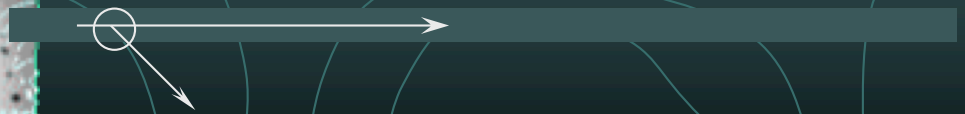
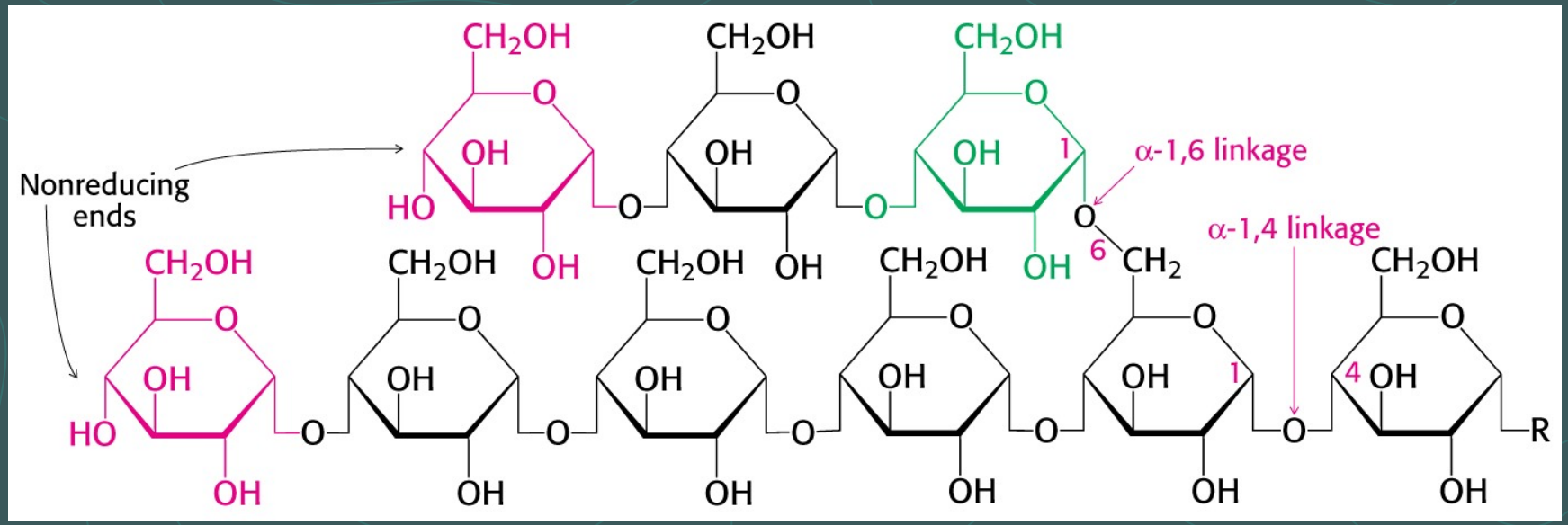
Glycogen Metabolism



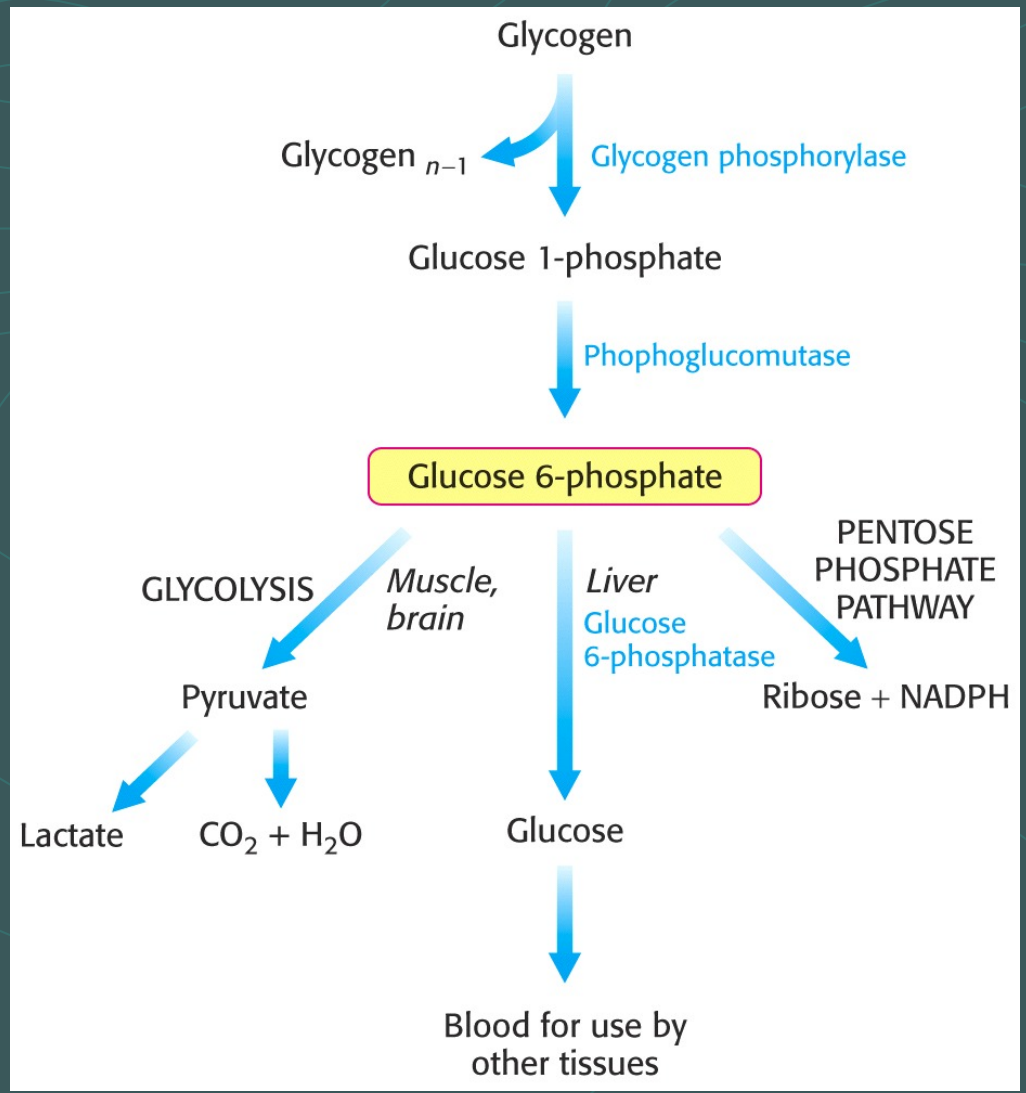
Glycogen Metabolism

- What is the importance of glycogen?
  - needed to maintain blood glucose levels
- Where is glycogen stored?
  - liver
  - muscle

Glycogen Metabolism

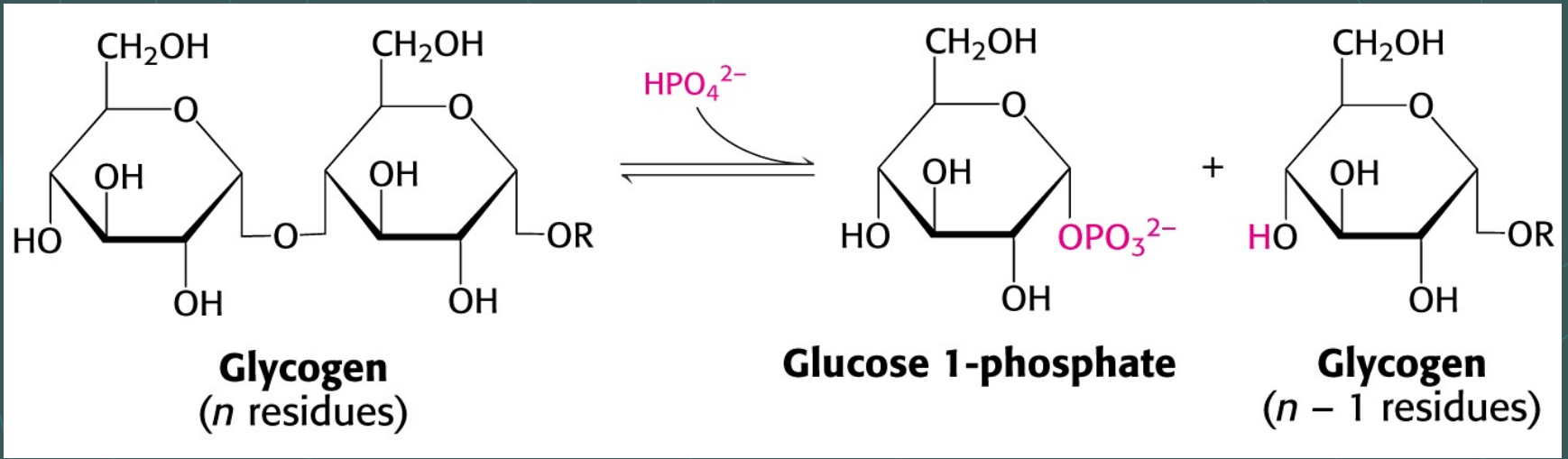


Glycogen Metabolism



Glycogen Degradation

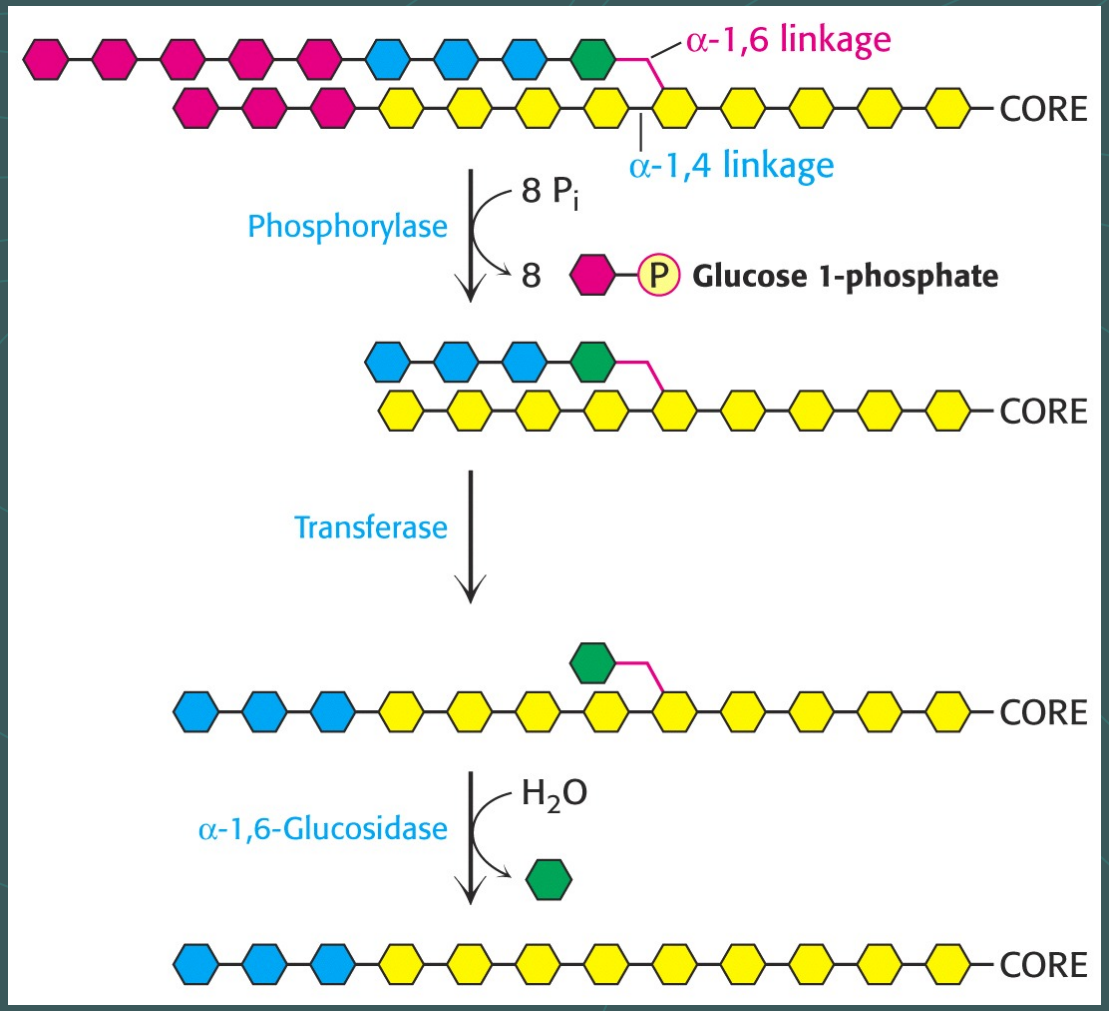
- Glycogen is cleaved to glucose 1-PO_4 and n-1 residues
  - glycogen phosphorylase
  - 1,4 linkage is broken



Glycogen Degradation

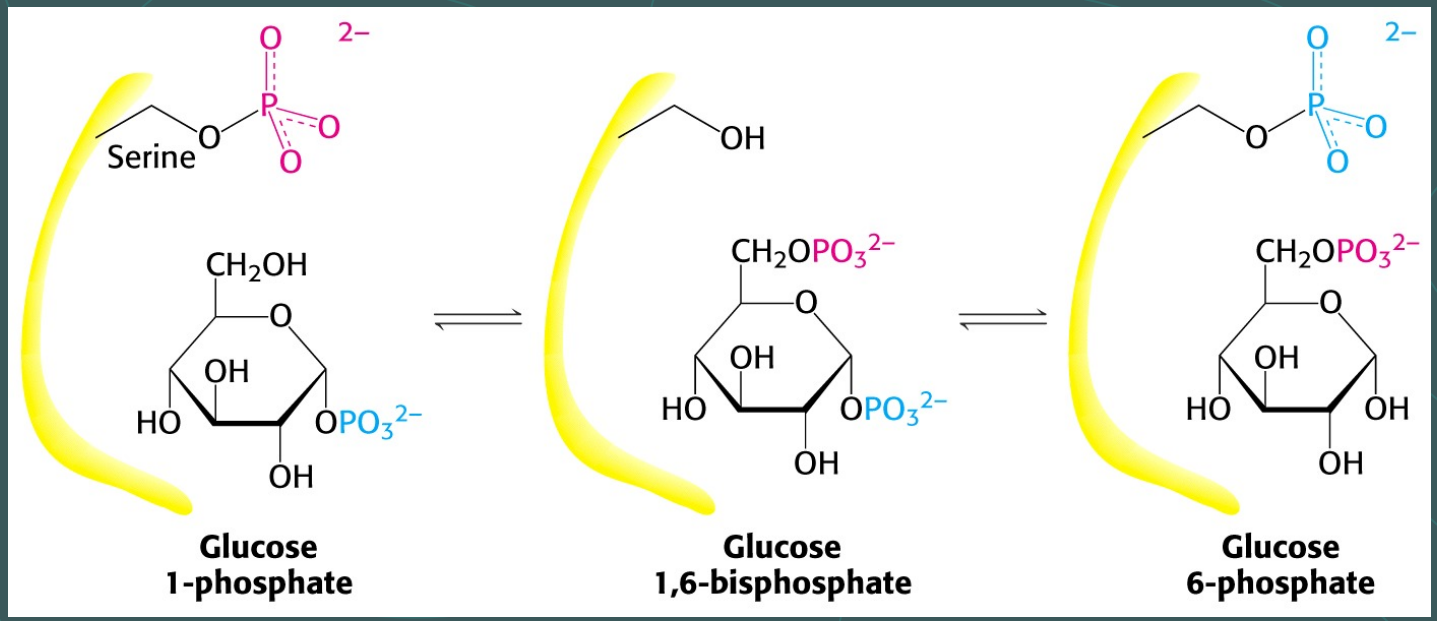
- Why are two additional enzymes needed for glycogen breakdown?
  - debranching
- What does glycogen transferase do?
  - shifts block of 3 glycosyl residues from outer branch
- What does α-1,6-glucosidase do?
  - hydrolzes 1,6 linkage

Glycogen Degradation



Glycogen Degradation

- What happens next?
  - conversion of glucose 1-PO_4 to glucose 6-PO_4
    - phosphoglucomutase

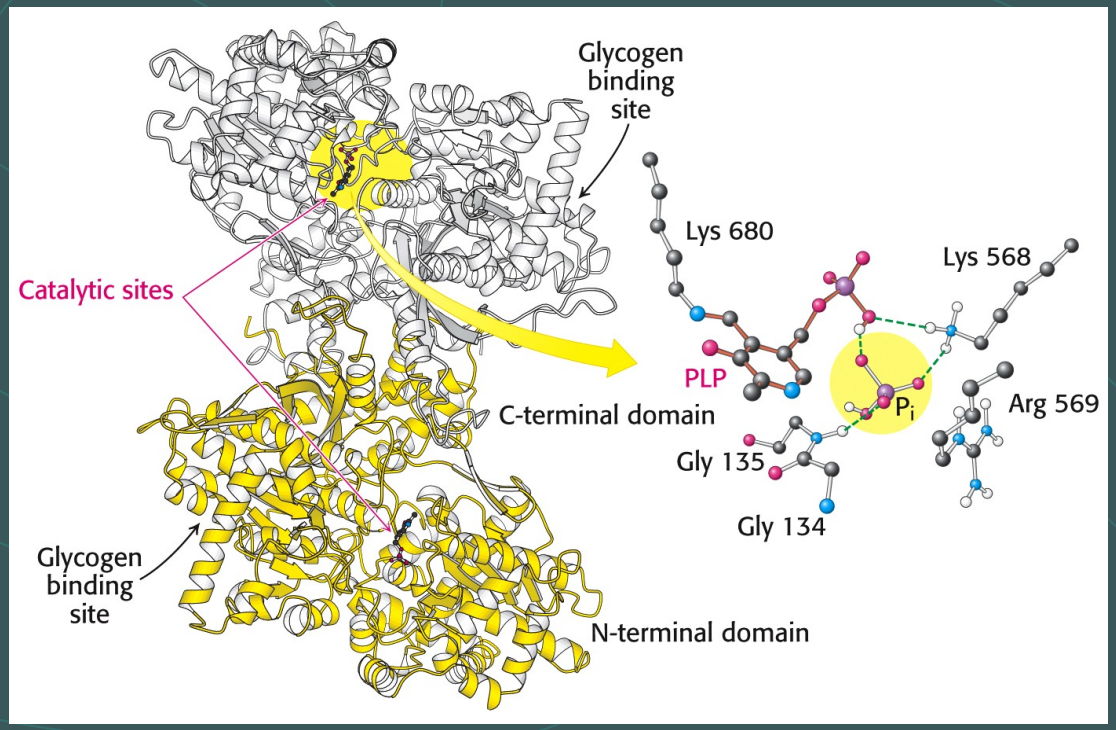


Glycogen Degradation

- What happens to glucose 6-PO_4 in liver?
  - cleaved to glucose and PO_4
    - glucose 6-phosphatase
    - regulates blood glucose levels

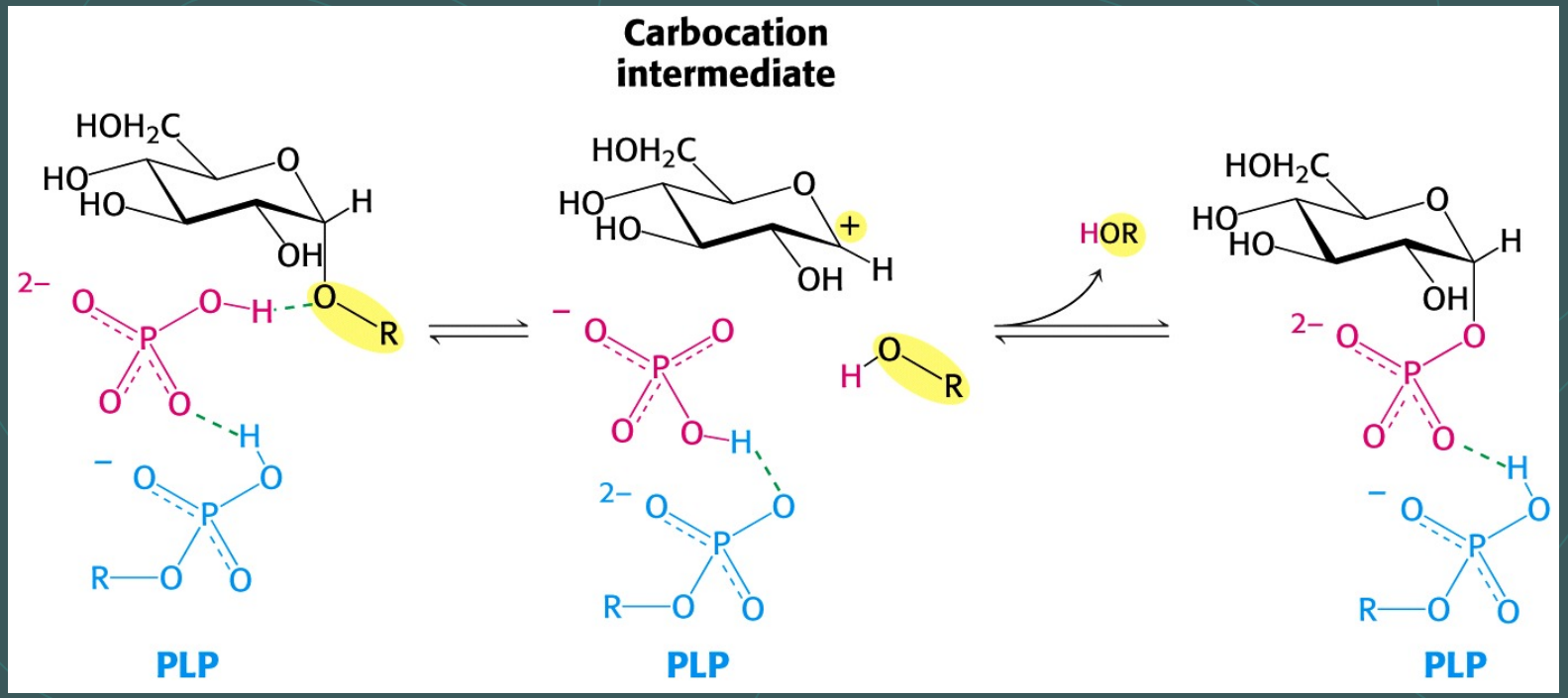
Glycogen Degradation

- What cofactor is involved in the catalytic mechanism of glycogen phosphorylase?
  - pyridoxyl phosphate



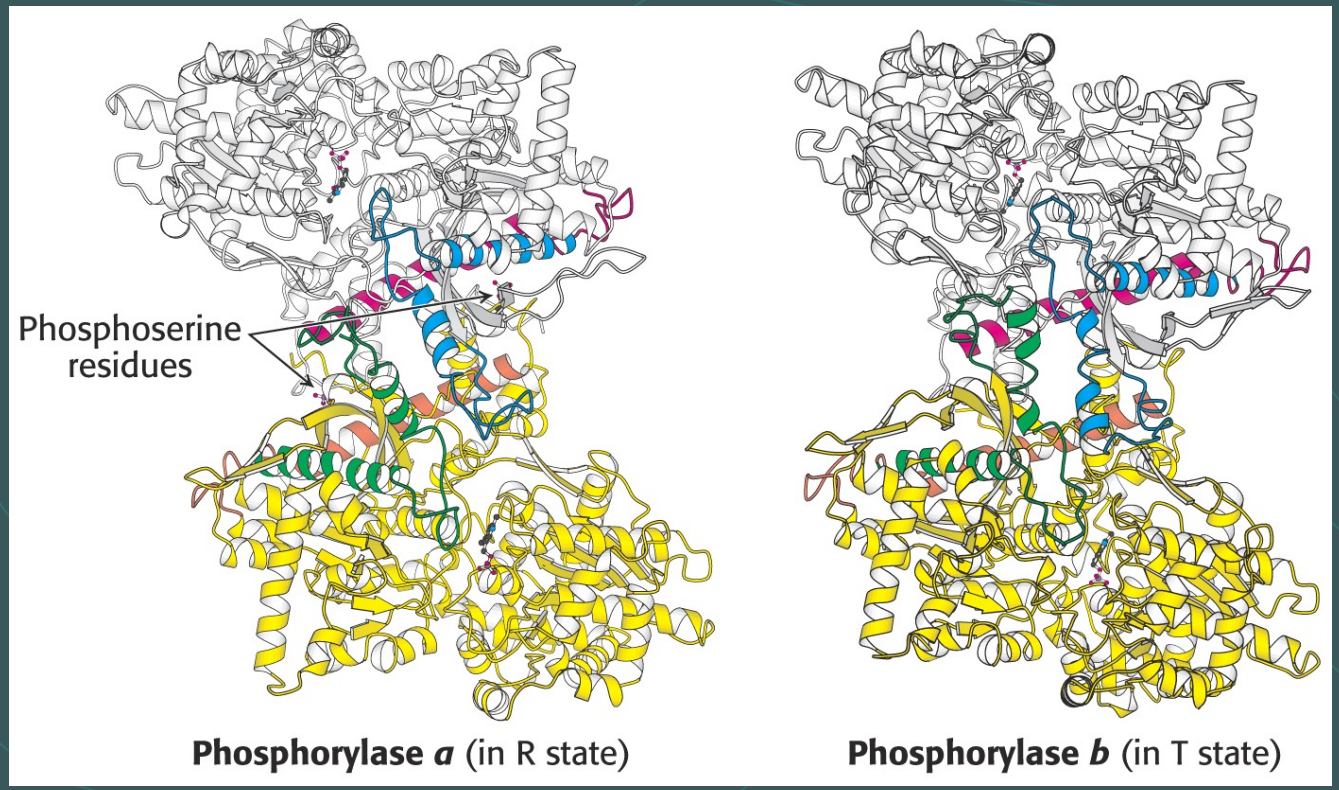
Glycogen Degradation

- What type of catalysis is illustrated by glycogen phosphorylase?
  - acid-base catalysis



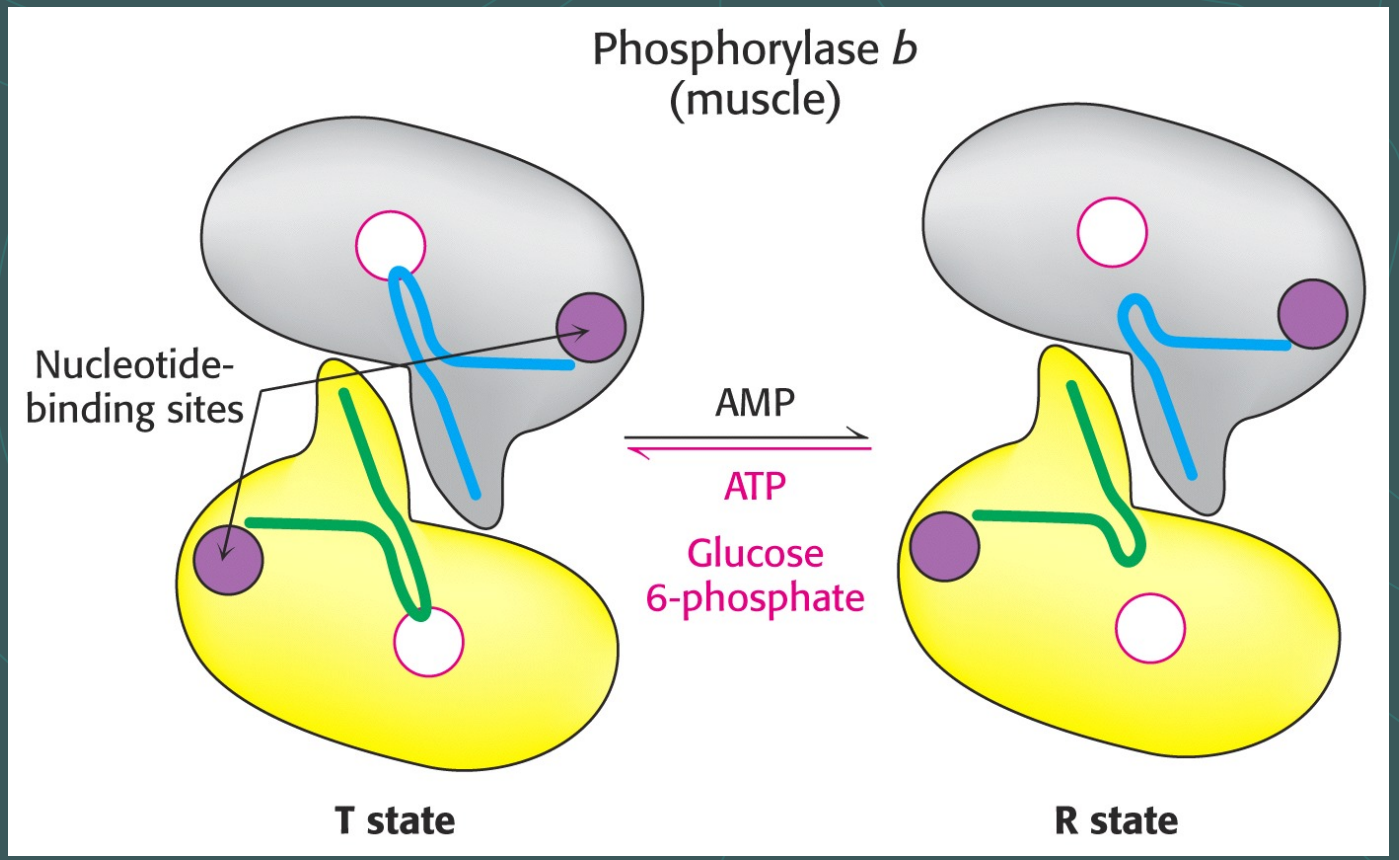
Regulation of Glycogen Phosphorylase

- phosphorylation shifts inactive form to active form in skeletal muscle
  - phosphorylase kinase



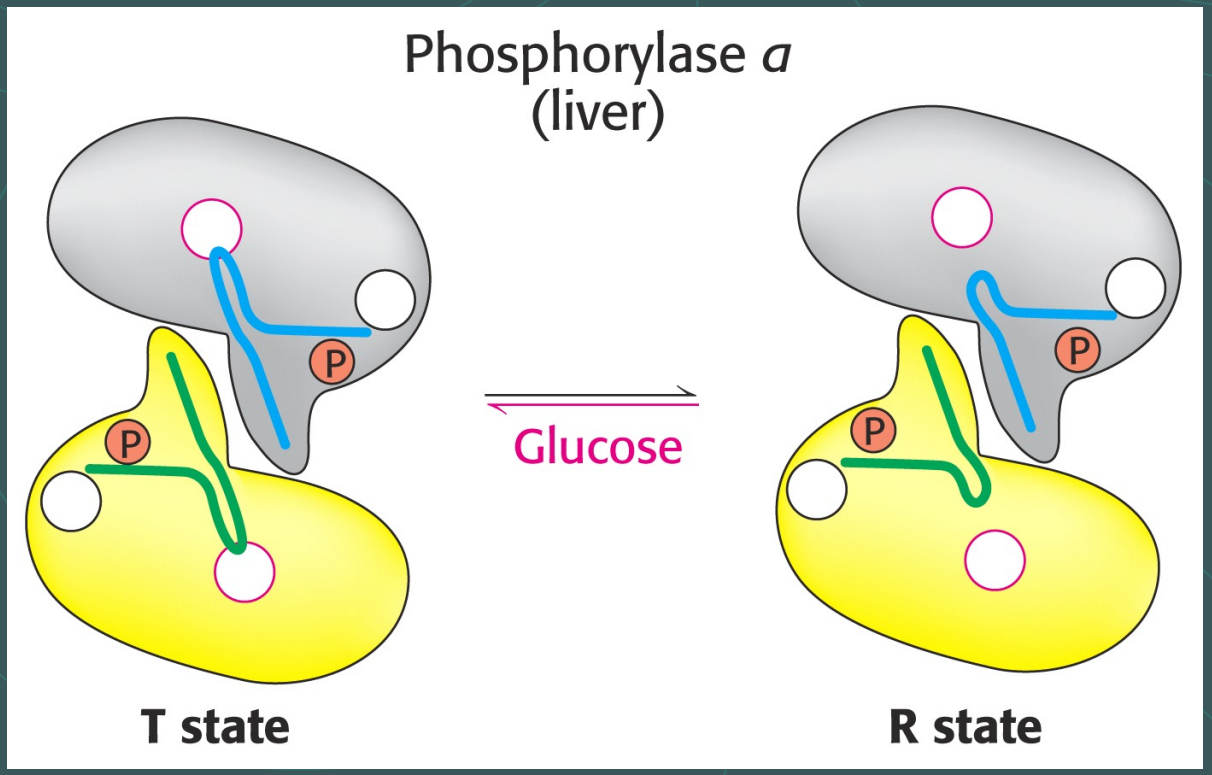
Regulation of Glycogen Phosphorylase

- Enzyme is also influenced by allosteric modulators



Regulation of Glycogen Phosphorylase

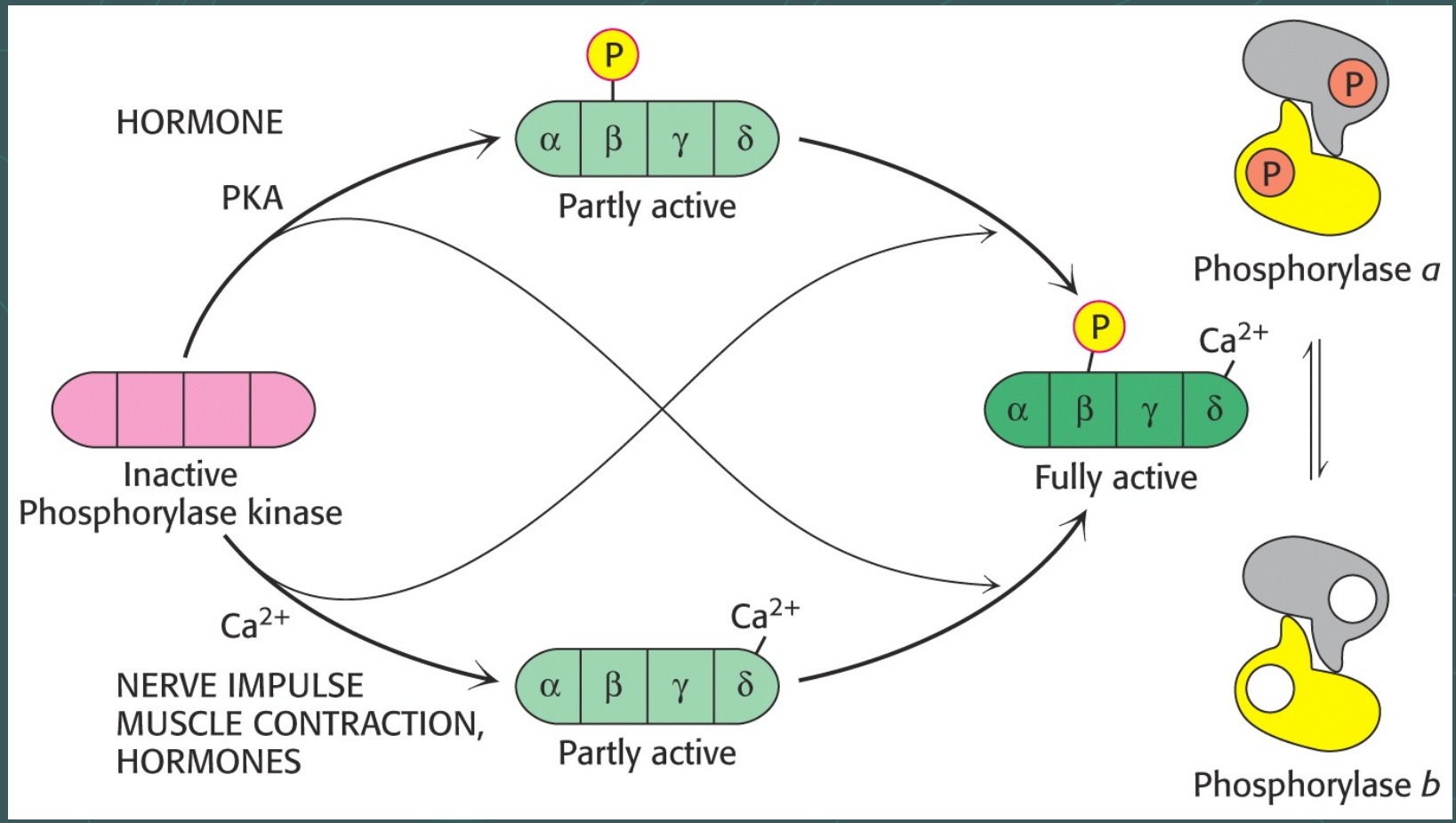
- Liver enzyme is influenced by glucose binding to a form



Regulation of Glycogen Phosphorylase

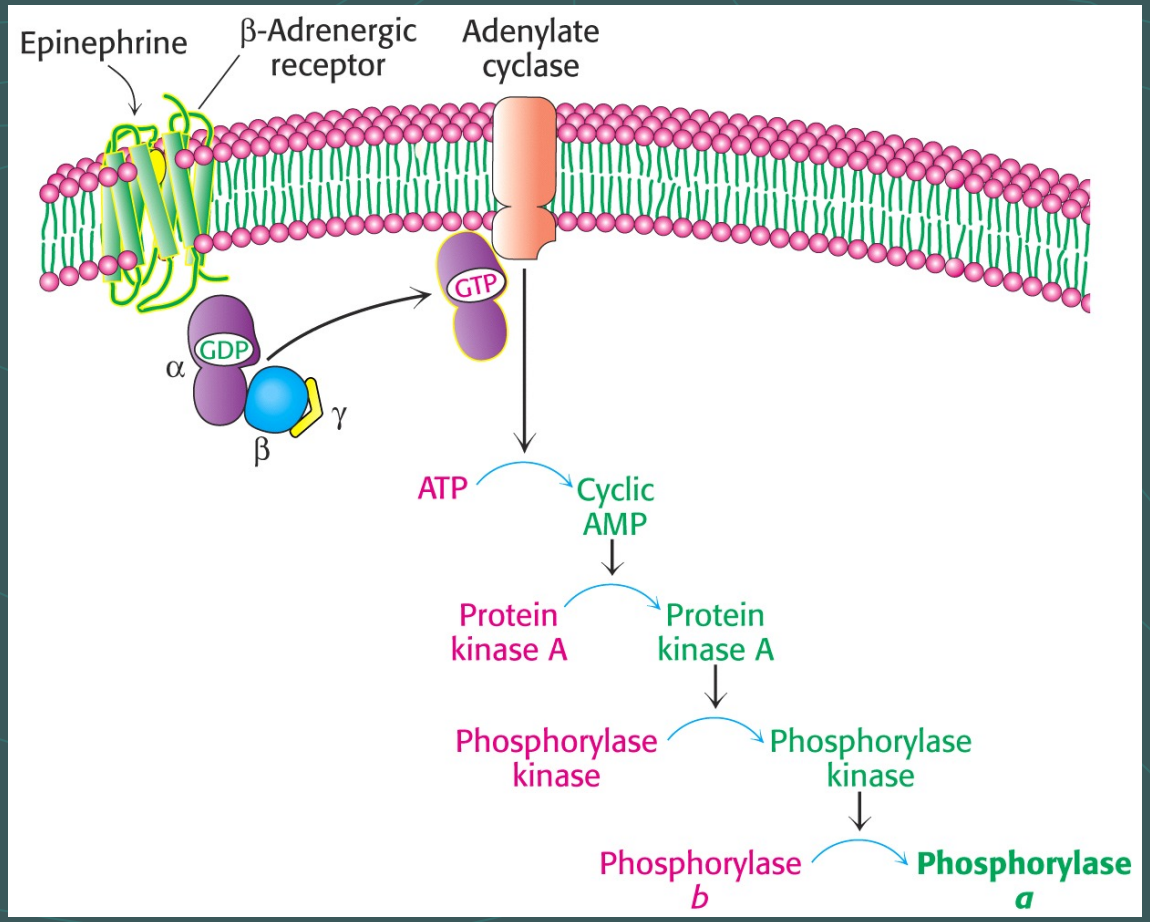
- What is the function of phosphorylase kinase?
  - activate glycogen phosphorylase
    - kinase activity also affected by phosphorylation
    - protein kinase A
      - switched on by cyclic AMP
- What role does Ca^{+2} have here?
  - partially activate phosphorylase kinase

Regulation of Glycogen Phosphorylase



Glycogen Degradation

- What is the role of hormones in glycogen breakdown?



Glycogen Degradation

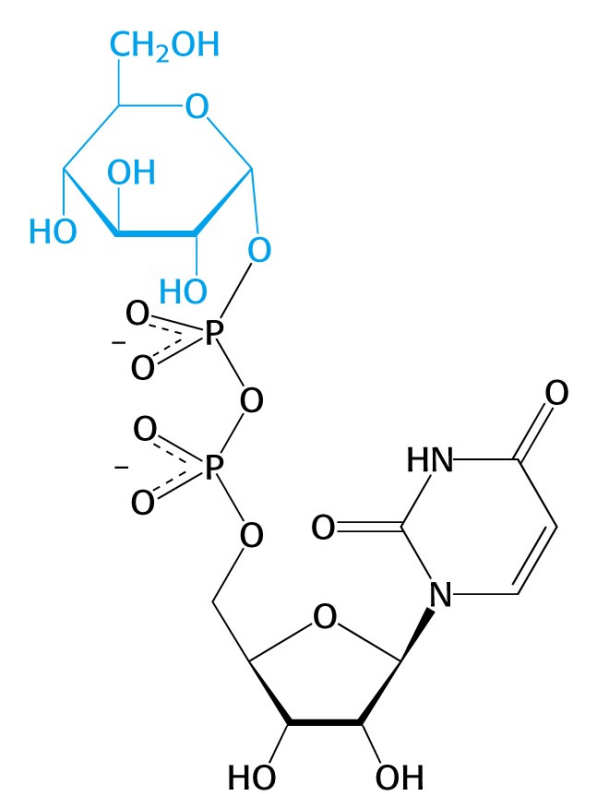
- What differences exist between muscle and liver?
  - epinephrine also binds to α-adrenergic receptor in liver
    - activate phosphoinositide cascade
    - increased Ca^{+2} leads to activation of phosphorylase kinase
  - liver is more responsive to glucagon

Glycogen Degradation

- Glycogen breakdown is shut down in two ways
  - GTPase activity of G protein breaks down GTP into GDP stopping signal transduction
  - protein kinase A adds phosphate group to α subunit of phosphorylase kinase
    - promotes dephosphorylation by protein phosphatase 1
      - enzyme also removes phosphate from phosphorylase to inactivate

Glycogen Synthesis

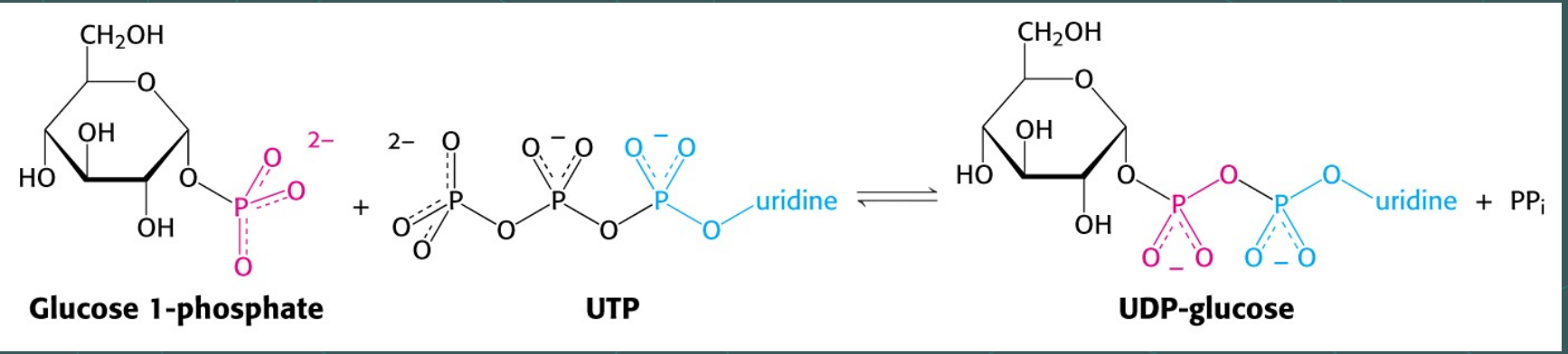
- What is a key molecule in glycogen synthesis?
  - UDP-glucose



Uridine diphosphate glucose (UDP-glucose)

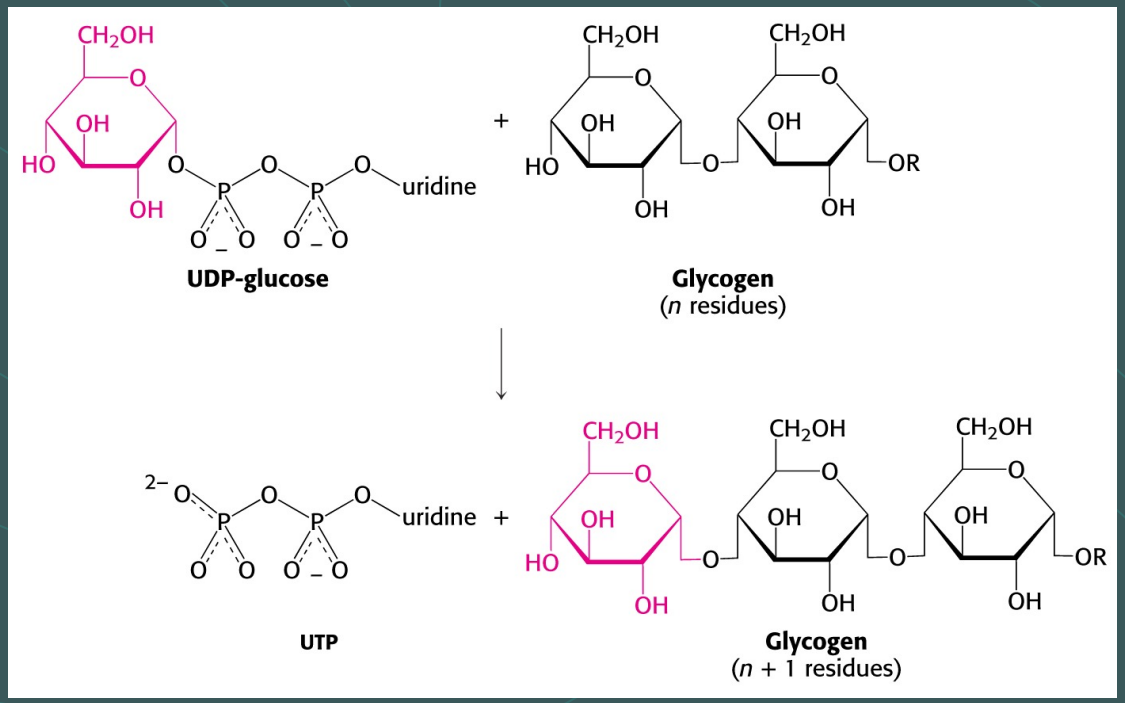
Glycogen Synthesis

- How is UDP glucose made?



Glycogen Synthesis

- What reactions are involved in glycogen synthesis?
  - formation of primer by glycogenin
  - addition of glycosyl residues by glycogen synthase

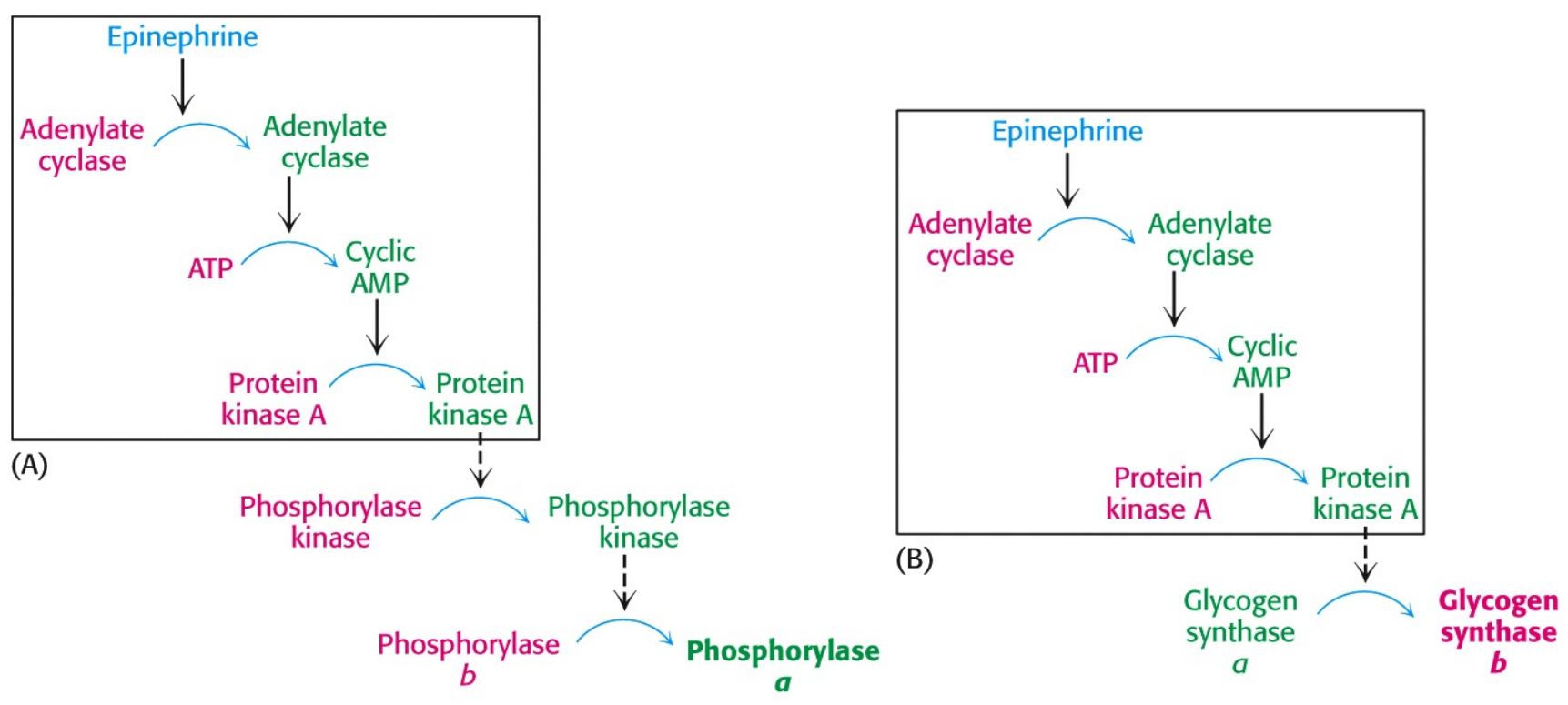


Glycogen Synthesis

- A branching enzyme is needed to form α-1,6 bonds
  - enzyme breaks α-1,4 bonds, removing block of 7 residues and transfers them to create 1,6 linkage
    - branching increases the solubility of glycogen
    - also increases rate of both synthesis and degradation
- Glycogen synthase is inactivated by phosphorylation

Regulation of Glycogen Metabolism

- Synthesis and degradation are reciprocally regulated

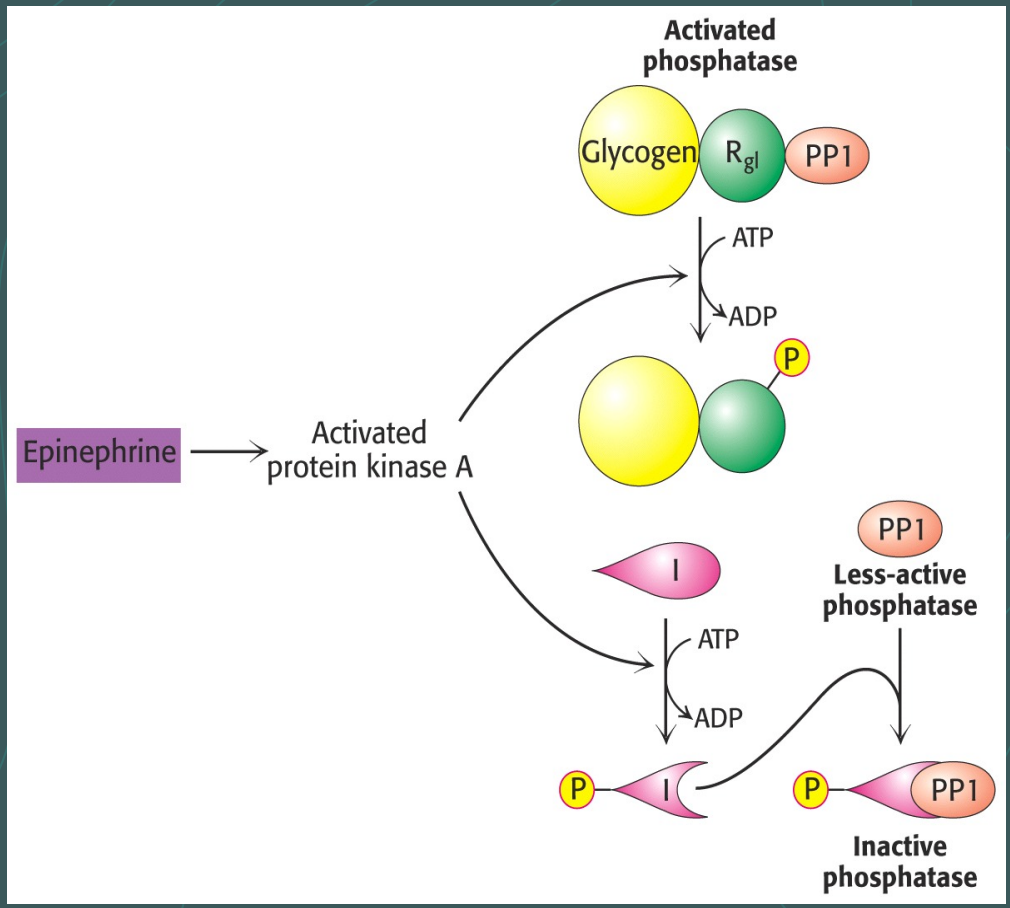


Regulation of Glycogen Metabolism

- Why is protein phosphatase 1 a key enzyme?
  - inactivates phosphorylase kinase and phosphorylase b
  - activates glycogen synthase

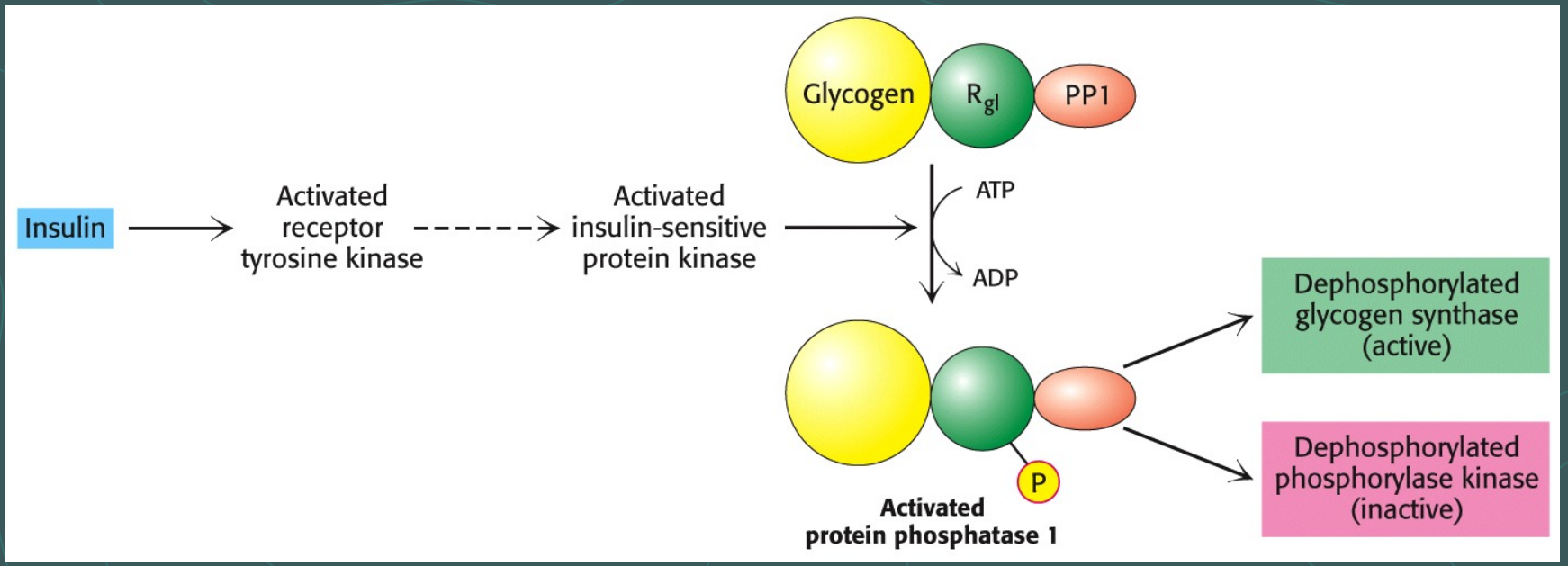
Regulation of Glycogen Metabolism

- Of what does protein phosphatase 1 consist and how is it regulated?
  - PP1 subunit
  - R_{G1} subunit
  - inhibitor 1 subunit



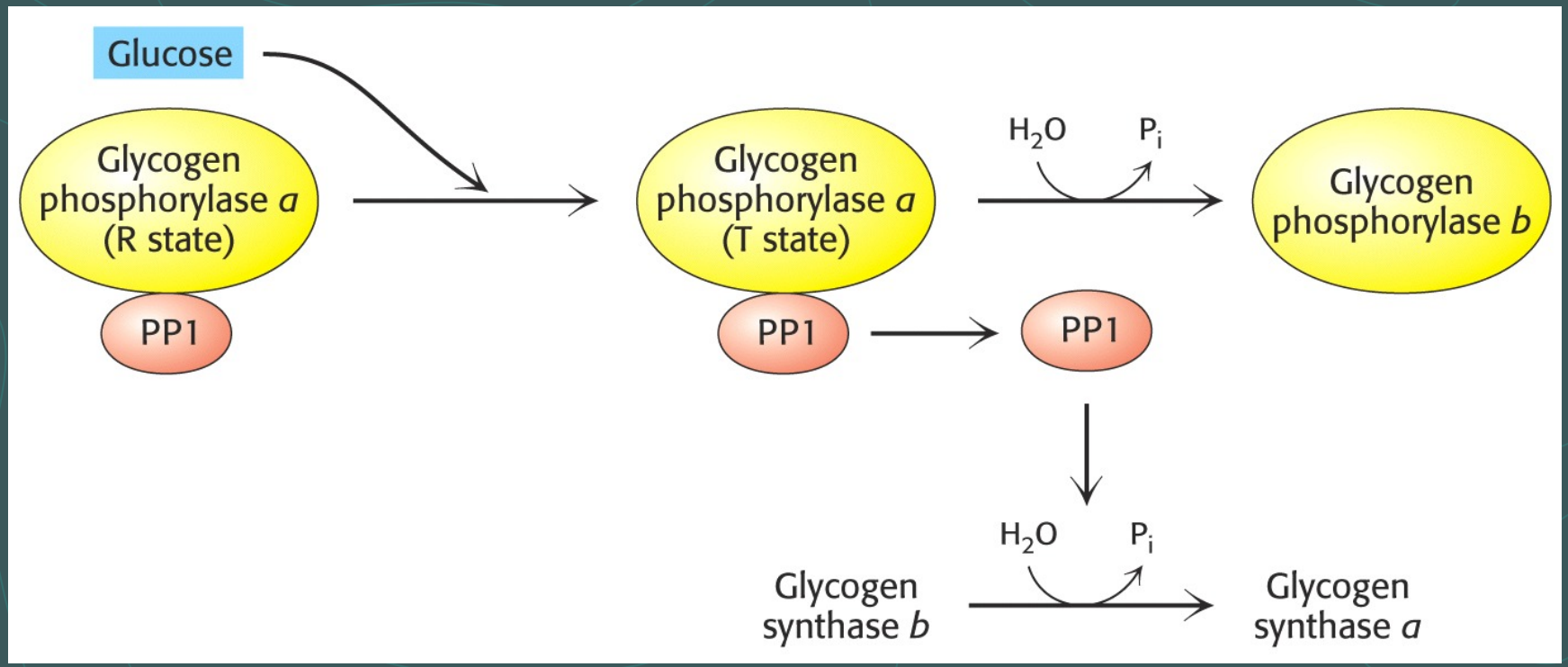
Regulation of Glycogen Metabolism

- What is the role of insulin in glycogen metabolism?



Regulation of Glycogen Metabolism

- What mechanism is involved in this regulation?



Regulation of Glycogen Metabolism

- What are glycogen-storage diseases?
  - inability to breakdown or utilize glycogen
  - genetically influenced enzymatic defects associated with various enzymes
    - phosphorylase
    - debranching enzyme
    - glucose 6-phosphatase
  - seen in muscle, liver, and kidney

Regulation of Glycogen Metabolism

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.