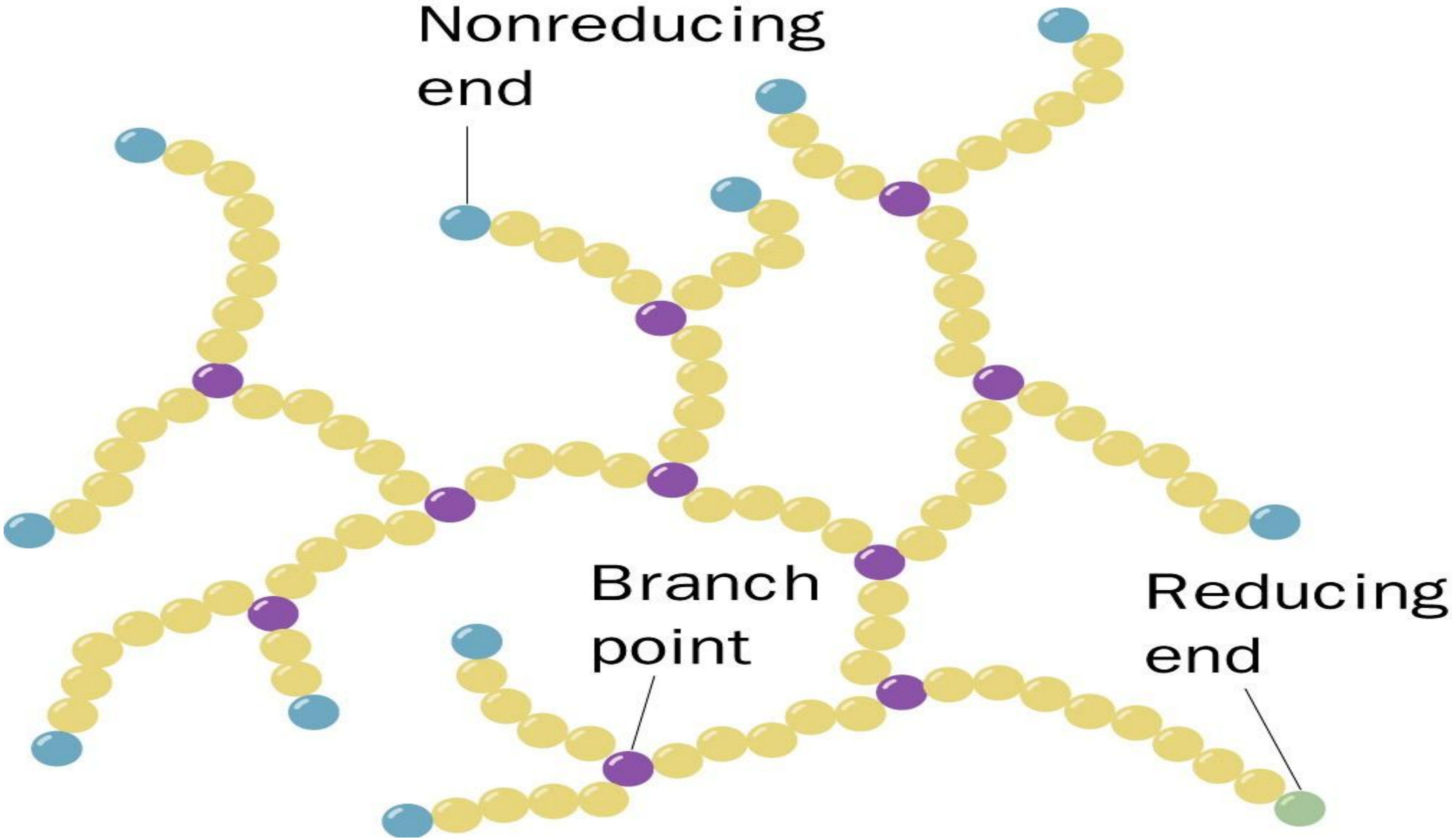
Glycogen Metabolism



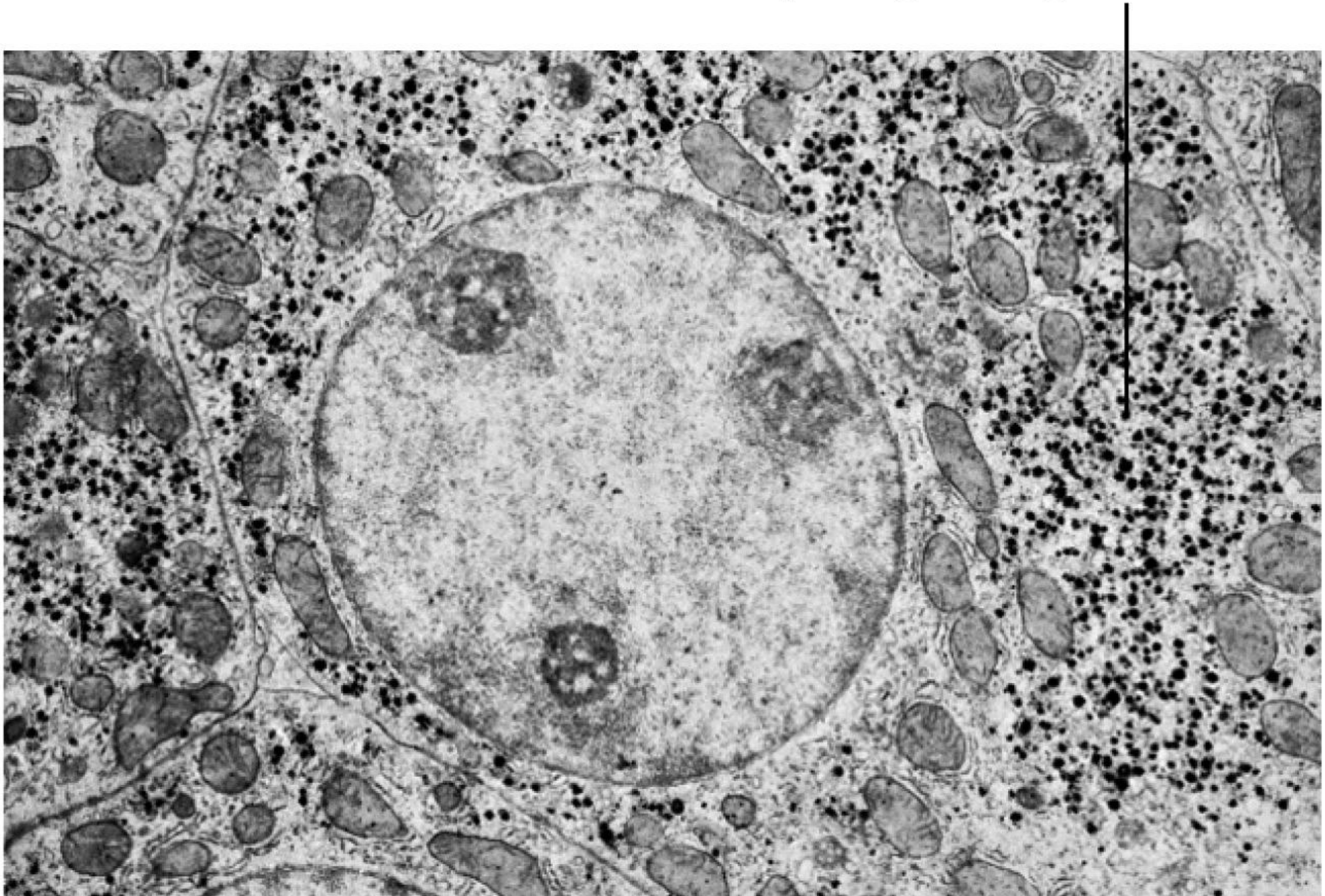
Glycogen Function

- In liver – The synthesis and breakdown of glycogen is regulated to maintain blood glucose levels.
- In muscle - The synthesis and breakdown of glycogen is regulated to energy requirements of the muscle cell.

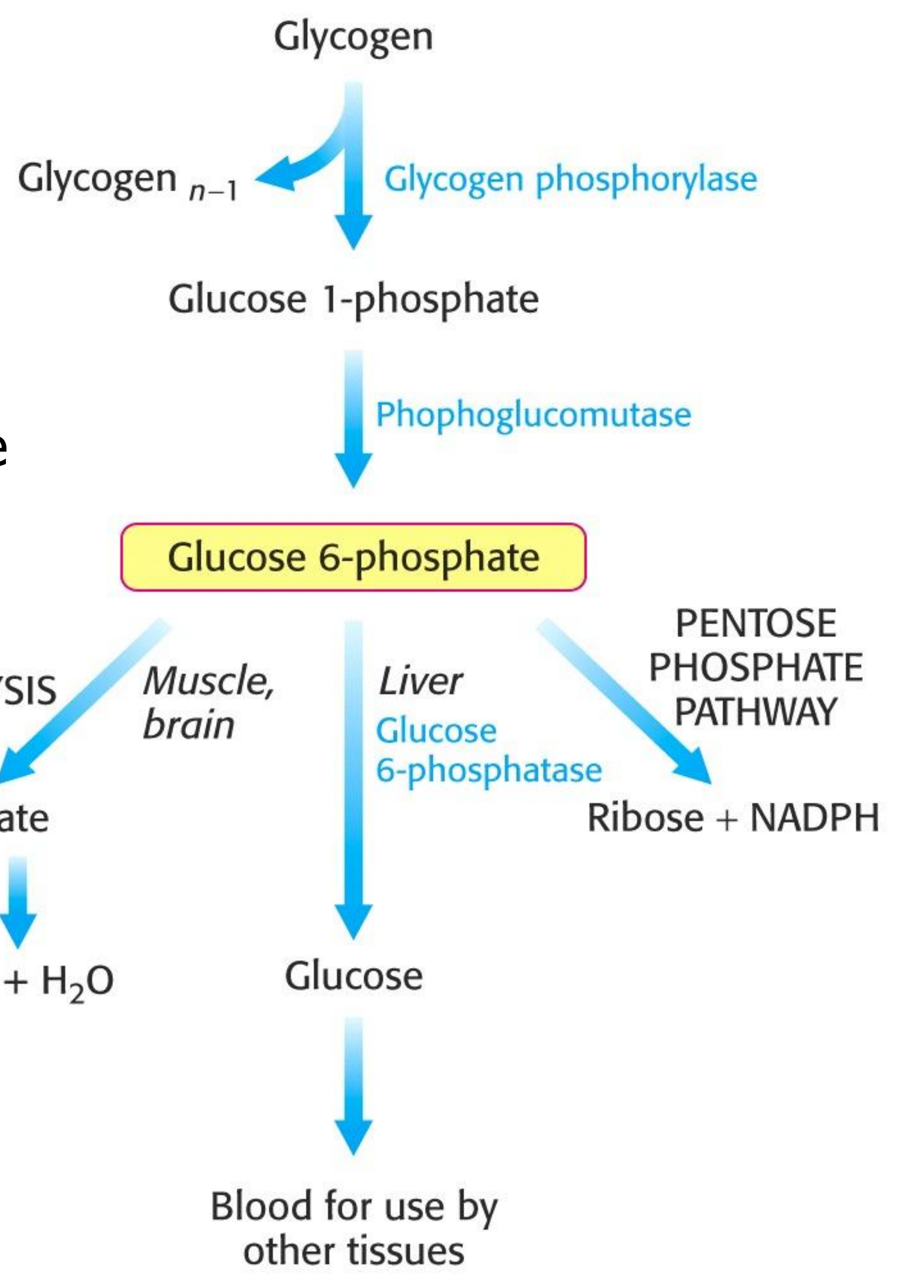
Glycogenolysis

- Glycogenolysis is a catabolic process; the breakdown of glycogen to glucose units.
- Glycogen is principally stored in the cytosol granules of -
  - Liver
  - Muscle

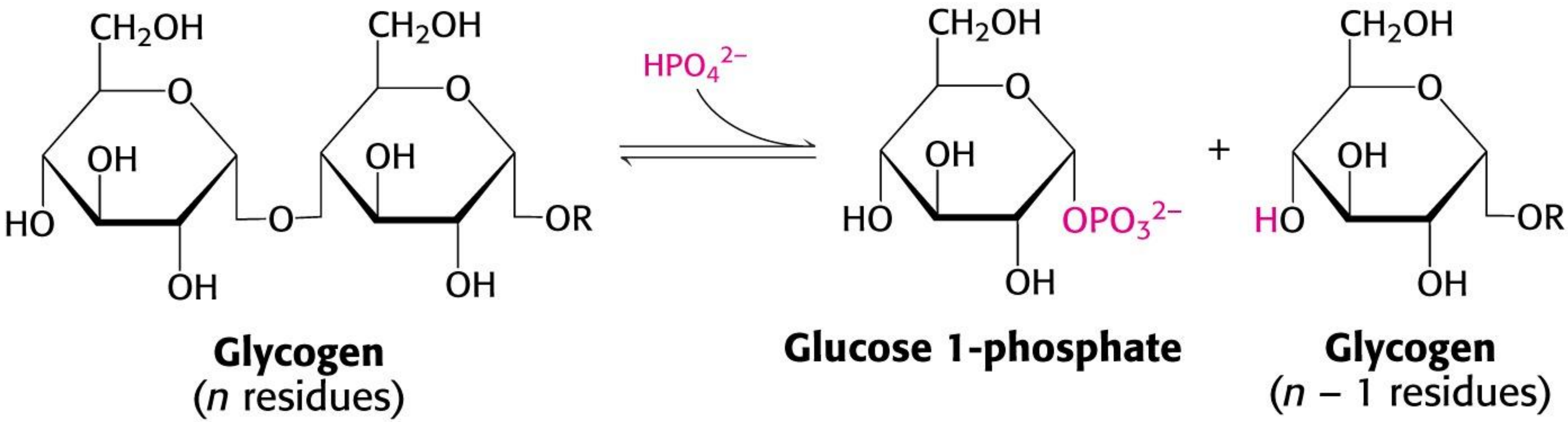
Liver Cell



Glucose 6-phosphate has 3 fates.



Glycogen phosphorylase catalyzes the breakdown of glycogen.



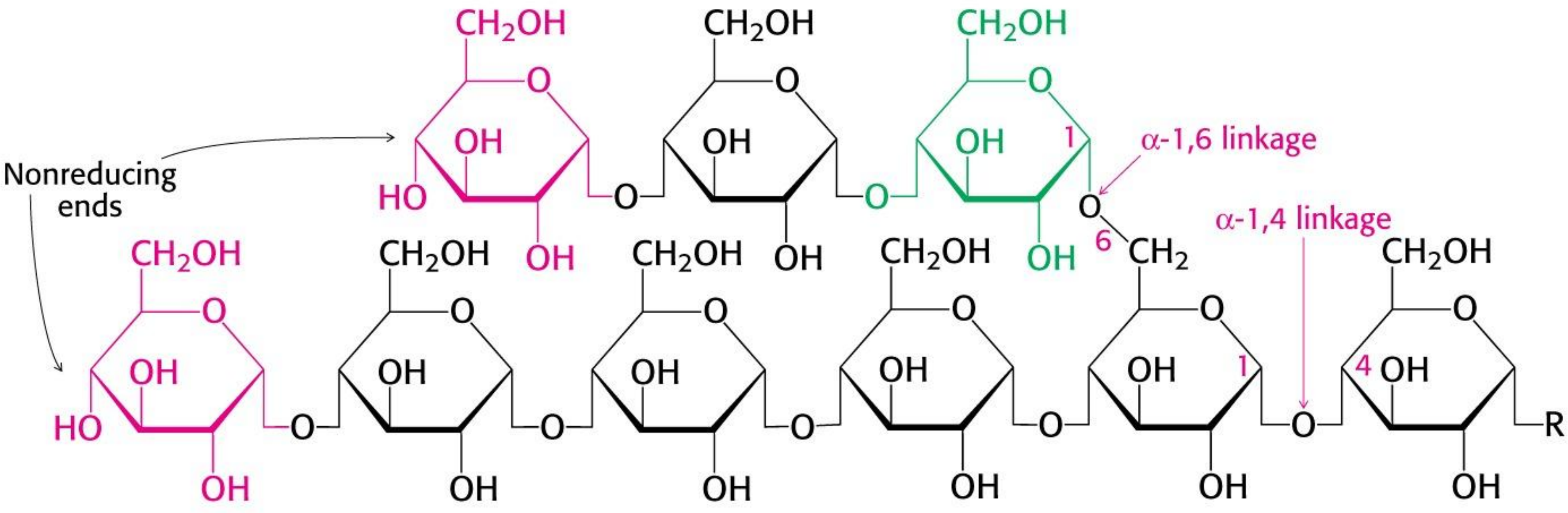
Glycogen + Pi ⇆ Glucose 1- phosphate + glycogen

(*n residues*) (*n-1 residues*)

A note on the energetics.

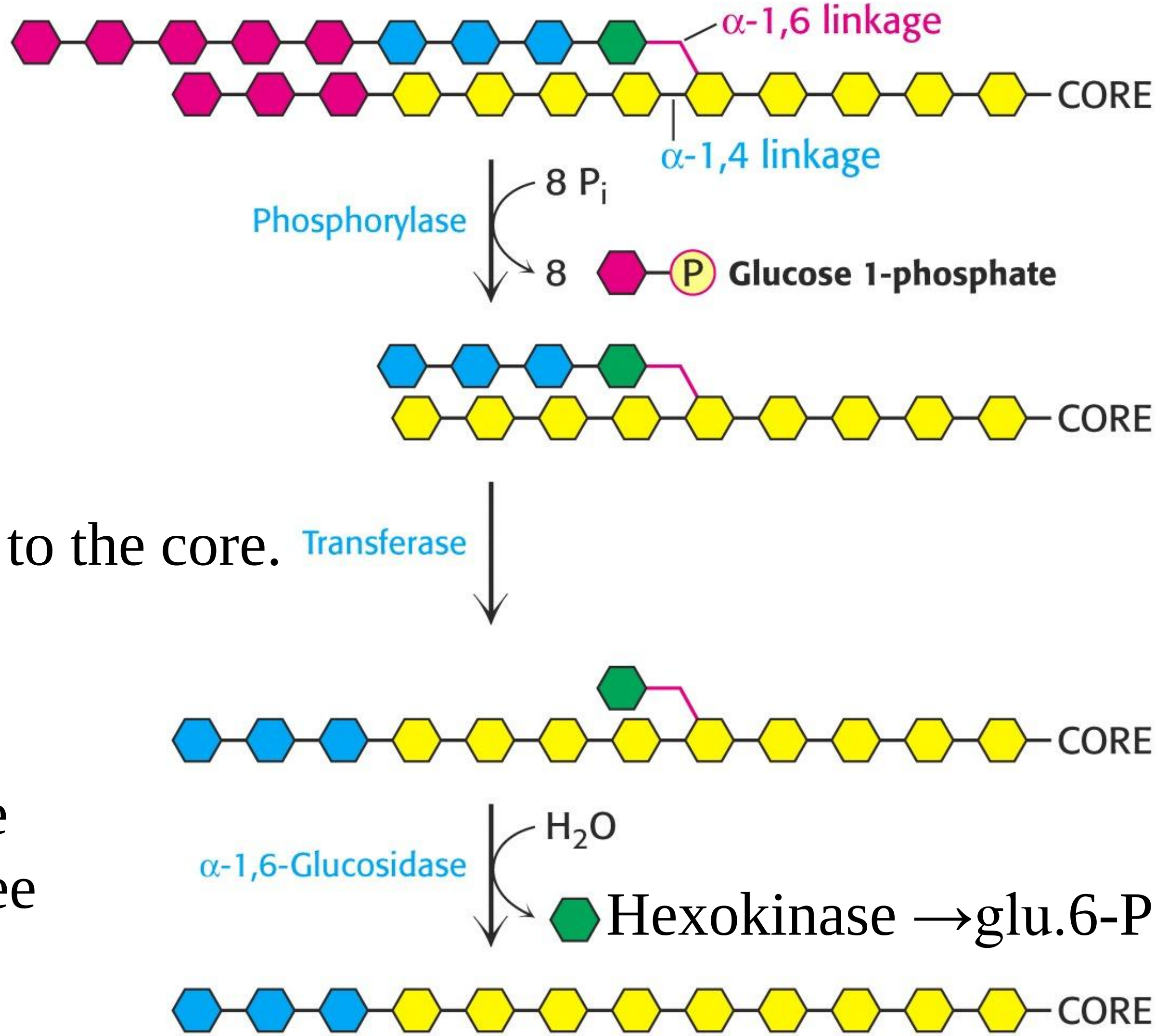
- The reaction is reversible
- It proceeds to the right (breakdown)
- Notice the release sugar is already phosphorylated. No investment of ATP is required and can enter glycolysis directly.
- The phosphorylated product (glucose 1-phosphate) can not leave the cell.

The α-1,4-linkage predominates.



Synthesis requires the addition of glucose to the non-reducing ends of glycogen via UDP-glucose.

Phosphorylase is specific for the α-1,4 linkage. Two additional enzymes are required.



Linear molecule
is created.

Shifts 3 glycosyl units to the core.

Hydrolyzes the single
1,6 glucose unit to free
glucose.

Note!

- The glucose 1-phosphate to converted to glucose 6-phosphate by phosphoglucomutase.

Remember!

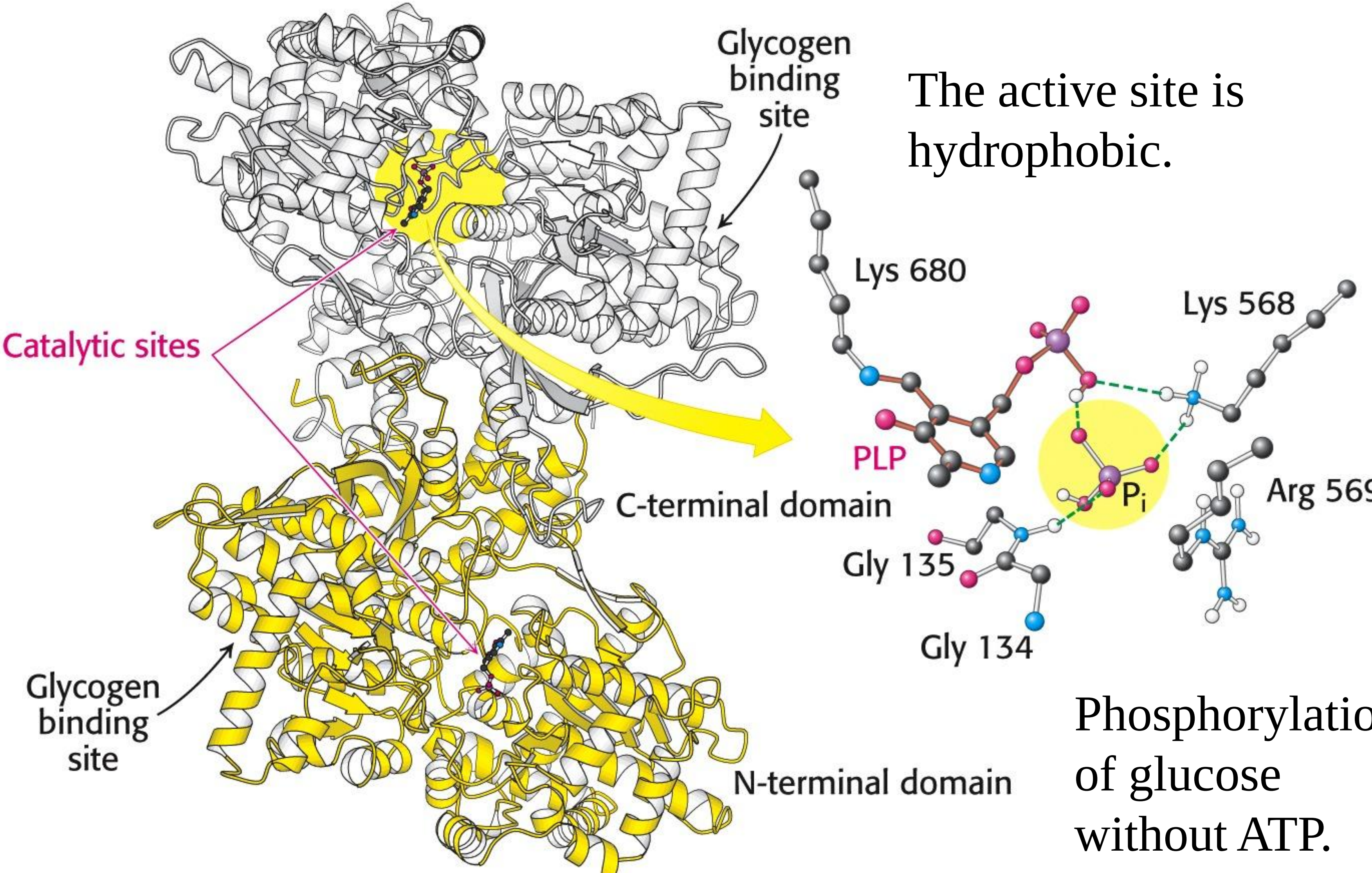
- Liver contains glucose 6-phosphatase.
- Muscle does not have this enzyme.

WHY?

The liver releases glucose to the blood to be taken up by brain and active muscle. The liver regulates blood glucose levels.

The muscle retains glucose 6-phosphate to be use for energy. Phosphorylated glucose is not transported out of muscle cells.

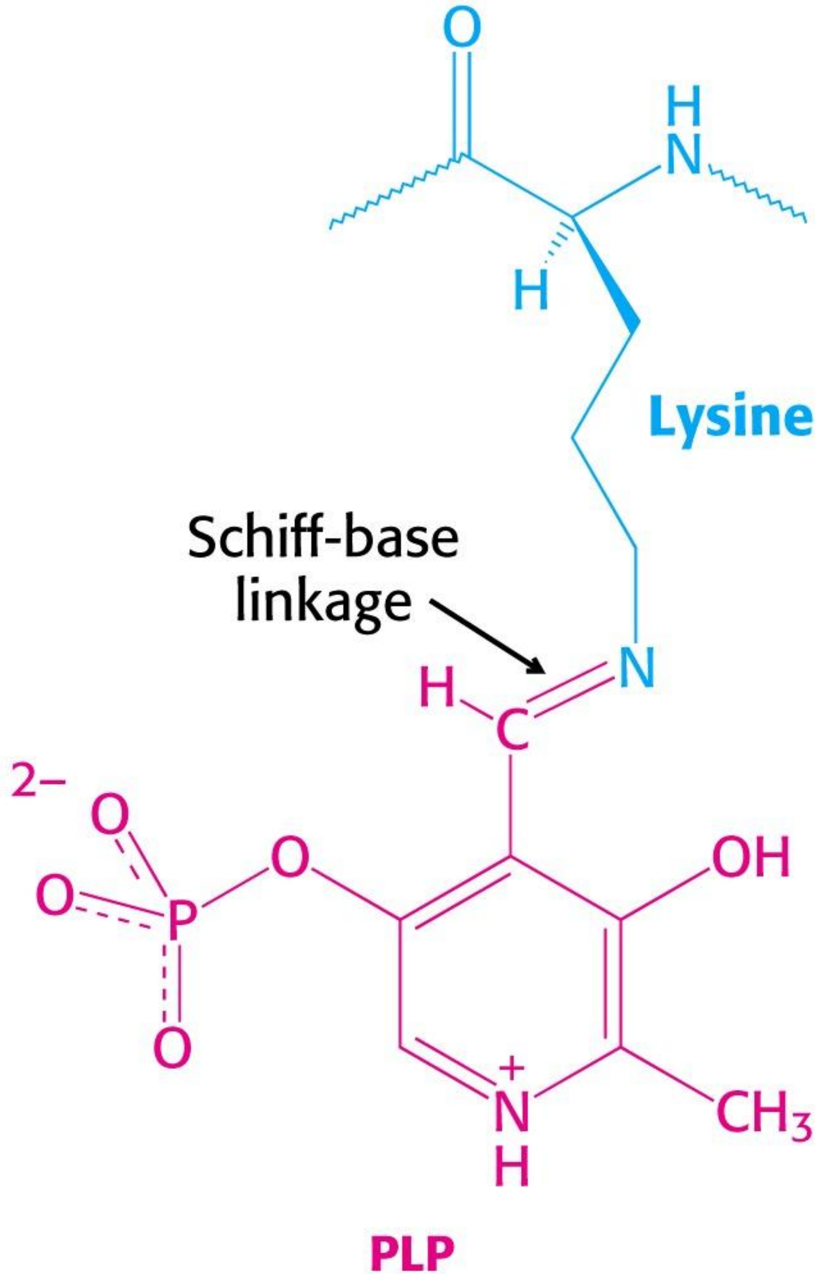
Pyridoxal phosphate is the coenzyme for phosphorylase.



The active site is hydrophobic.

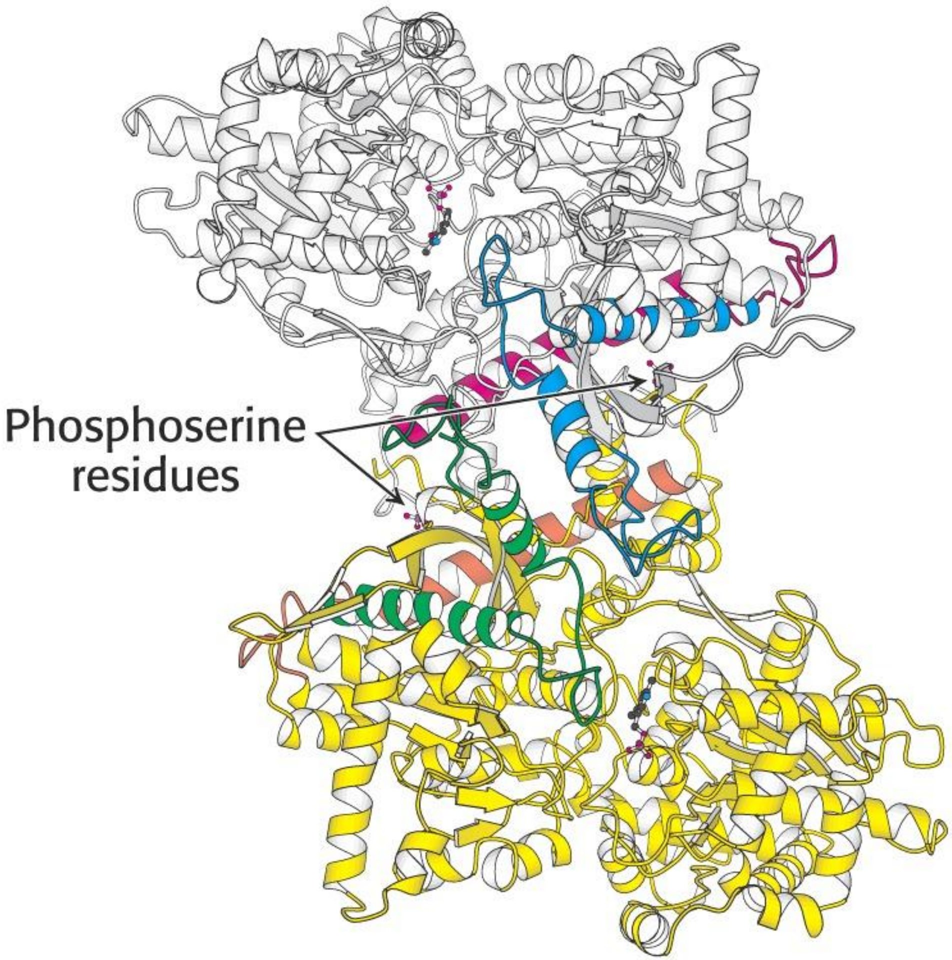
Phosphorylation of glucose without ATP.

Glycogen phosphorylase uses pyridoxal phosphate (PLP) a derivative of pyridixine (vitamine B_6) as a coenzyme.



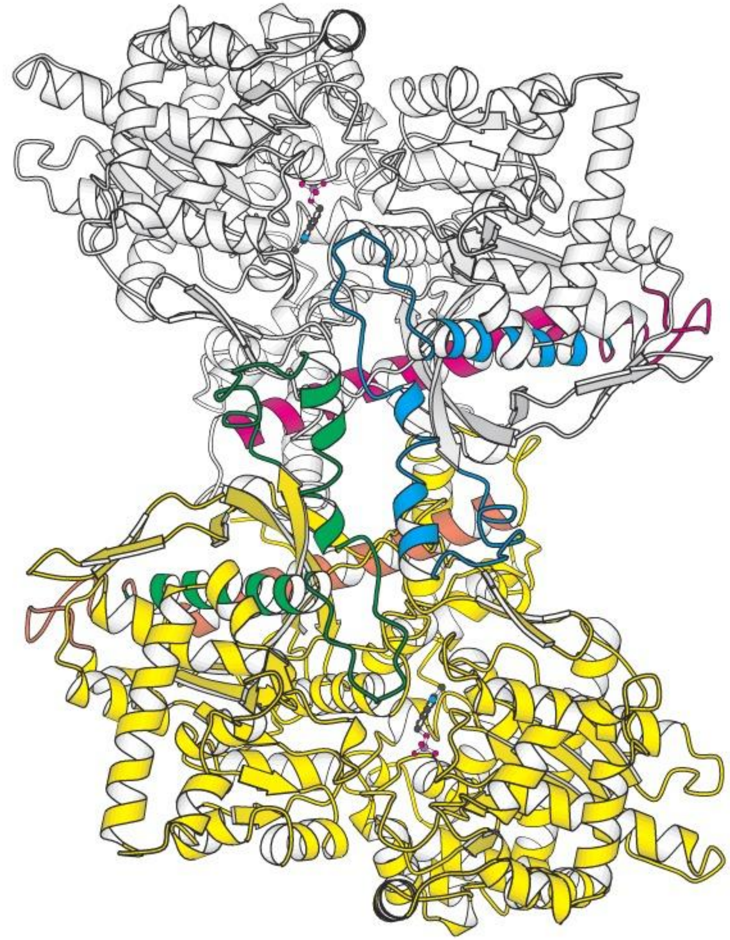
B_6 is required for the mobilization of glucose from glycogen. It is also required for other biochemical reactions such as transamination.

Phosphorylase is an allosteric enzyme.



Phosphorylase *a* (in R state)

Active



Phosphorylase *b* (in T state)

Inactive

- Each of the two forms are in equilibrium between an active relaxed (R) state and less active (T) state.
- The equilibrium for phosphorylase a favors the R state (active).
- The equilibrium for phosphorylase b favors the T state (less active).

- Phosphorylase b is converted to Phosphorylase a (active) with the phosphorylation of serine 14 by the enzyme *phosphorylase kinase*.

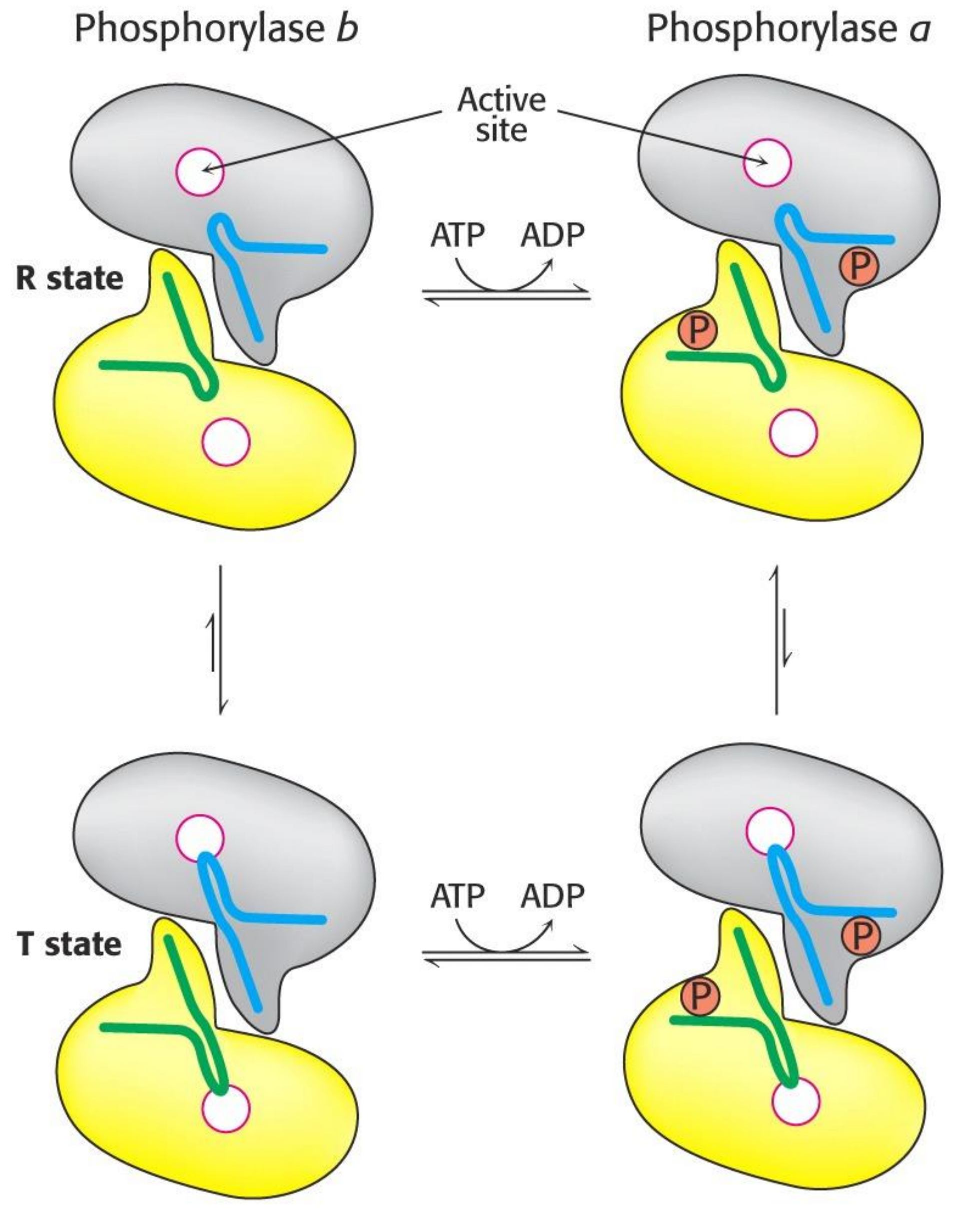
The Bottom Line

- Phosphorylase kinase converts phosphorylase b inactive to phosphorylase a active.
- The T state is less active because the active site is partially blocked.
- The R state is active because the active site is exposed.

Each of the two forms are in equilibrium between an active relaxed (R) state and less active (T) state.

The equilibrium for phosphorylase a favors the R state.

The equilibrium for phosphorylase b favors the T state.



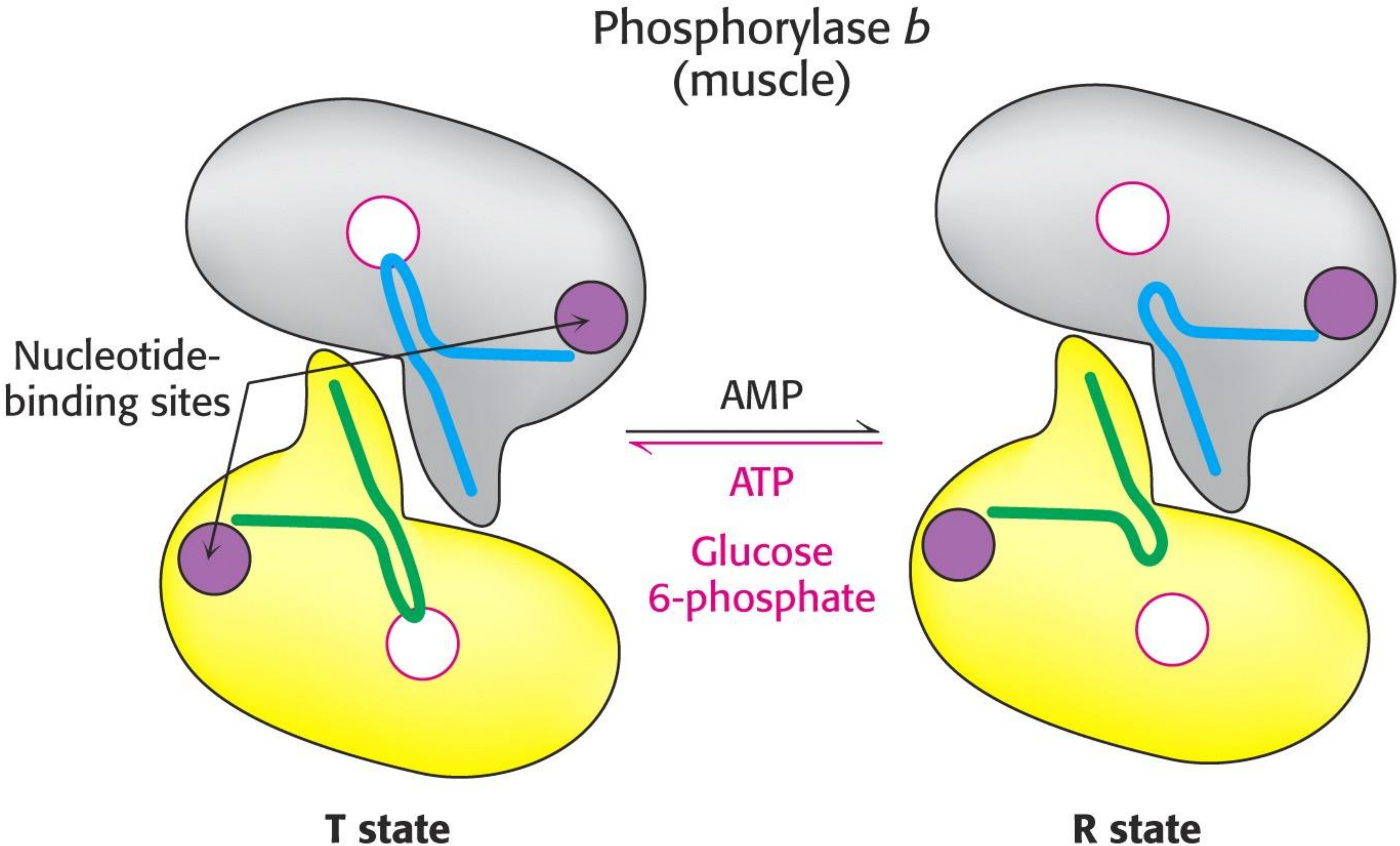
Muscle

In Muscle

- High [AMP] shifts the equilibrium to the active R state.
  - The muscle cell has a low energy charge.
- High [ATP] and [glucose 6-phosphate] shifts the equilibrium to the less active T state.
- So the energy charge in muscle cells regulates the transition between T and R states for phosphorylase b.

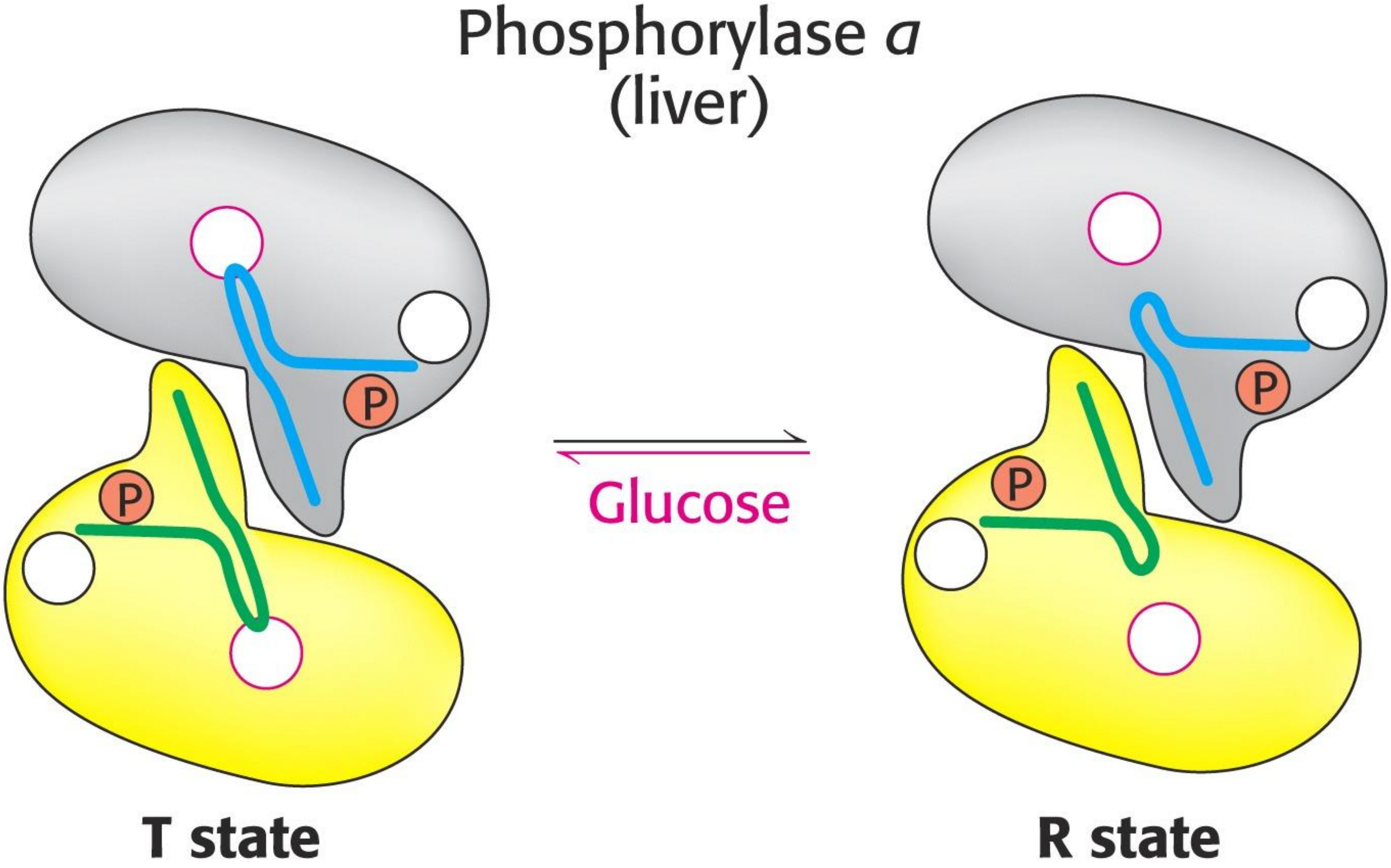
In Muscle

- Phosphorylase b predominates.
- In resting muscle phosphorylase b is in the inactive T state.
- With exercise the increase [AMP] shifts the equilibrium to the active R state.
- Exercise will also stimulate the hormone epinephrine which will convert phosphorylase b to phosphorylase a.


Phosphorylase *b*
(muscle)
Nucleotide-
binding sites
AMP
ATP
Glucose
6-phosphate
T state
R state

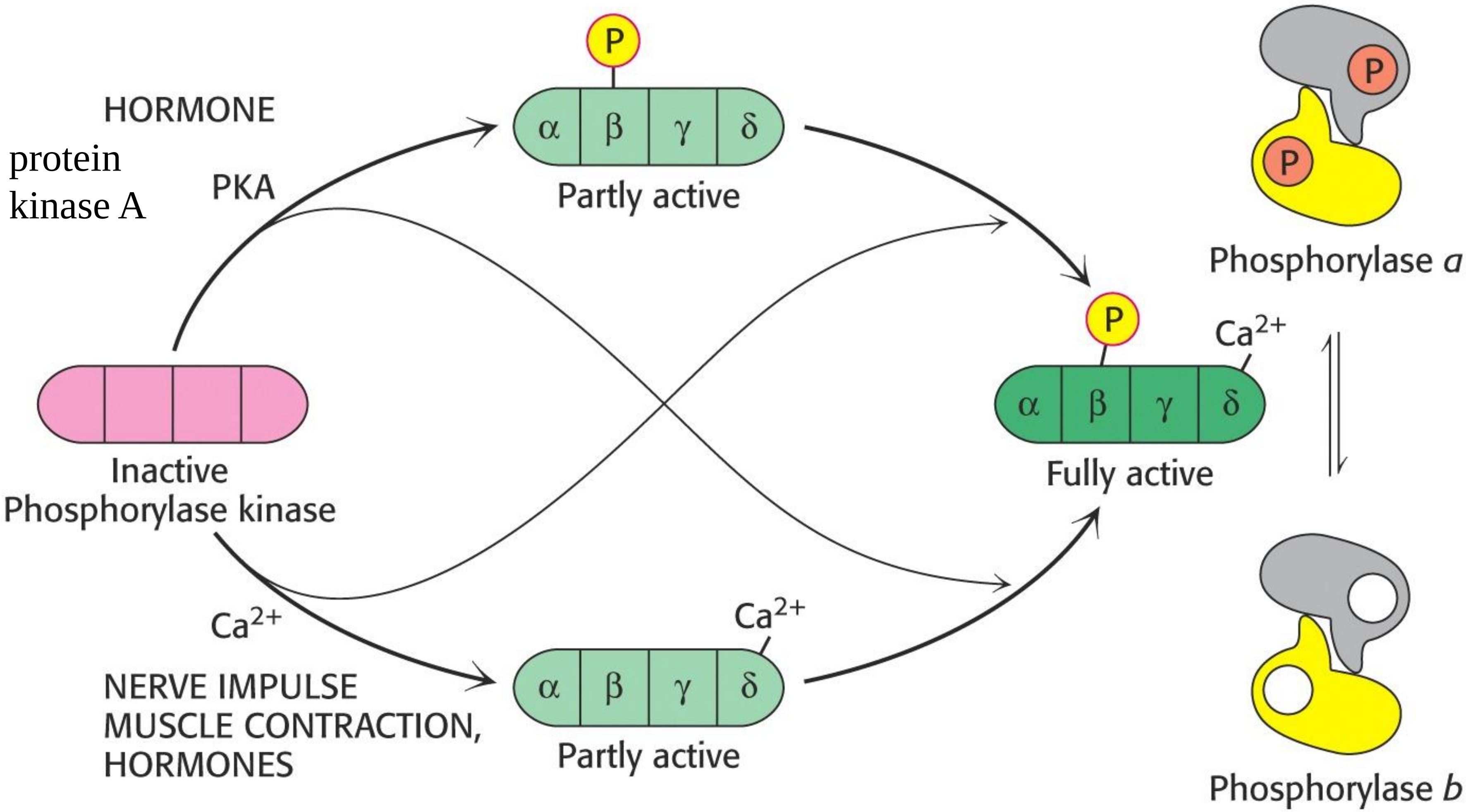
In Liver - A different story

- Glucose shifts the phosphorylase to the T state, deactivating the enzyme.
- Glucose is a negative regulator of liver Phosphorylase.
  - Glucose is not mobilized when glucose is abundant.
- Liver phosphorylase is insensitive to AMP.
  - Liver does not exhibit dramatic changes in energy charge as in contracting muscle.



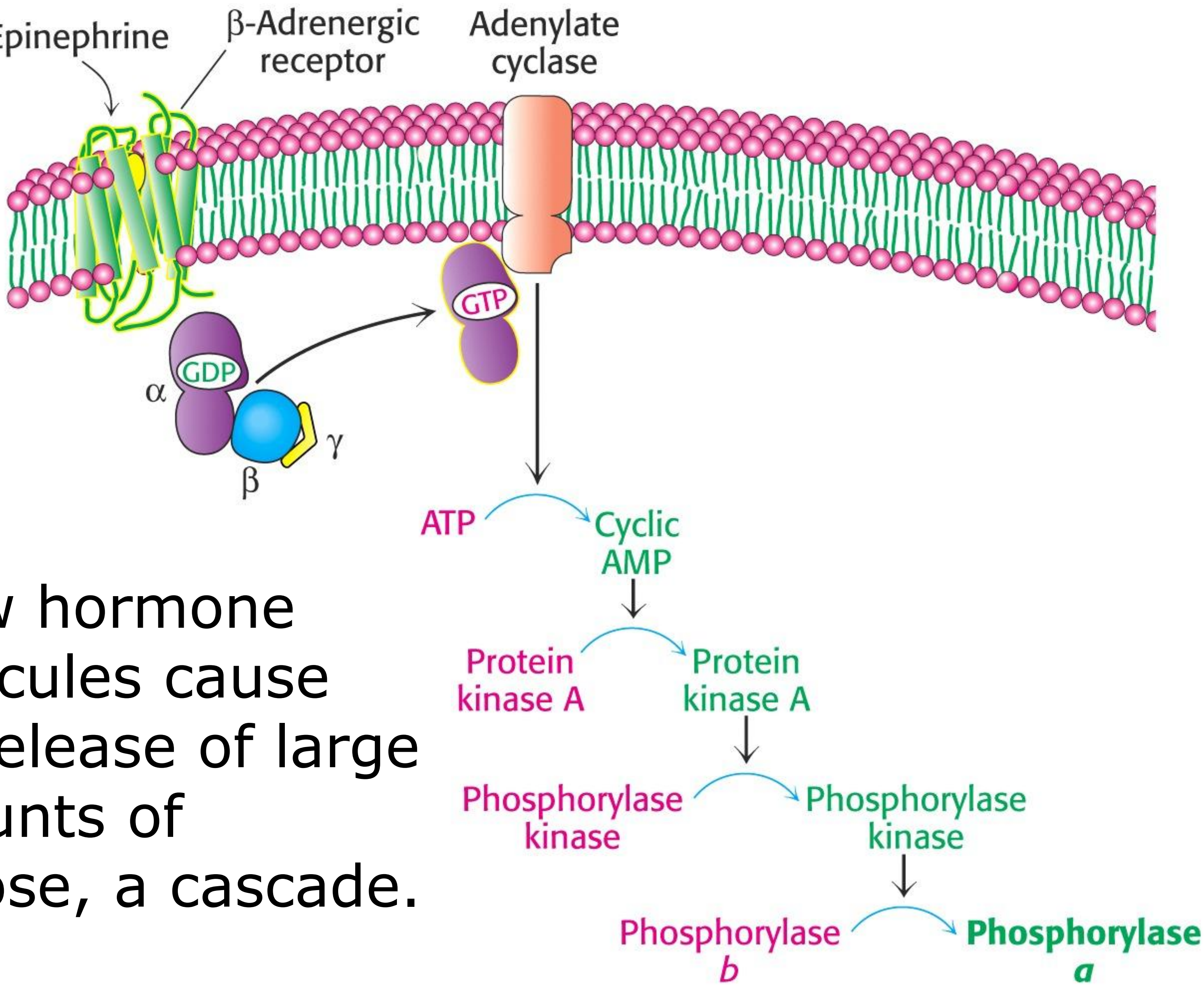
Liver slightly different aa sequence than muscle

Fully active phosphorylase kinase requires Ca^{++} and a phosphate.



Epinephrine and Glucagon Stimulate Glycogen breakdown

- Muscle is responsive to epinephrine.
- Liver is responsive to glucagon and somewhat responsive to epinephrine.
- Both signal a cascade of molecular events leading to glycogen breakdown.
- Both utilize a G-protein-dependent signal-transduction pathway.



A few hormone molecules cause the release of large amounts of glucose, a cascade.