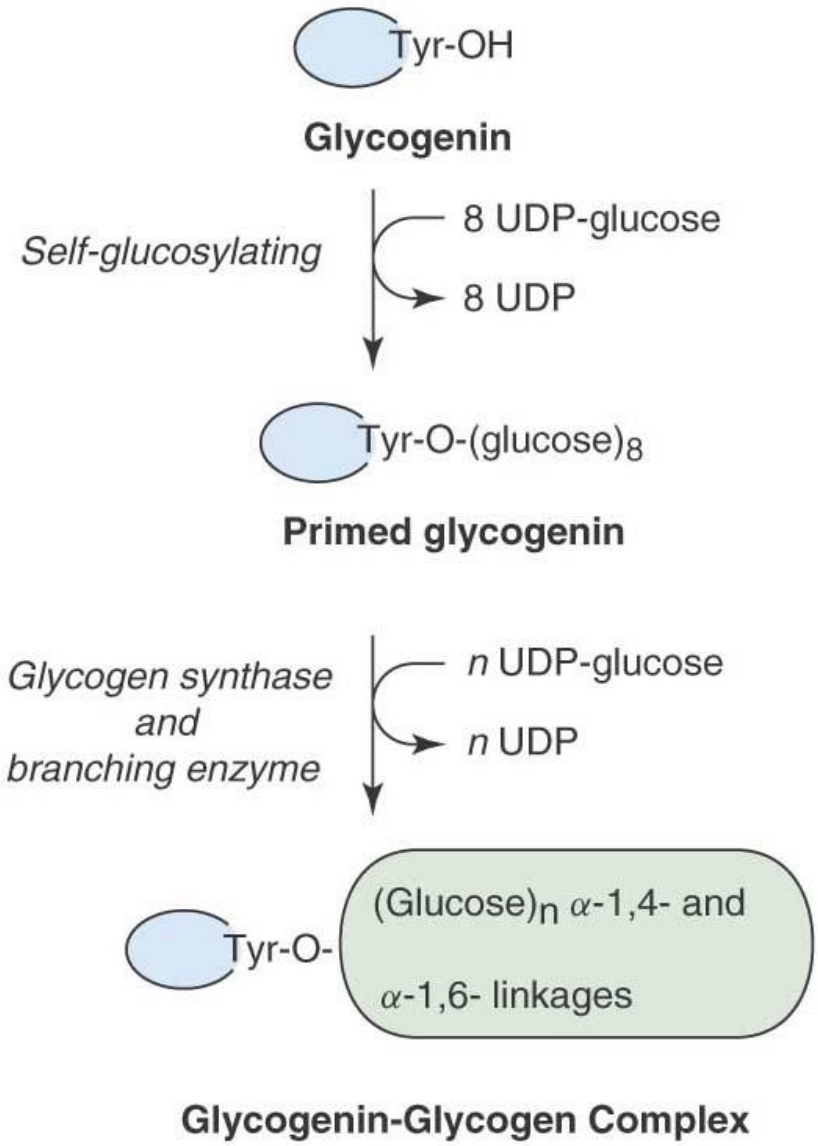
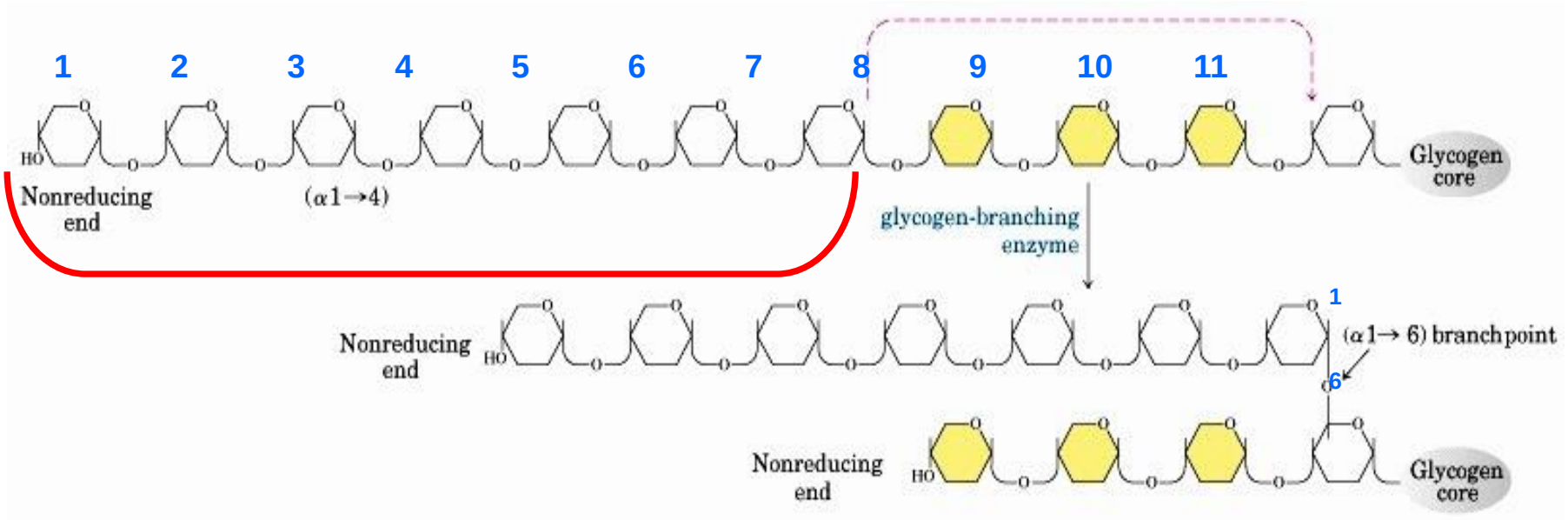


Figure 15.55. Glycogenin provides a primer for glycogen synthesis by glycogen synthase.

Textbook of Biochemistry With Clinical Correlations, *Sixth Edition*, Edited by Thomas M. Devlin. Copyright © 2006 John Wiley & Sons, Inc.

6) *Branching enzyme* forms the α-1,6 linkages that make glycogen a branched polymer.

Transfers a terminal fragment, 7 glucosyl residues in number, from the non-reducing end of a glycogen branch having at least 11 residues, to the C-6 hydroxyl group of a glucose residue of the same or another glycogen chain at a more interior point, thereby creating a branch.



<u>Branching:</u> increases the solubility of glycogen (by increasing the number of hydroxyl groups); AND
increases the rate of glycogen synthesis and degradation by creating a large number of terminal residues at which the appropriate enzymes phosphorylase or synthase can act. Branching increases the rate of glycogen synthesis and degradation.AND makes glycogen a compact polymer.

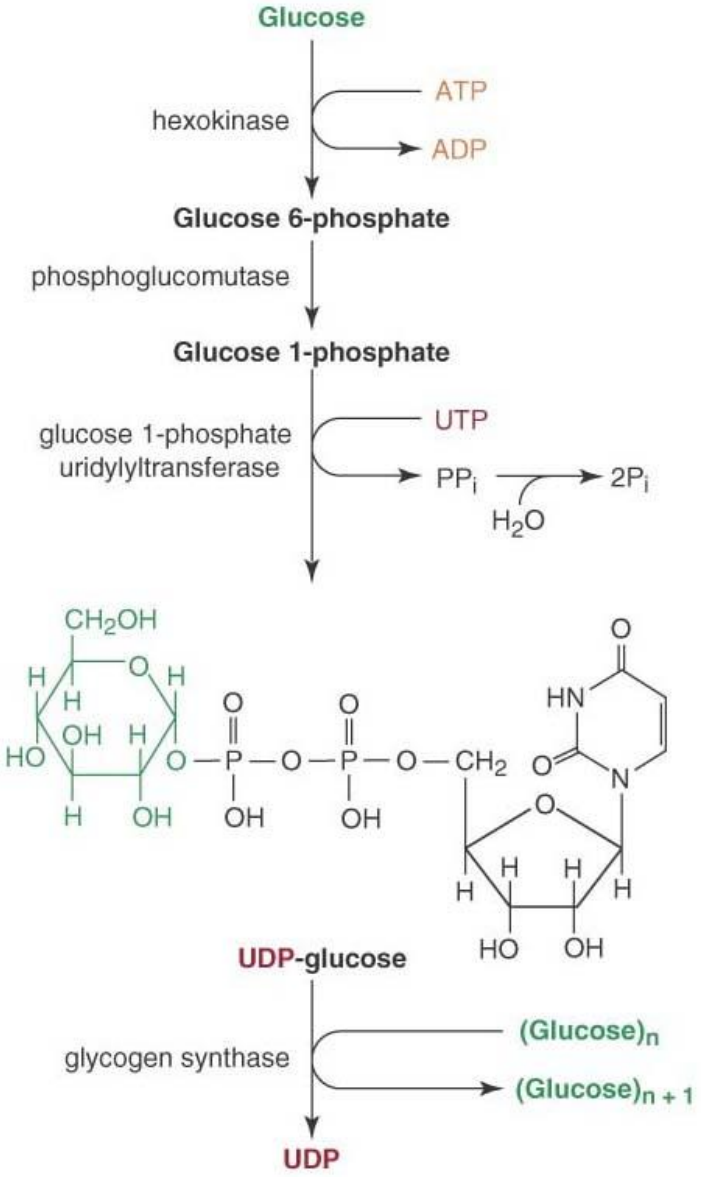


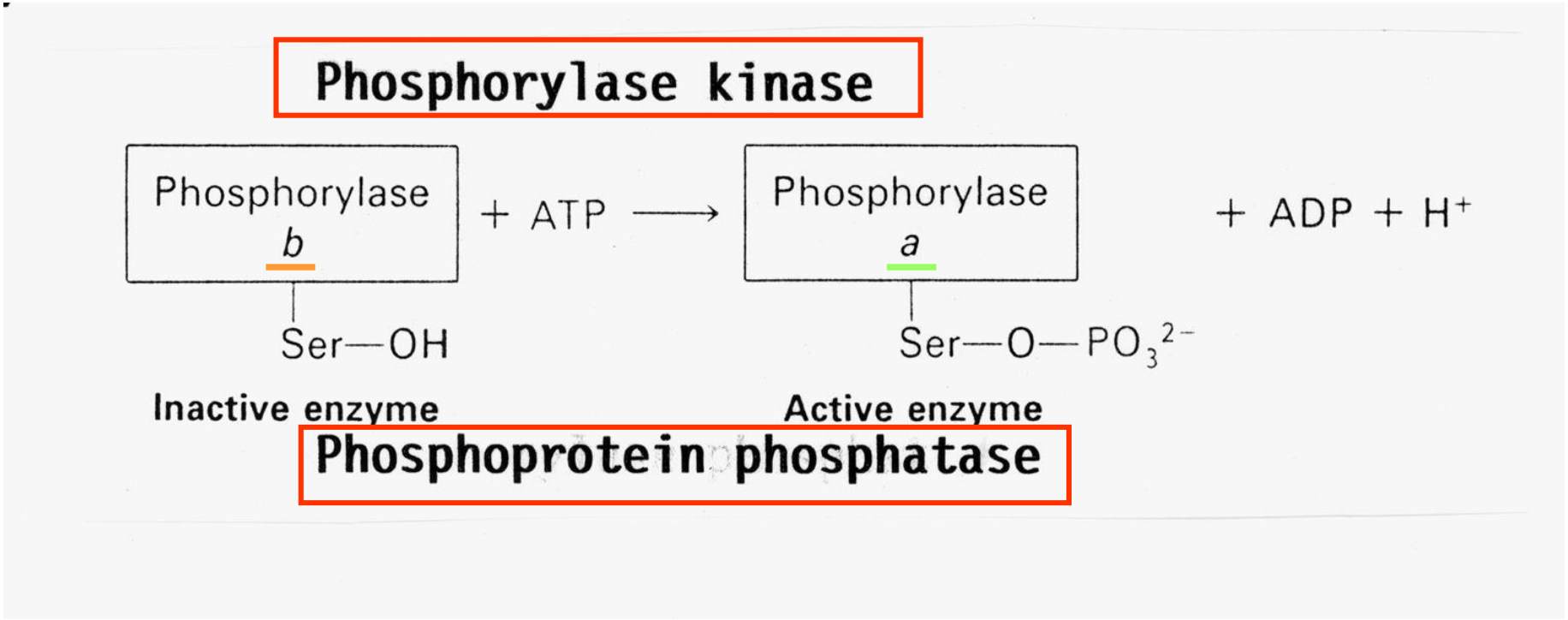
Figure 15.53. Pathway of glycogenesis.

Textbook of Biochemistry With Clinical Correlations, *Sixth Edition*, Edited by Thomas M. Devlin. Copyright © 2006 John Wiley & Sons, Inc.

Regulation of Glycogen Metabolism

Regulation of Glycogen Phosphorylase

Regulated by both reversible phosphorylation and by allosteric effectors.



Allosteric regulation :

In skeletal muscles :

Phosphorylase allosterically regulated

+ only in the presence of AMP.

- ATP , glucose 6-phosphate

At rest, most of the enzyme exists in the b form. During exercise, elevated AMP activates phosphorylase.

In the liver:

allosteric regulation differs in two respects:

1- AMP does not activate the liver phosphorylase.

2- liver phosphorylase is inhibited by glucose.

Thus when blood glucose is sufficiently high to supply other tissues, and glycogen breakdown is not needed, phosphorylase is inhibited.

G*lycogen phosphorylase* acts as a glucose sensor in liver, slowing glycogen breakdown when blood glucose is high.

Regulation of glycogen phosphorylase:

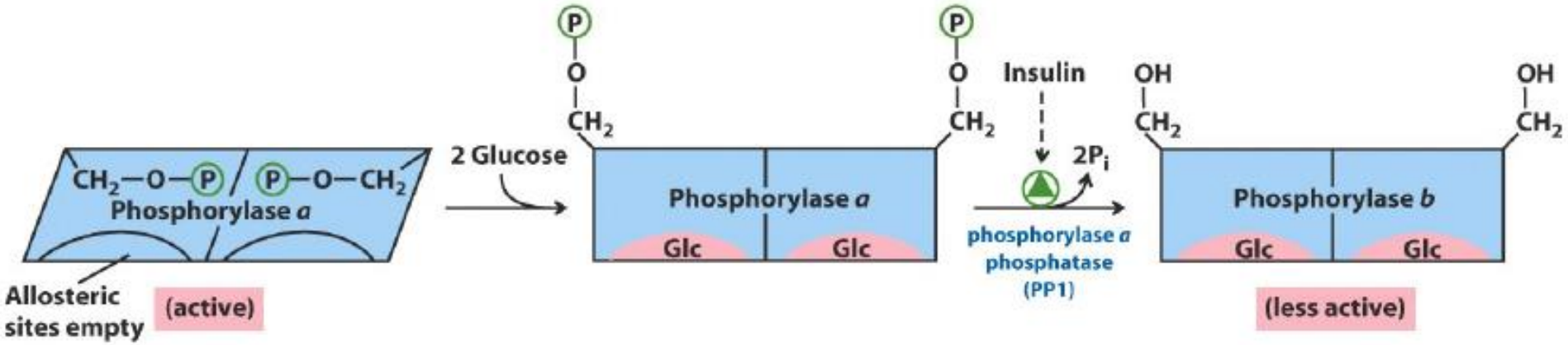
glucose binding to phosphorylase a ⟶ inactive T form(phosphorylase b)

phosphoryl groups exposed to phosphatase.

PP1 binds tightly to phosphorylase a but functions only when glucose induces it.

phosphorylase b does not bind phosphatase

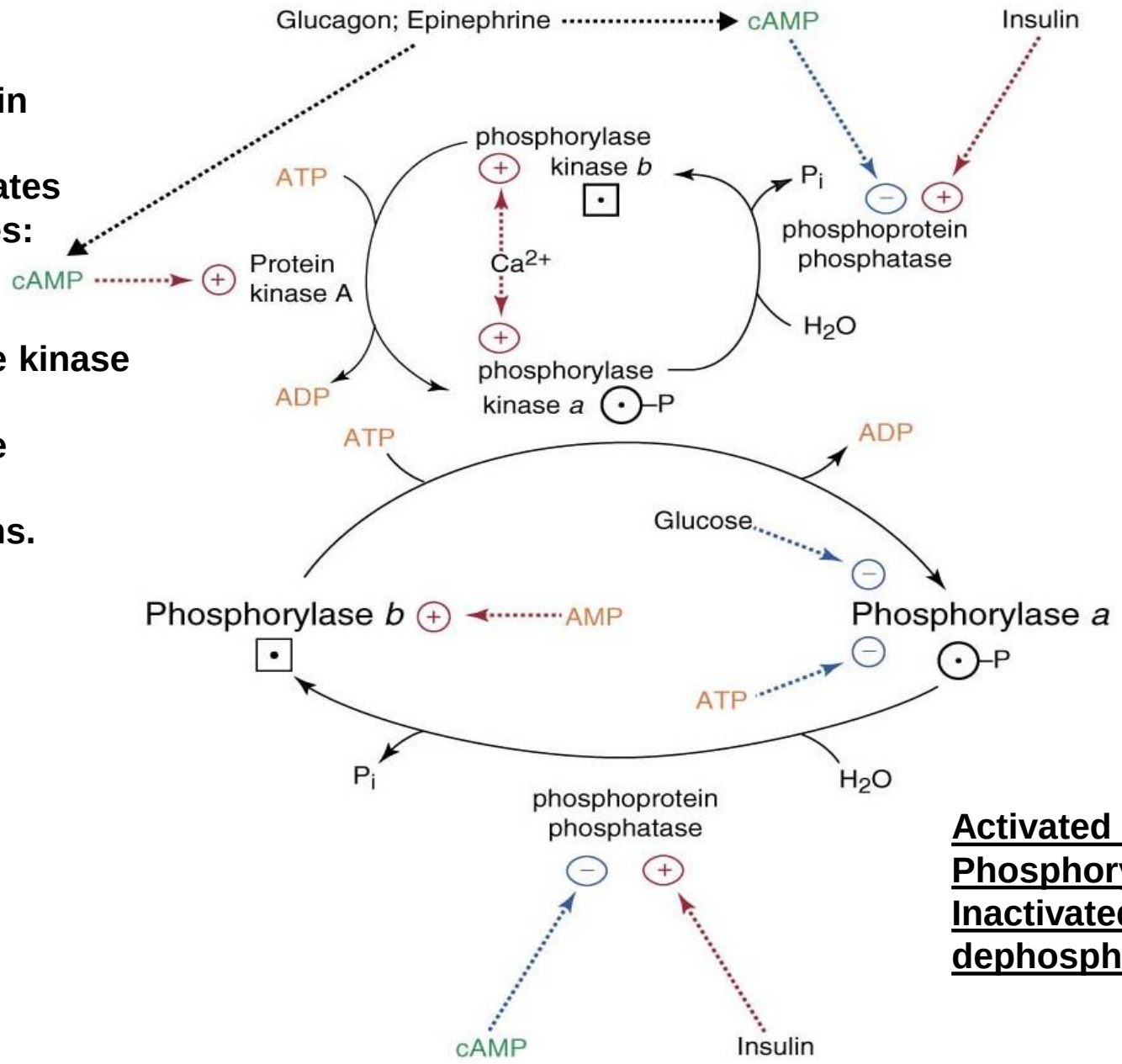
so the conversion of a to b leads to the release of phosphatase free to activate the synthase.



Phosphoprotein phosphatase dephosphorylates and inactivates:

phosphorylase kinase and phosphorylase

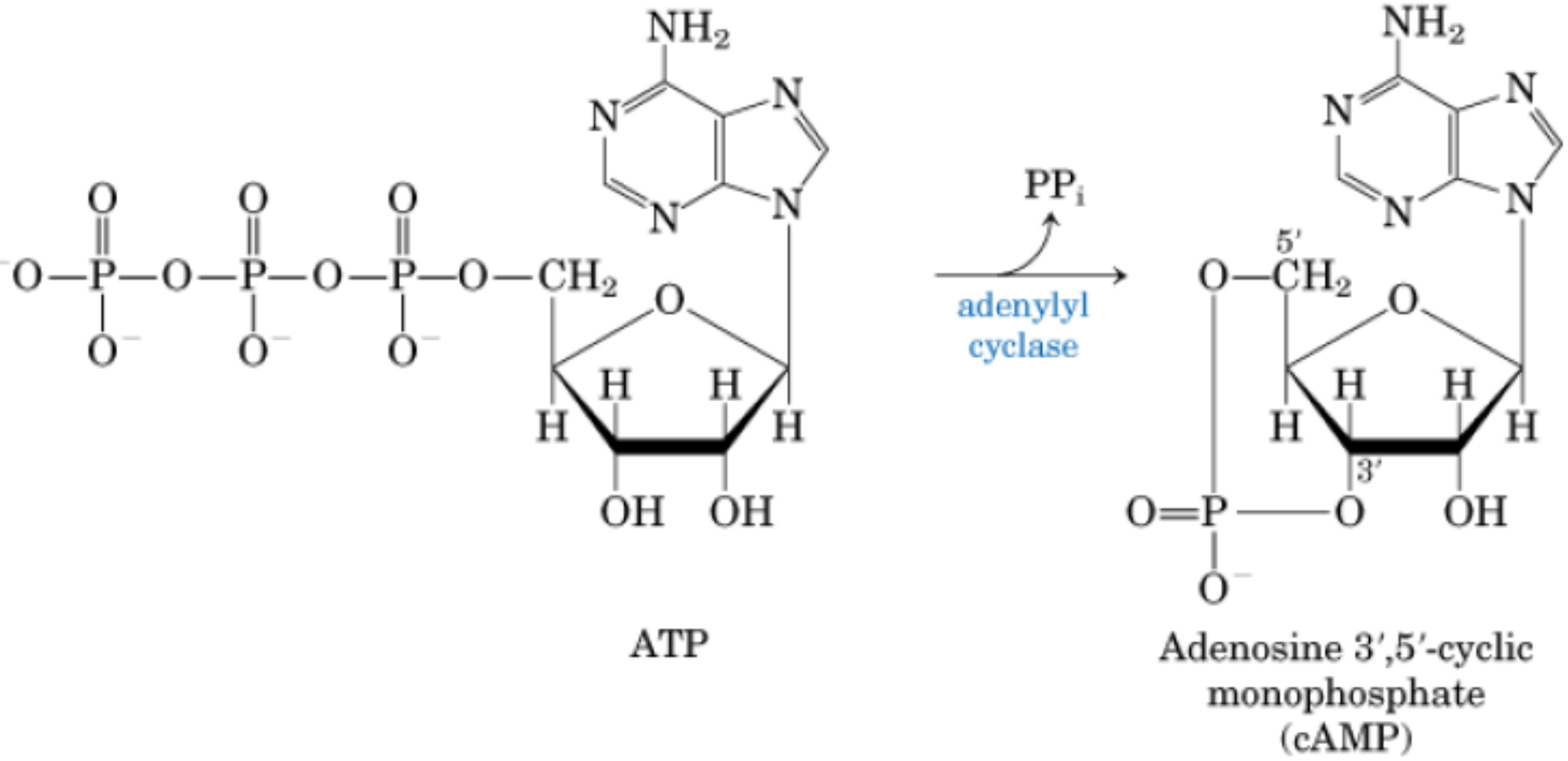
a ⟶ b forms.



Activated by Phosphorylation
Inactivated by dephosphorylation

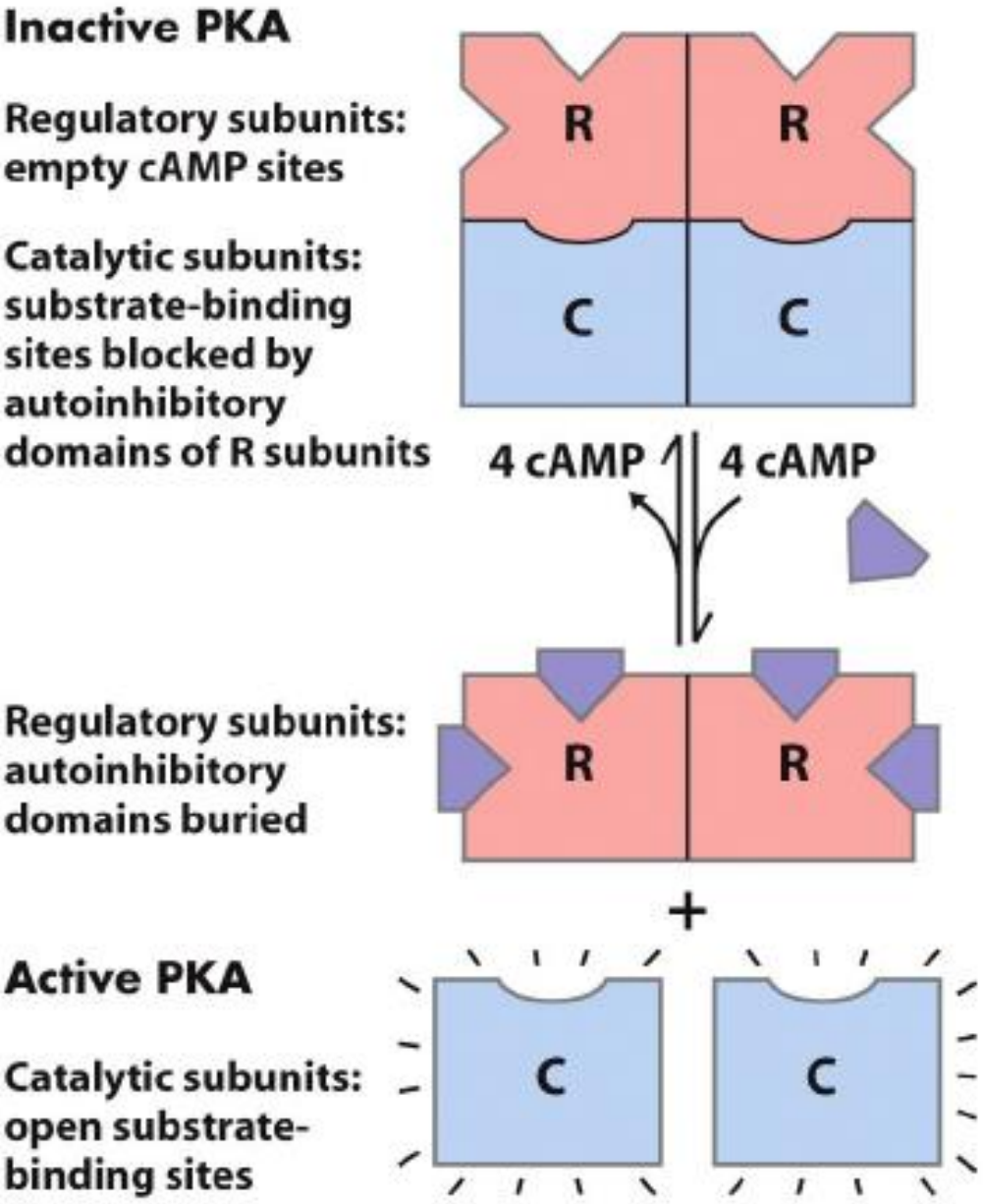
Figure 15.56. Regulation of glycogen phosphorylase by covalent modification and allosteric effectors.

Textbook of Biochemistry With Clinical Correlations, Sixth Edition, Edited by Thomas M. Devlin. Copyright © 2006 John Wiley & Sons, Inc.

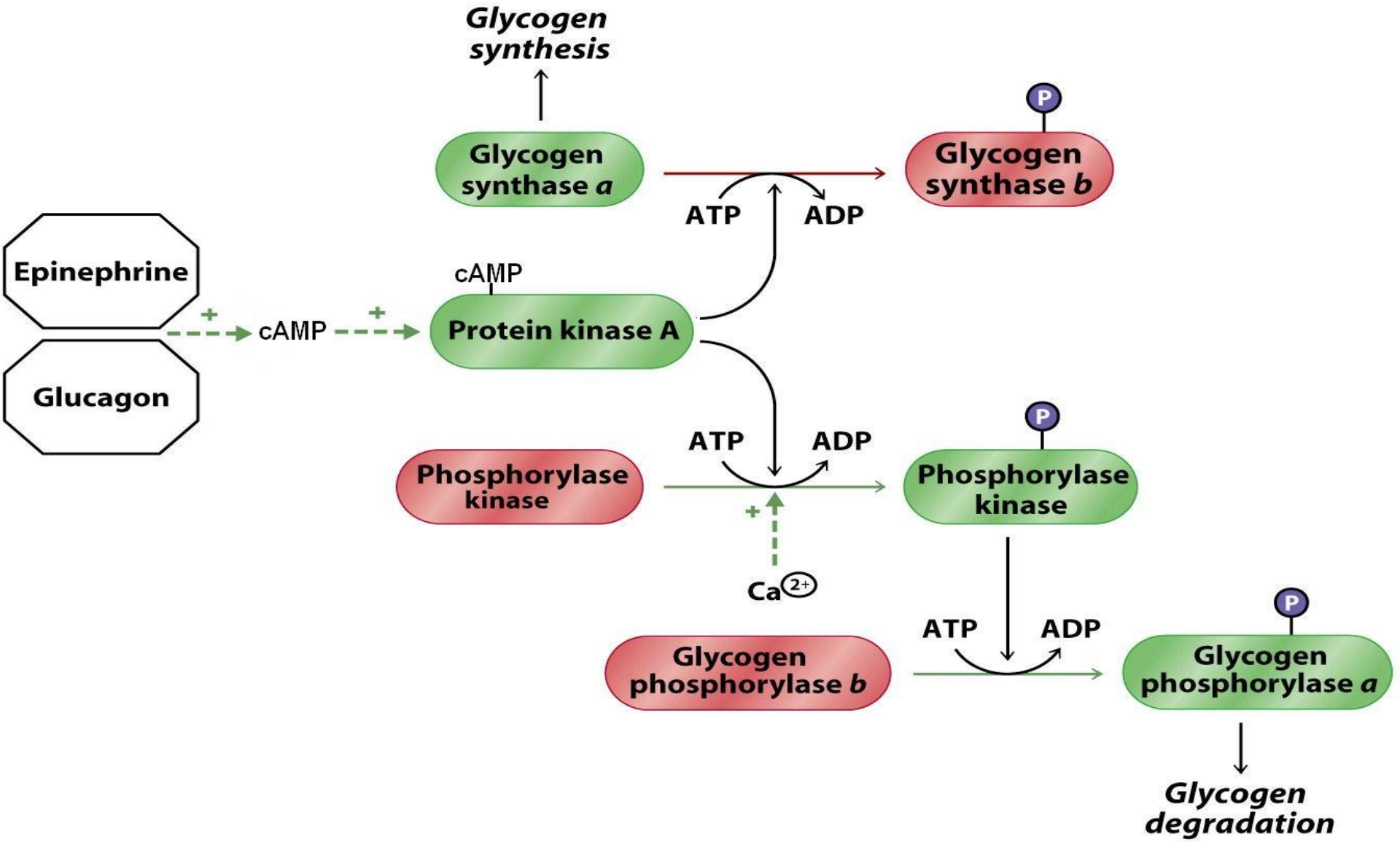


Synthesis of cyclic-AMP

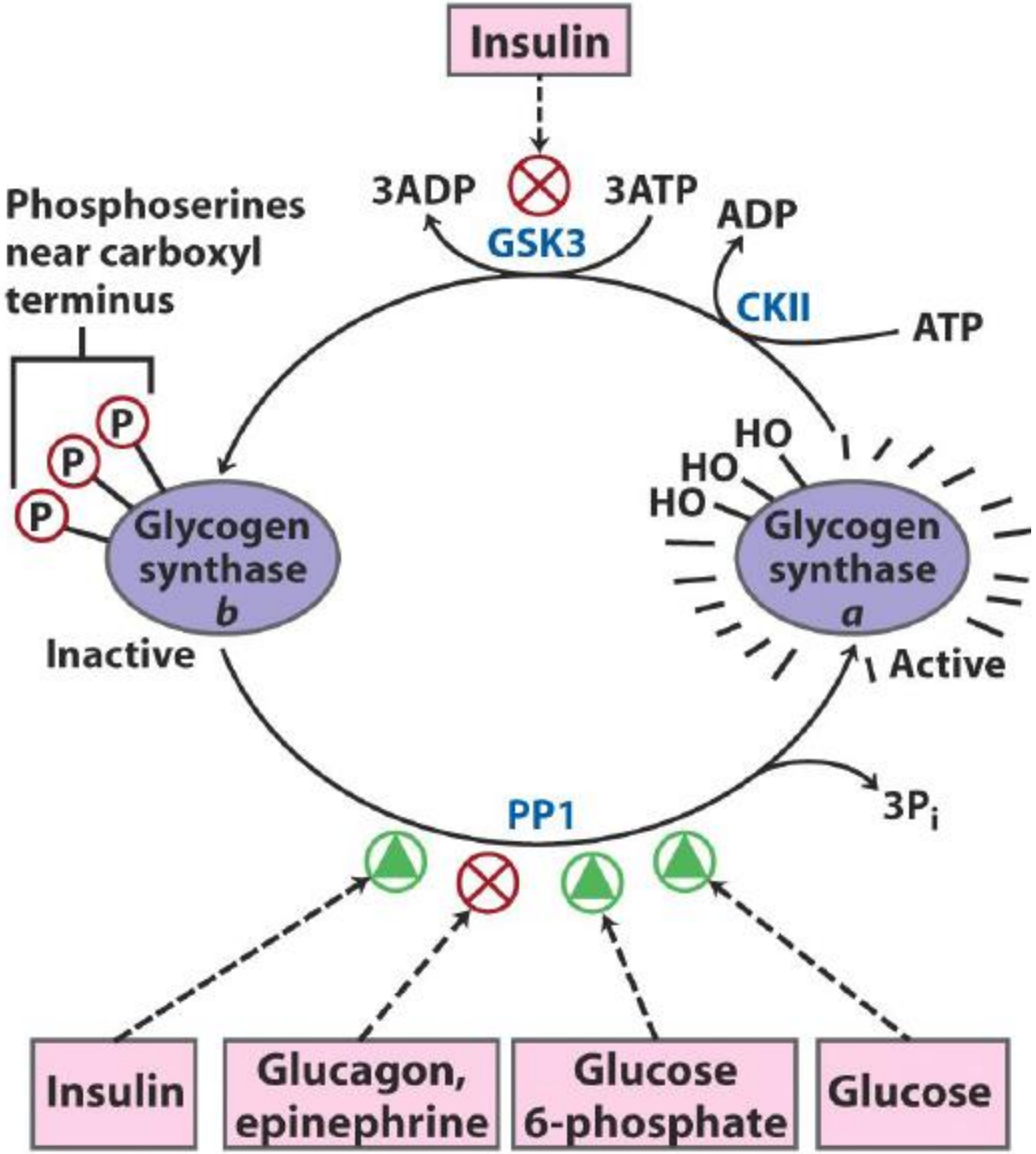
Activation of cAMP-dependent protein kinase A



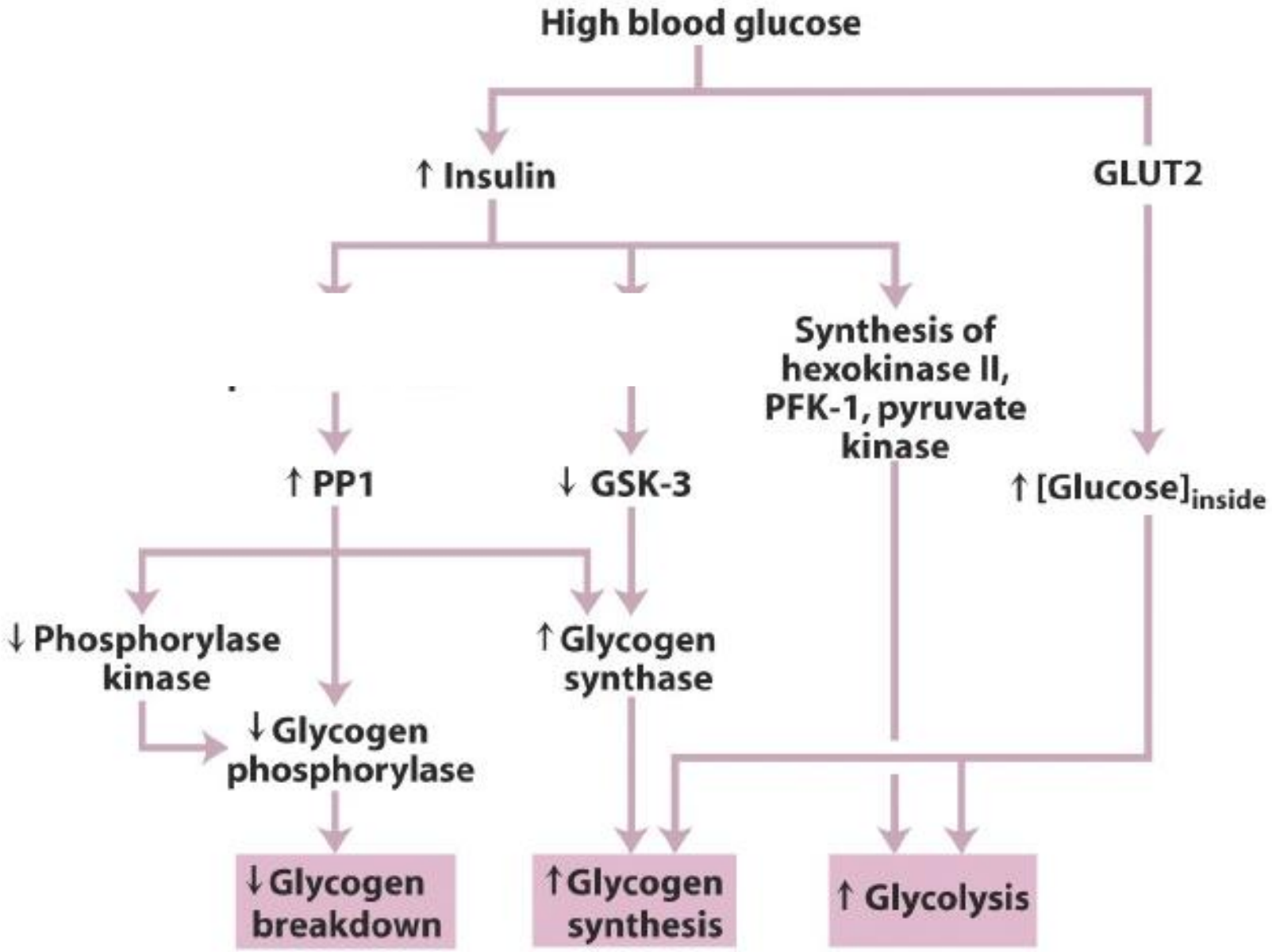
Regulation of Glycogen Synthesis



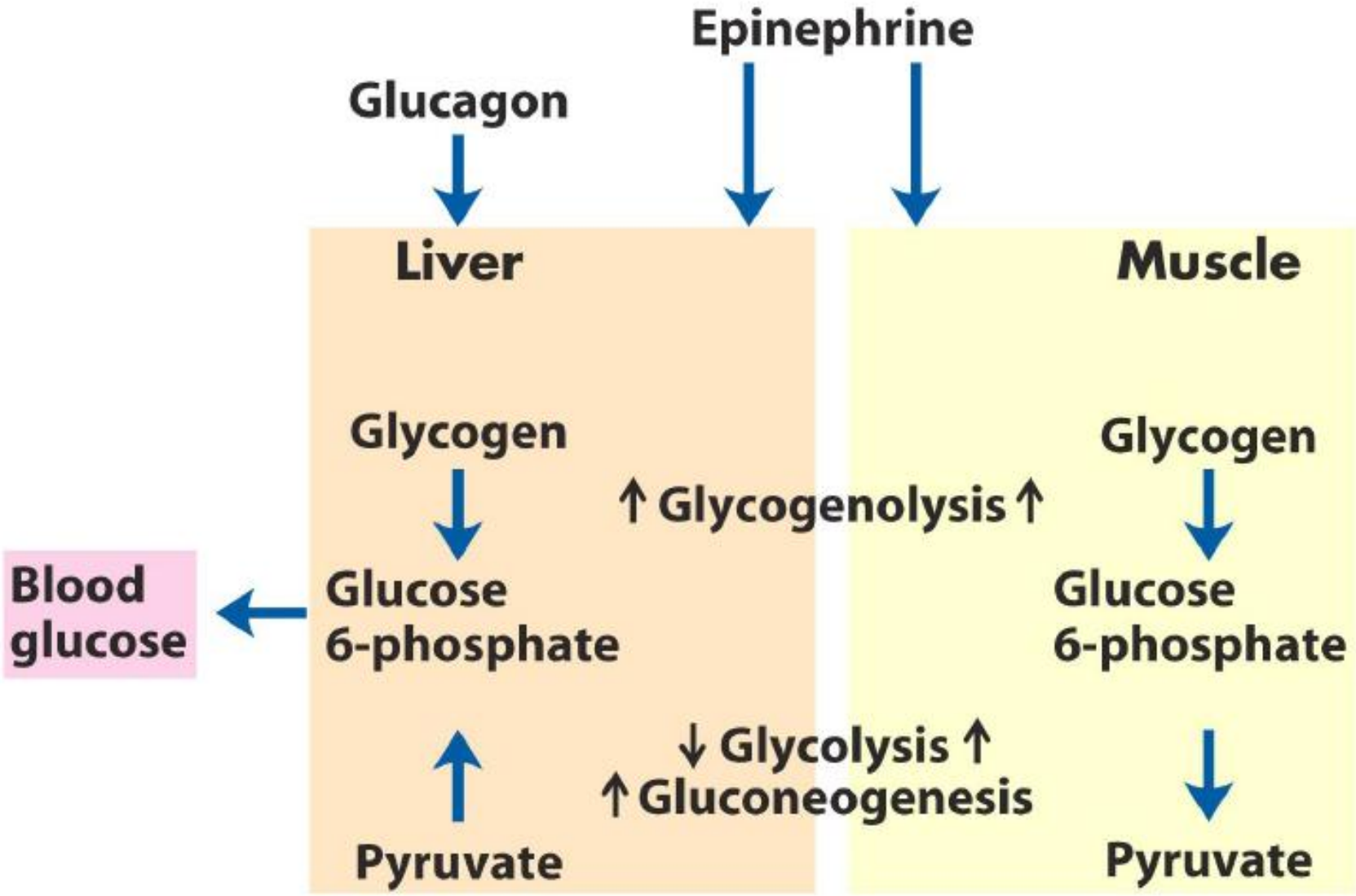
Principles of Biochemistry, 4/e
© 2006 Pearson Prentice Hall, Inc.

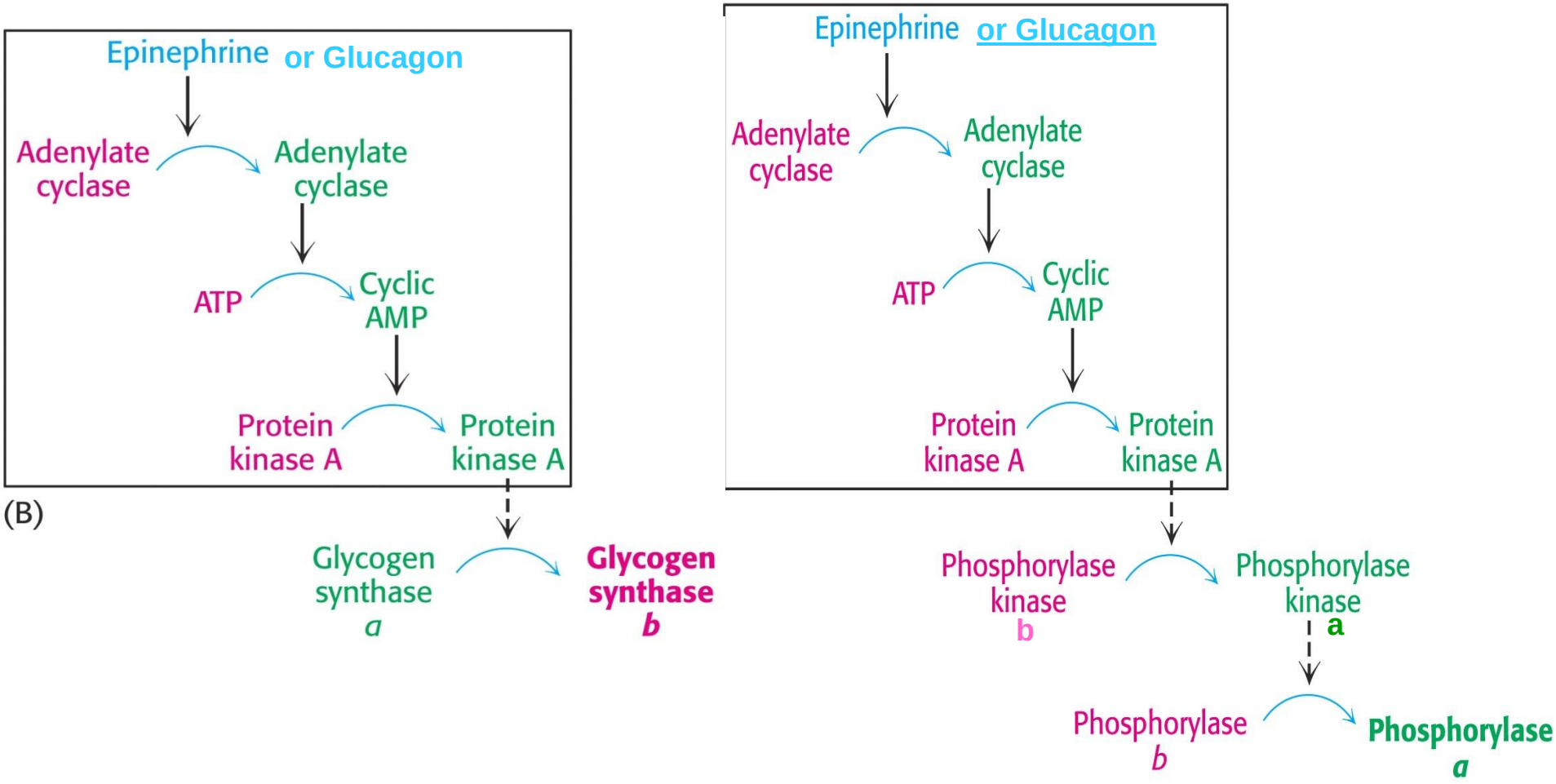

Insulin
3ADP
3ATP
GSK3
ADP
CKII
ATP
Phosphoserines near carboxyl terminus
P
P
P
Glycogen synthase b
Inactive
HO
HO
HO
Glycogen synthase a
Active
3Pi
PP1
Insulin
Glucagon, epinephrine
Glucose 6-phosphate
Glucose

Regulation of Carbohydrate metabolism in Liver



Differences in the regulation of carbohydrate metabolism In muscles and liver





This cascade of reactions results in a tremendous amplification of a hormonal signal which stimulates liver glycogenolysis and inhibits glycogenesis in order to increase blood glucose.

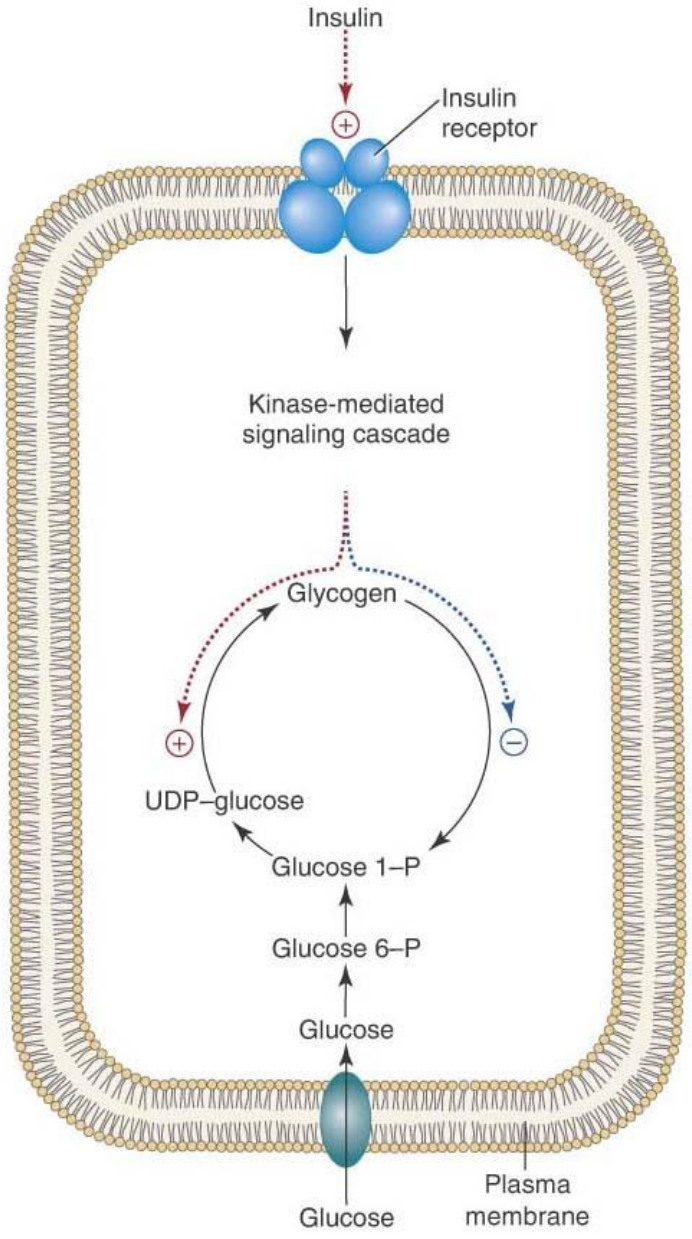


Figure 15.66. Insulin acts by a plasma membrane receptor to promote glycogenesis in liver.

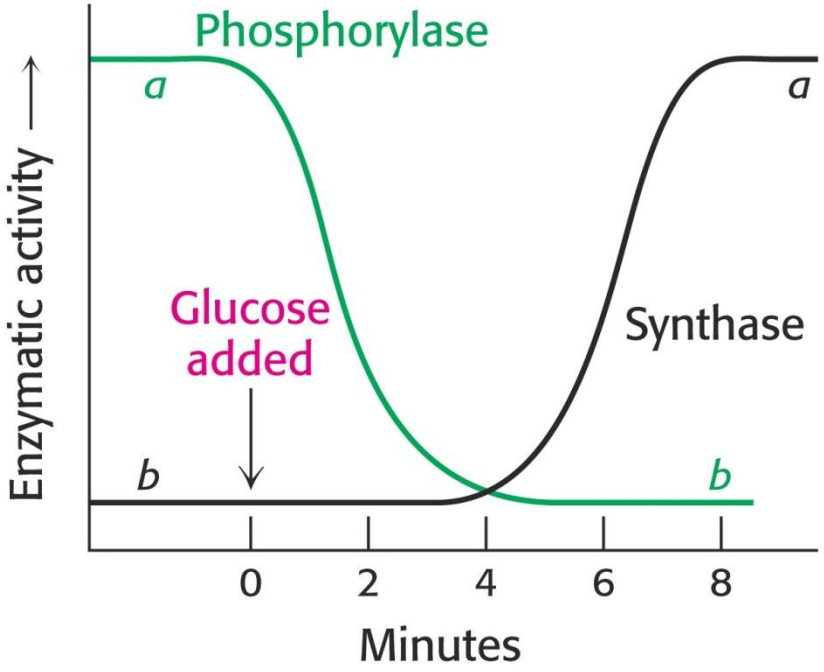
Textbook of Biochemistry With Clinical Correlations, *Sixth Edition*, Edited by Thomas M. Devlin. Copyright © 2006 John Wiley & Sons, Inc.

Glucose conc. In blood= 80-120 mg/100ml

liver senses [glucose in blood]
takes up or releases glucose accordingly.

Phosphorylase a is the glucose sensor in liver cells.

The binding of glucose to phosphorylase a shifts the equilibrium to the T (tense or inactive) form.
This exposes the phosphoryl group serine 14 to hydrolysis by phosphatase.



Regulation of Glycogen Synthesis/ Breakdown

Low blood glucose:hypoglycemia

↑glucagon, ↓insulin, ↑PKA,
↑phosphorylase kinase
↑glycogen phosphorylase
↓glycogen synthase
↑glycogen breakdown, ↓synthesis

High blood glucose:hyperglycemi

↑insulin, ↓glucagon,
↑phosphoprotein phosphatase
↓phosphorylase kinase
↓glycogen phosphorylase
↑glycogen synthase
↓glycogen breakdown, ↑glycogen synthesis