Glycogenesis

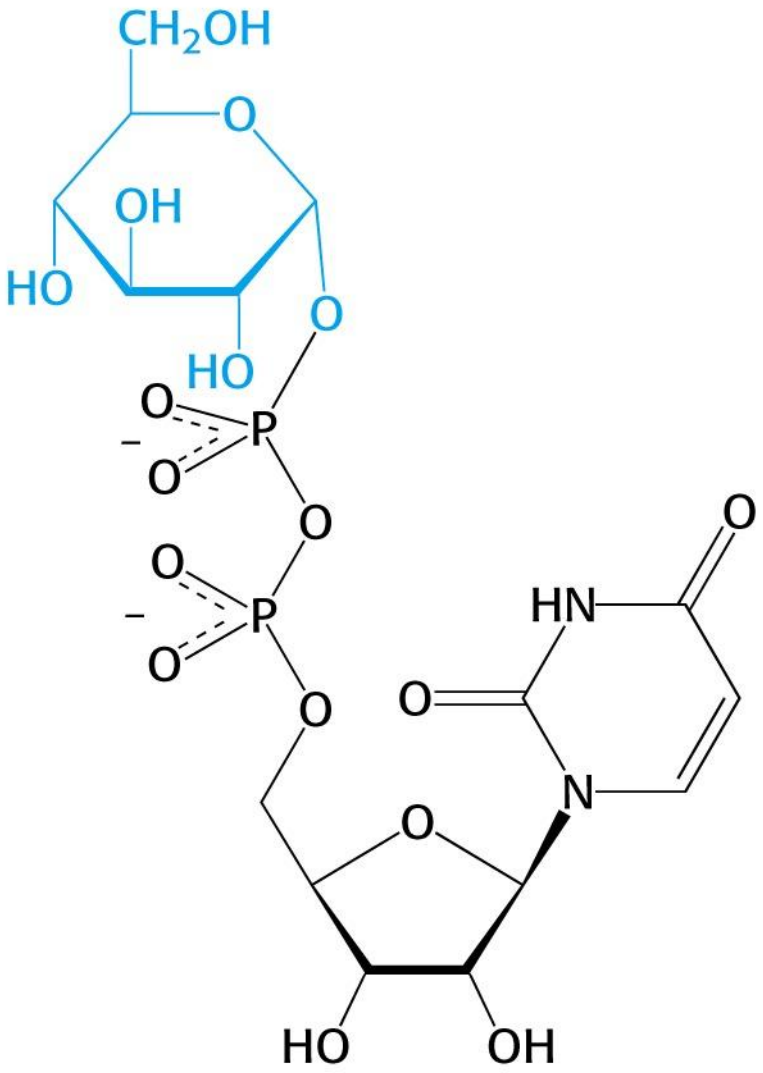
- Glycogen is synthesized via uridine diphosphate glucose (UDP – glucose).
- Synthesis: $Glycogen_n$ + UDP-glucose $\rightarrow$ $glucogen_{n+1}$ + UDP.
- Degradation: $glucogen_n + P_i \rightarrow Glycogen_{n-1}$ + glucose 1-phosphate.

Glycogen synthesis and degradation utilize separate pathways.

Luis Leloir
Nobel Prize in Chemistry, 1970

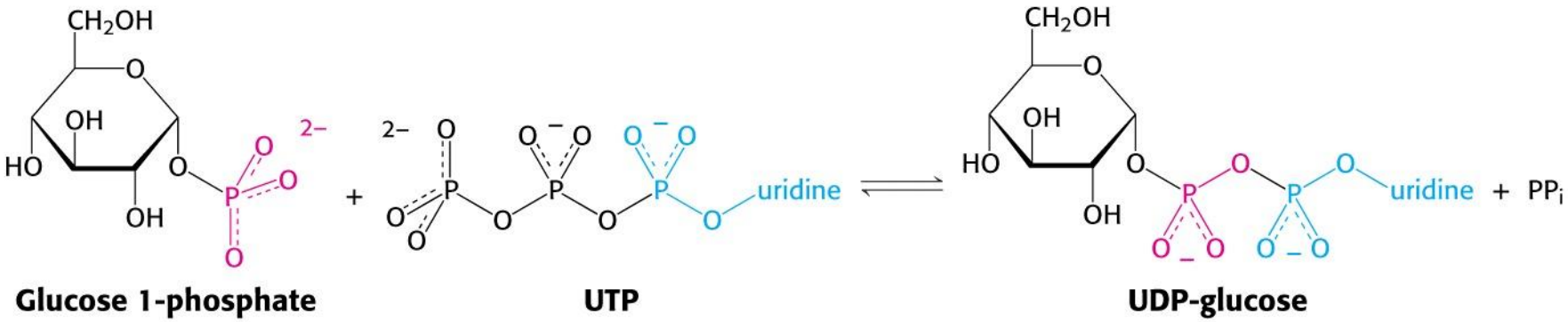
“ for his discovery of sugar nucleotides and their role in the biosynthesis of carbohydrates”

UDP glucose is the activated form of glucose.
Acetyl CoA is the activated form of acetate.
AA-tRNA is the activated form of amino acids.



Uridine diphosphate glucose (UDP-glucose)

UDP-glucose pyrophosphorylase



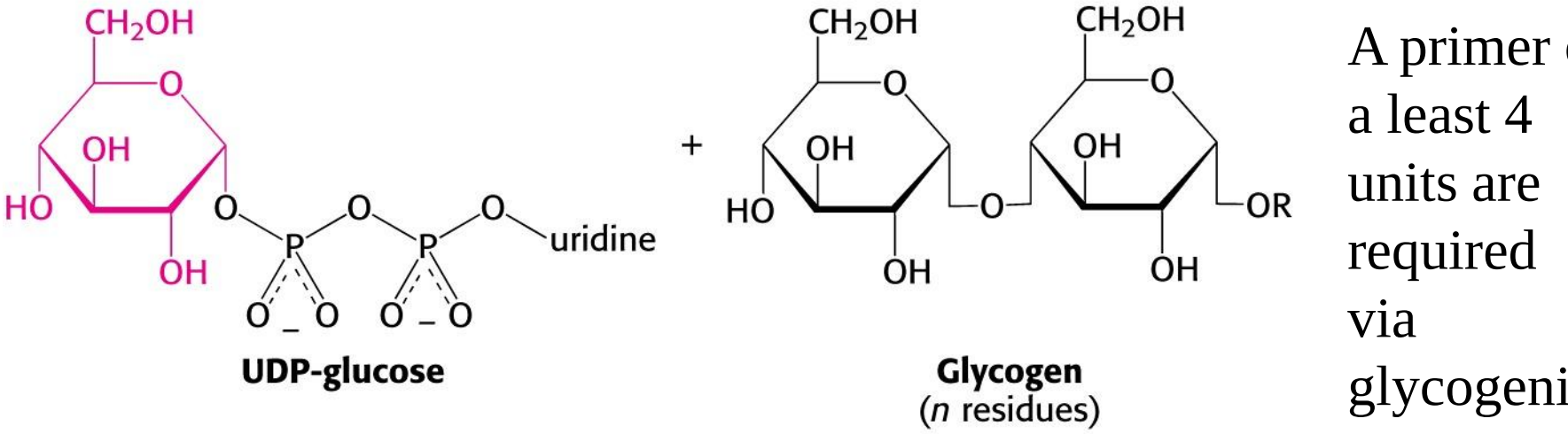
Glucose 1-phosphate + UTP ⇆ UDP-glucose + PP_i.

$pp_i + H_2O \rightarrow 2P_i$.

Glucose 1-phosphate + UTP + $H_2O \rightarrow$ UDP-glucose + $2P_i$.

Although the reaction is reversible the hydrolysis of the pyrophosphate pushes it to the right.

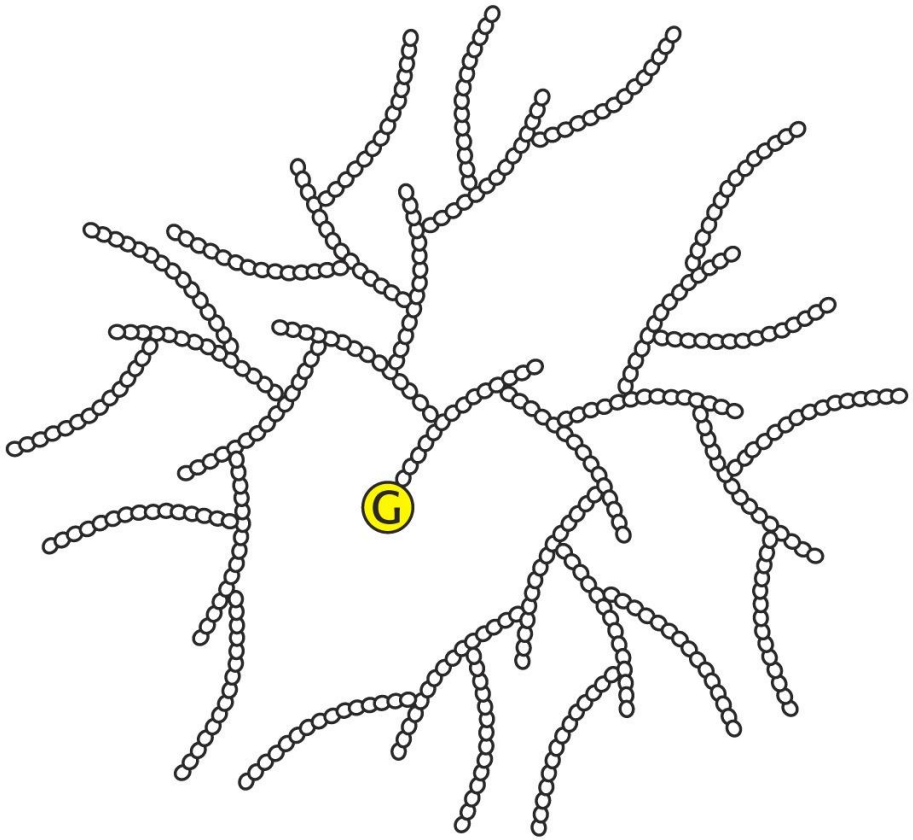
Glycogen synthase catalyzes α-1,4 linkages



A primer of a least 4 units are required via glycogenin.

Branching enzyme forms α-1,6 linkages: Remodeling

The enzyme breaks the α-1,4 link and forms a α-1,6 link. A large number of terminal residues are now available for glycogen phosphorylase; degradation.



Branching increases the solubility of glycogen.

Glycogen synthase is the regulatory enzyme in the synthesis of glycogen.

The enzyme is regulated by covalent modification; phosphorylation.

Regulation of Glycogen Synthase

- When the enzyme is phosphorylated, it is inactivated.
  - Active “a” form to inactive phosphorylated “b” form.
- Notice that phosphorylation has the opposite effect on glycogen phosphorylase; phosphorylation activates.

Glycogen synthesis

Glucose 6-P$\rightarrow$ glucose 1-P.

glucose 1-P + UTP$\rightarrow$UDP-glucose + PP_i.

$PP_i + H_2O \rightarrow 2\ P_i$.

UDP-glucose + $glycogen_n \rightarrow glycogen_{n+1}$.

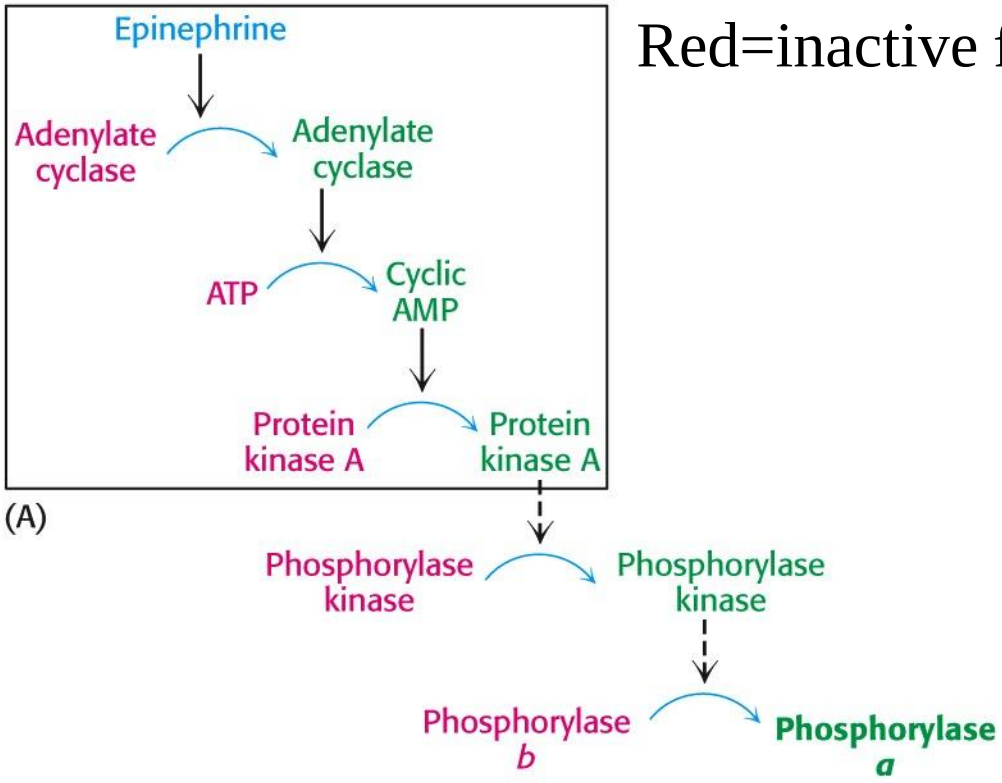
UDP + ATP $\rightarrow$ UTP + ADP.

Glucose 6-P + ATP + $glycogen_n$ + $H_2O \rightarrow$ $glycogen_{n+1}$ + ADP + $2P_i$.

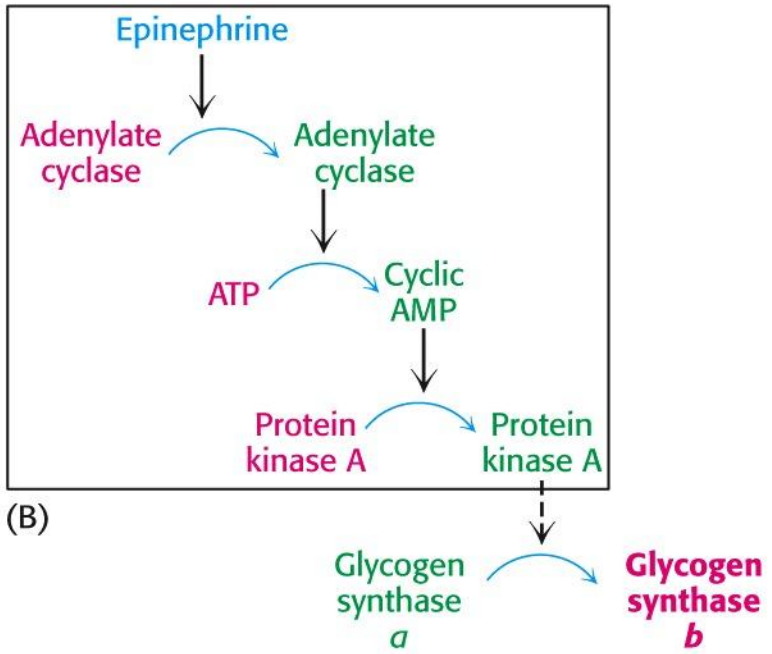
Only one ATP is used to store one glucose residue in glycogen.

(nucleoside diphosphokinase)

Glycogen synthesis and breakdown are reciprocally regulated



Red=inactive forms, green = active forms.



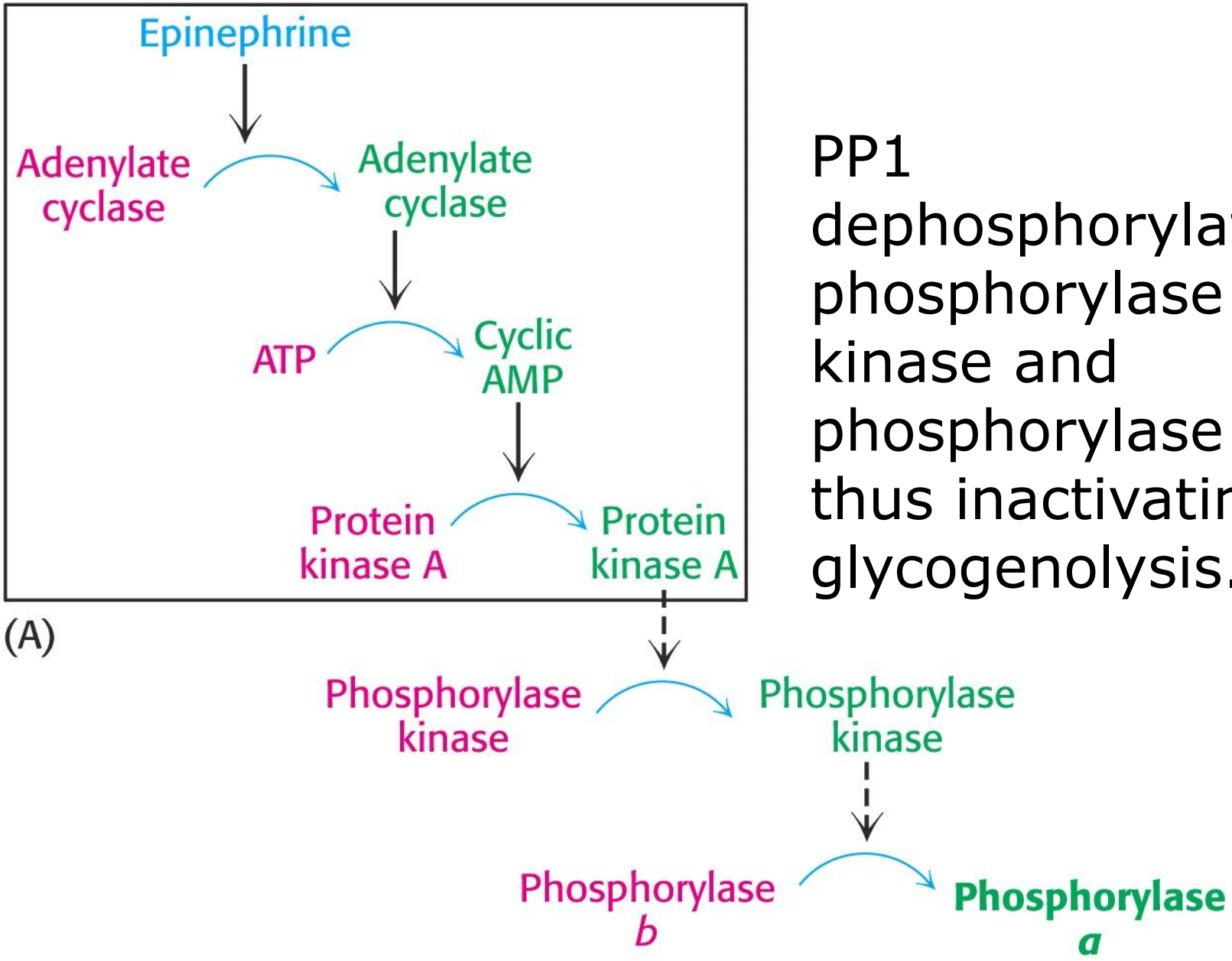
Active

Inactive

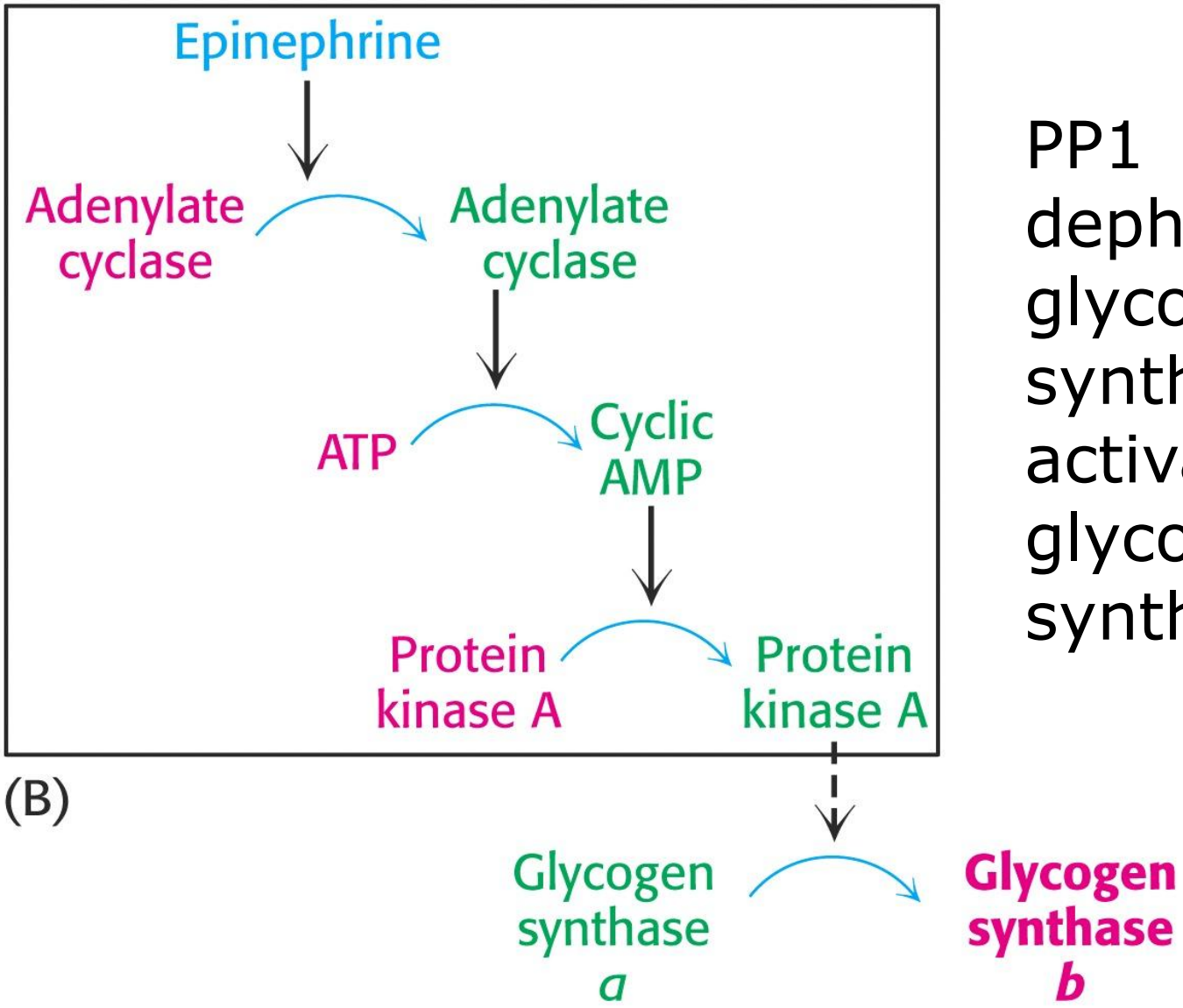
Protein phosphatase 1 (PP1) regulates glycogen metabolism.

Protein Phosphatase 1

- PP1 dephosphorylates phosphorylase kinase and phosphorylase a, thus inactivating glycogenolysis.
- PP1 also dephosphorylates glycogen synthase b, thus activating glycogen synthesis.



PP1 dephosphorylates phosphorylase kinase and phosphorylase a thus inactivating glycogenolysis.



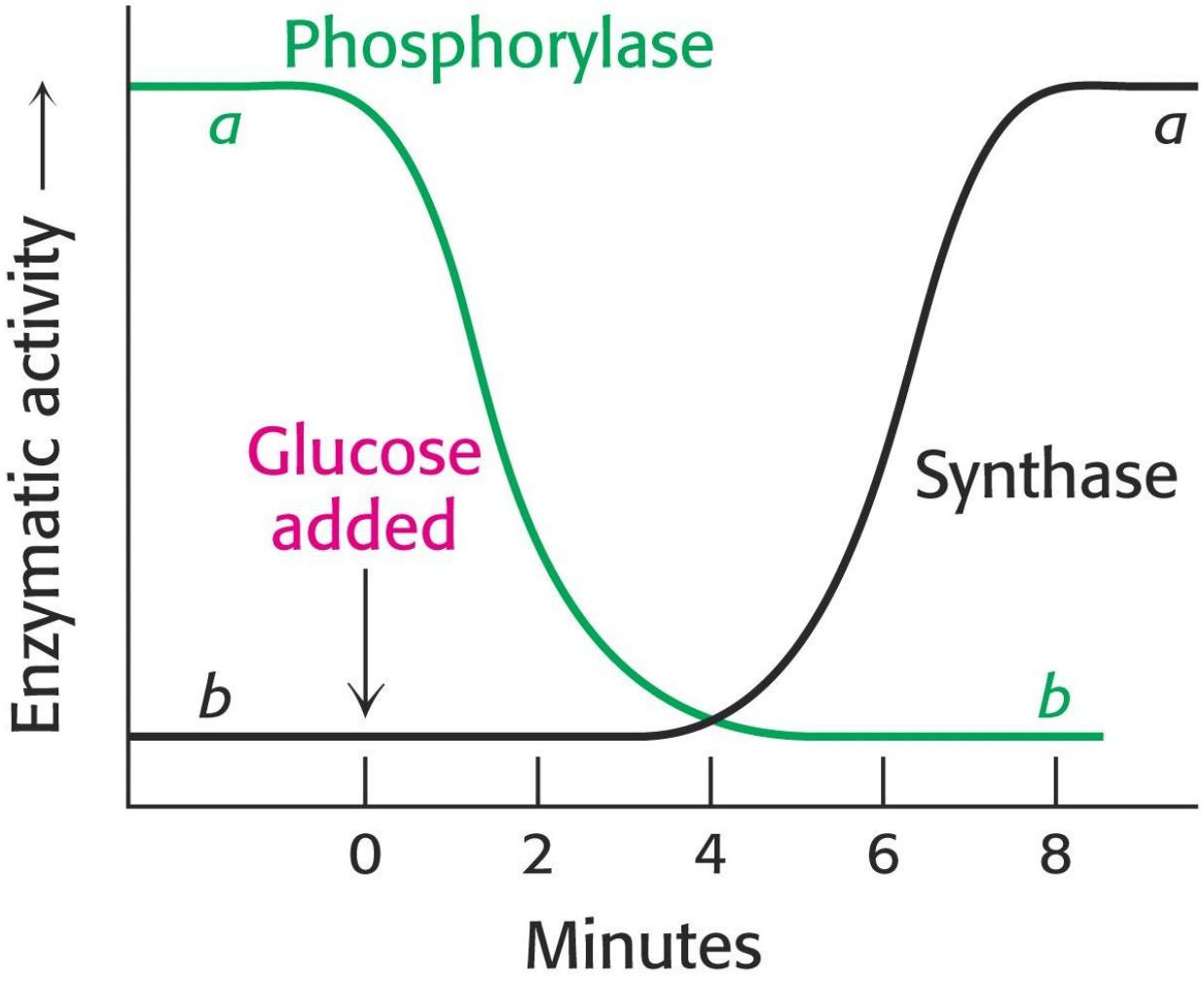
PP1 dephosphorylates glycogen synthase b thus activating glycogen synthesis

- When blood glucose levels are high, insulin activates protein phosphatase 1 which stimulates glycogen synthesis.
  - This is accomplished through a complex highly regulated signal transduction pathway.
- Remember: Glycogen metabolism in liver regulates blood glucose levels.

Blood glucose levels rise after ingestion of carbohydrates, leading to glycogen synthesis.

Inactivation of phosphorylase and an activation ofglycogen synthase.

Liver

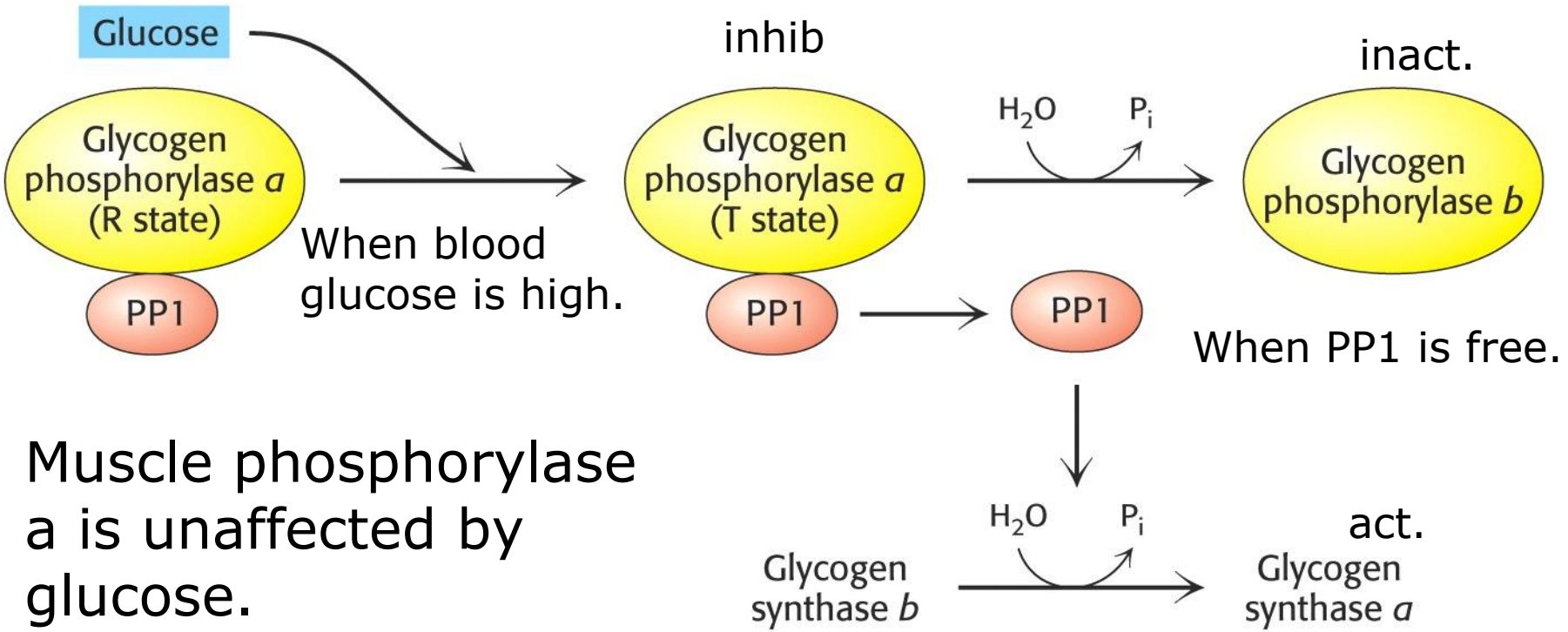


Besides insulin, glucose itself binds to phosphorylase a.

PP1 acts as a catalyst only when phosphorylase a is in the T state.

The conversion of a→b releases PP1 to activate glycogen synthase.

In liver



Muscle phosphorylase a is unaffected by glucose.

A Take Home Lesson!

- Glucogon = starved state; stimulates glycogen breakdown, inhibits glycogen synthesis.
- High blood glucose levels = fed state; insulin stimulates glycogen synthesis and inhibits glycogen breakdown.