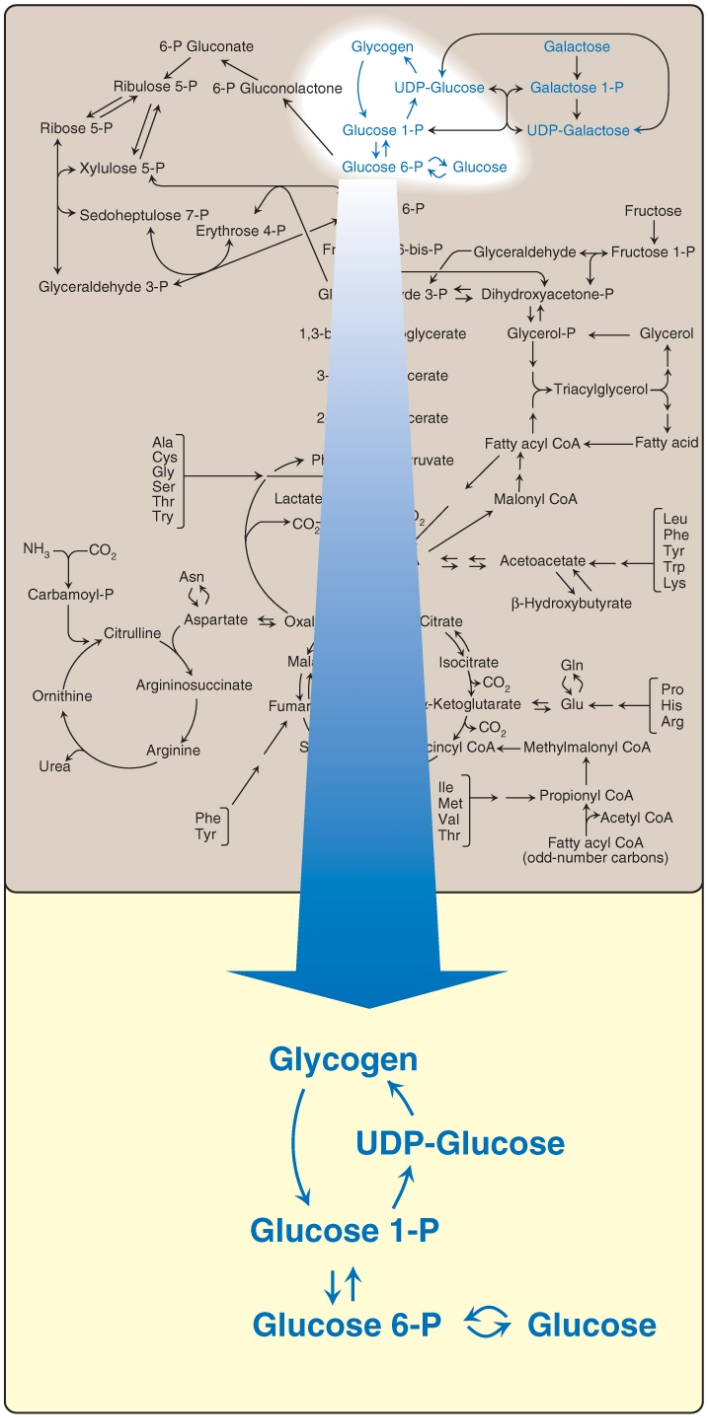


Glucose is essential for life. We have previously studied the various pathways of glucose and its contribution to energy needs of the body. We have studied glycolysis, gluconeogenesis (slow response to blood glucose), hexose monophosphate pathway, monosaccharide and disaccharide metabolism and the citric acid cycle. Now we will look at another source of glucose, glycogen. Main stores of glycogen in the body are found in skeletal muscle (fuel reserve for ATP due to contraction) and liver (maintain blood glucose levels). About 6-8% of the liver weight is (100 g) glycogen. The clear area in the diagram summarizes the glycogen metabolism. Notice that glycogen is produced from Glucose 1-P through UDP-Glucose.

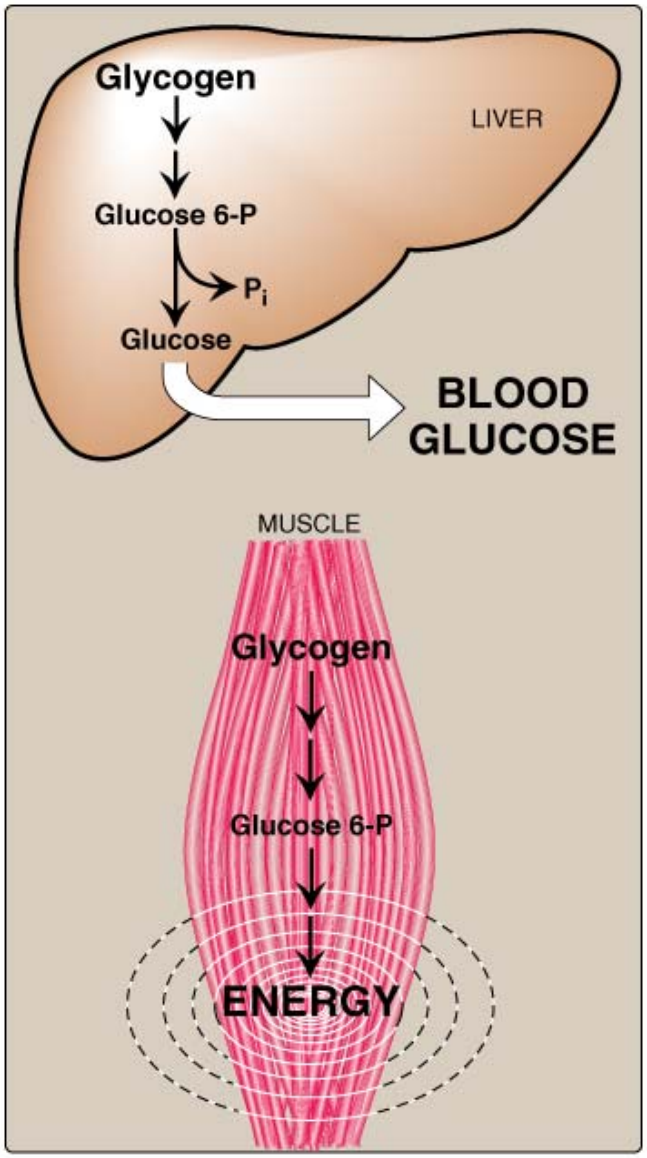
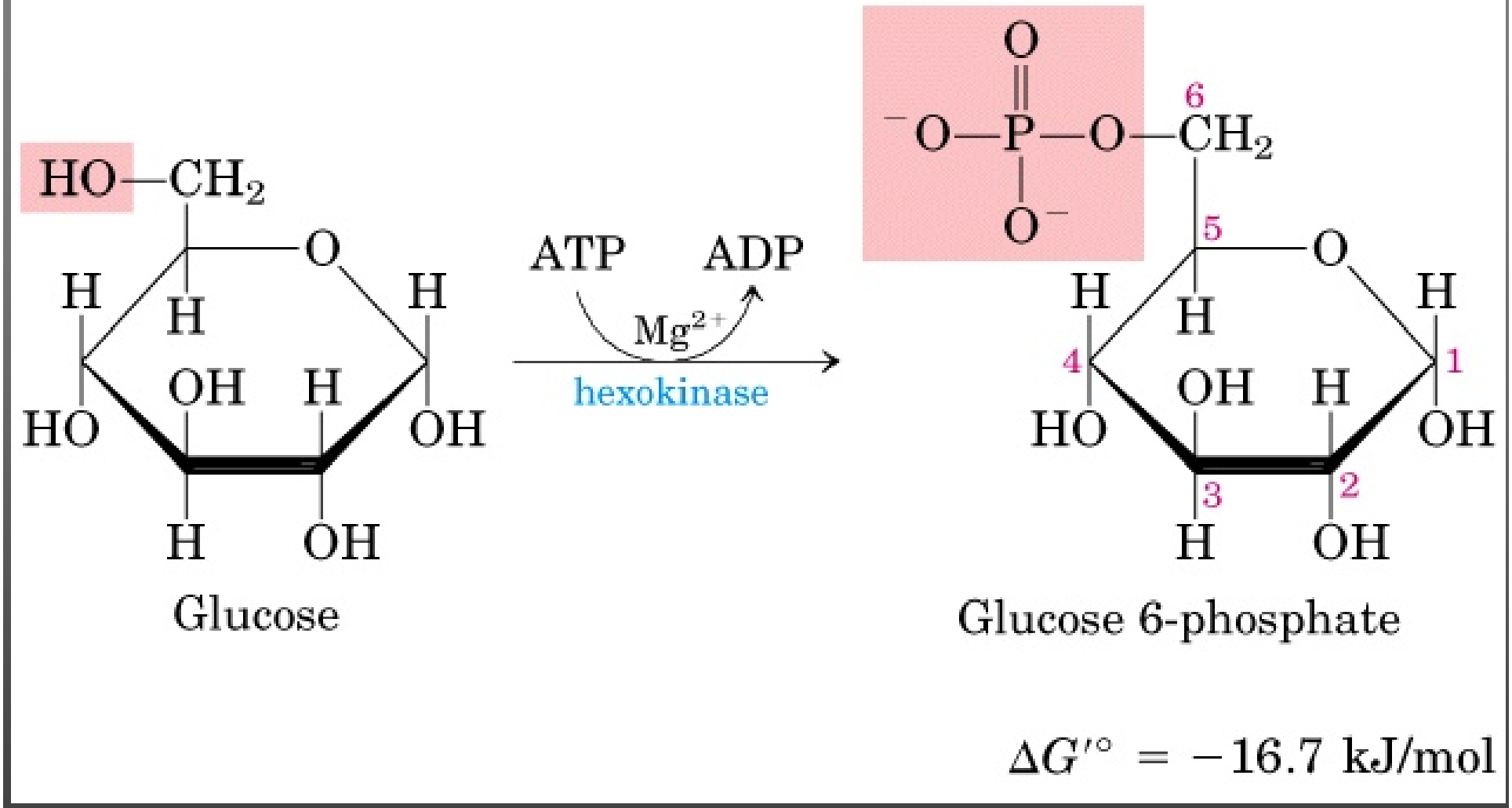


Figure 11.2
Functions of muscle and liver glycogen.

The function of glycogen in both tissues is shown in the adjacent figure. A single molecule of glycogen could have a mass of up to 10^8 daltons. They exist in cytoplasmic granules that contain the enzymes for glycogen synthesis and degradation. The primary glycosidic bond is a α-1-4 linkage. After each 8 to 10 glycosyl residue there is a branch containing α-1,6 linkage. Muscle glycogen stores are not depleted in short periods of fasting and is moderately depleted in prolonged fasting (18 hr).


HO—CH2
O
H
H
H
HO
OH
H
OH
H
OH
ATP
ADP
Mg2+
hexokinase
O
⁻O—P—O—CH2
O⁻
6
5
4
1
3
2
Glucose
Glucose 6-phosphate
ΔG′° = −16.7 kJ/mol

Formation of Glucose 1P

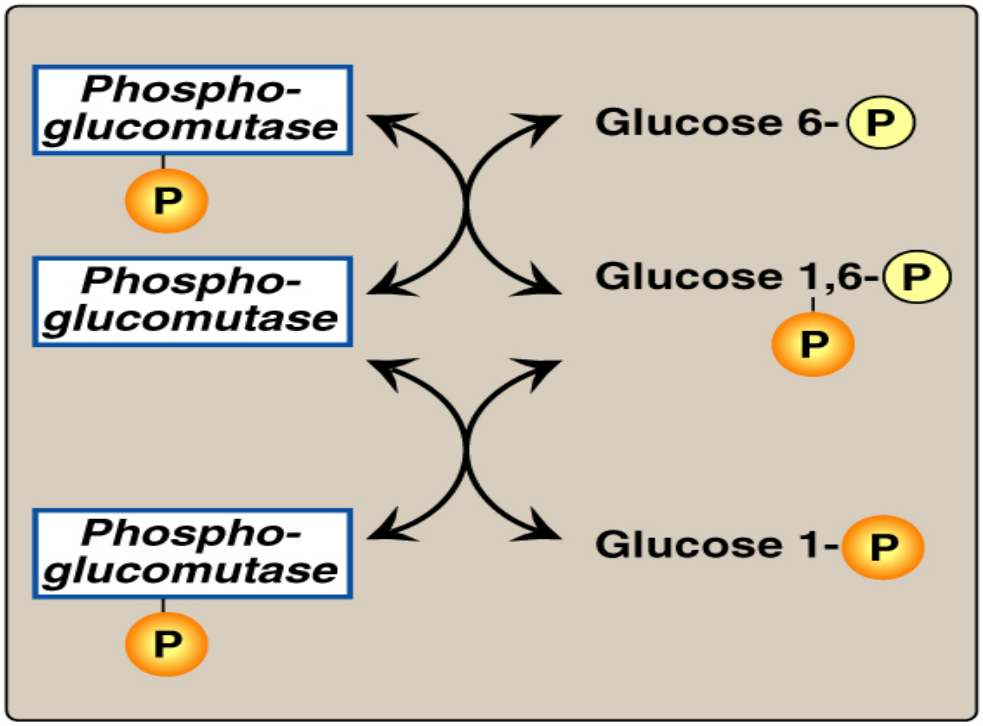
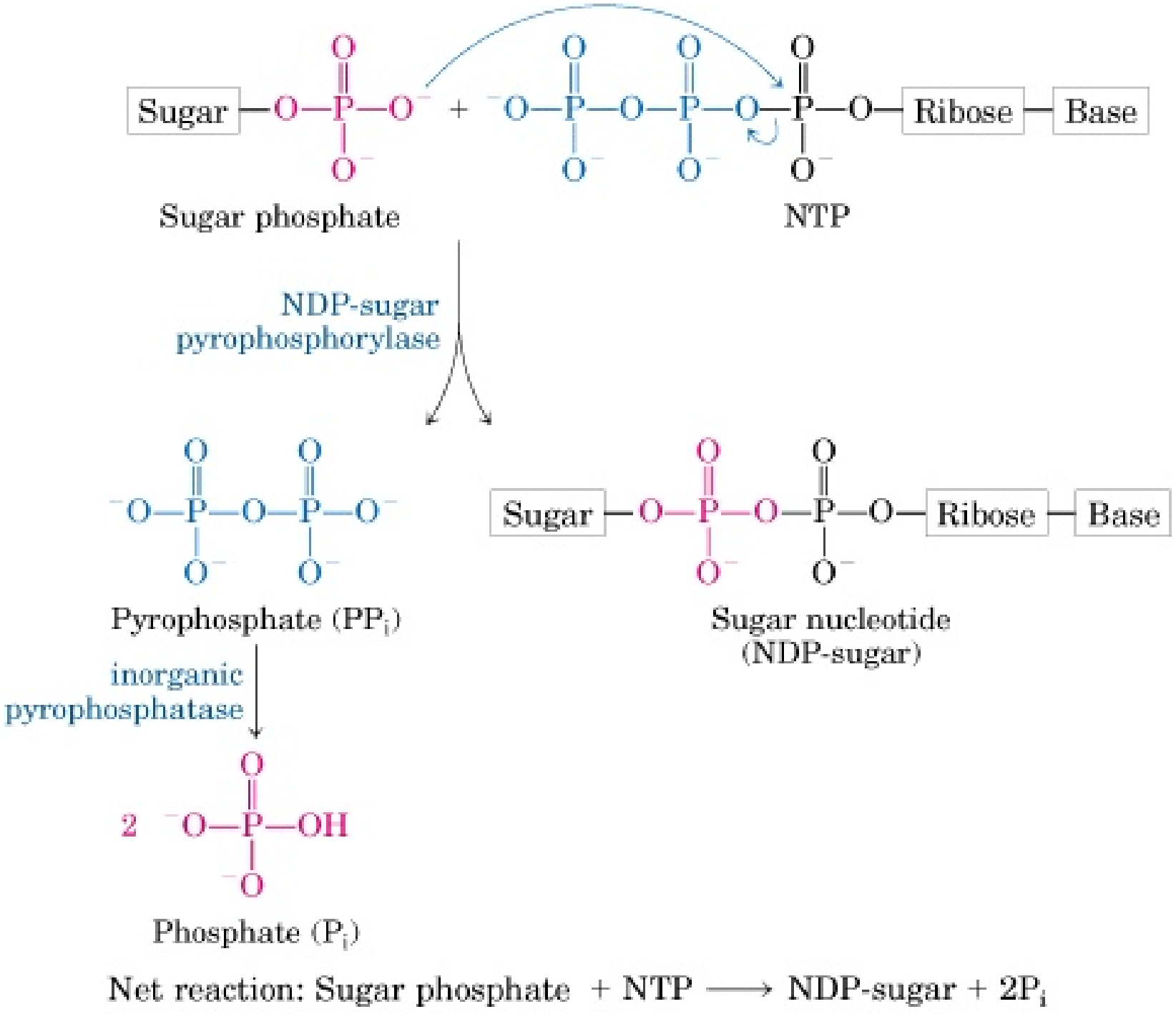
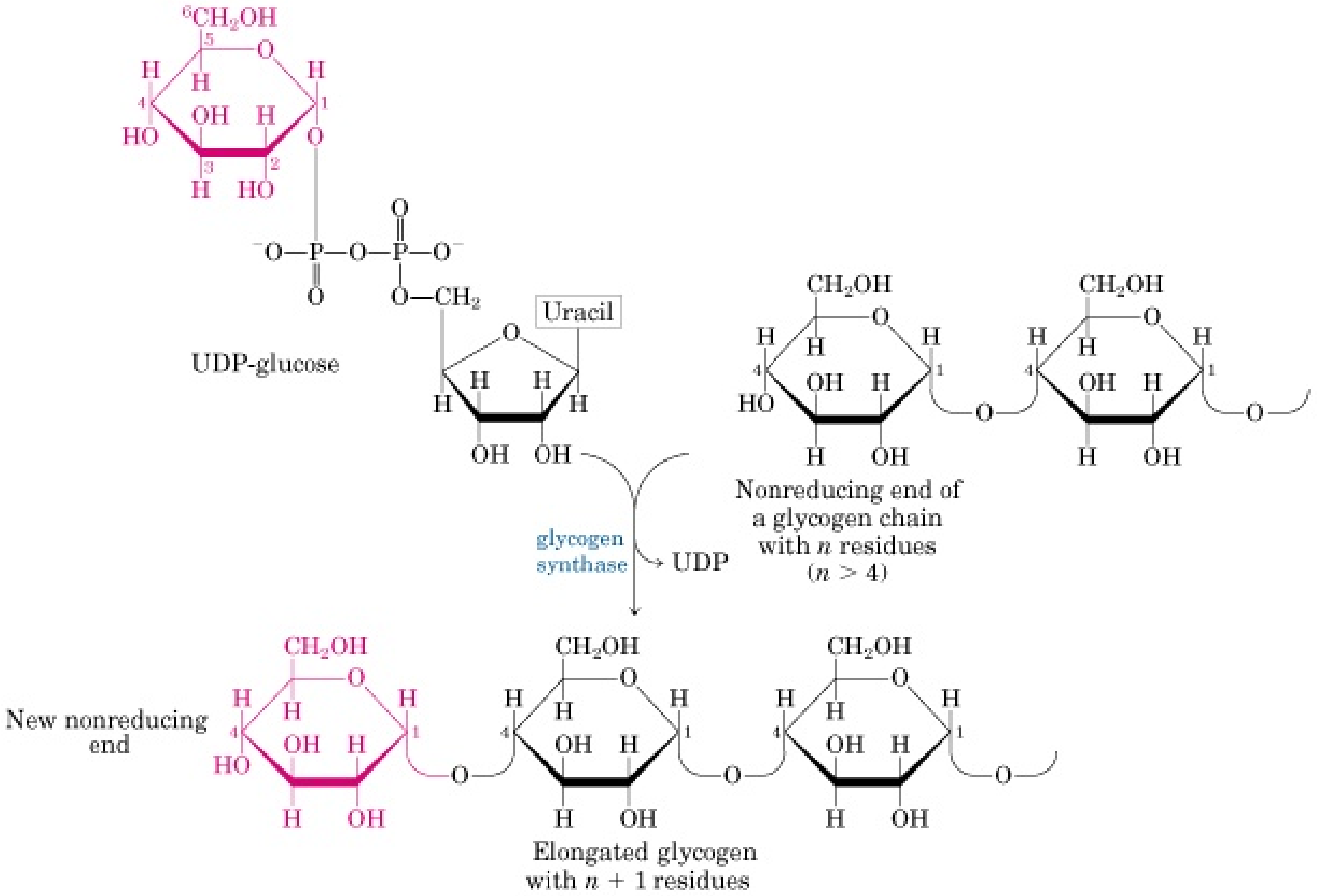
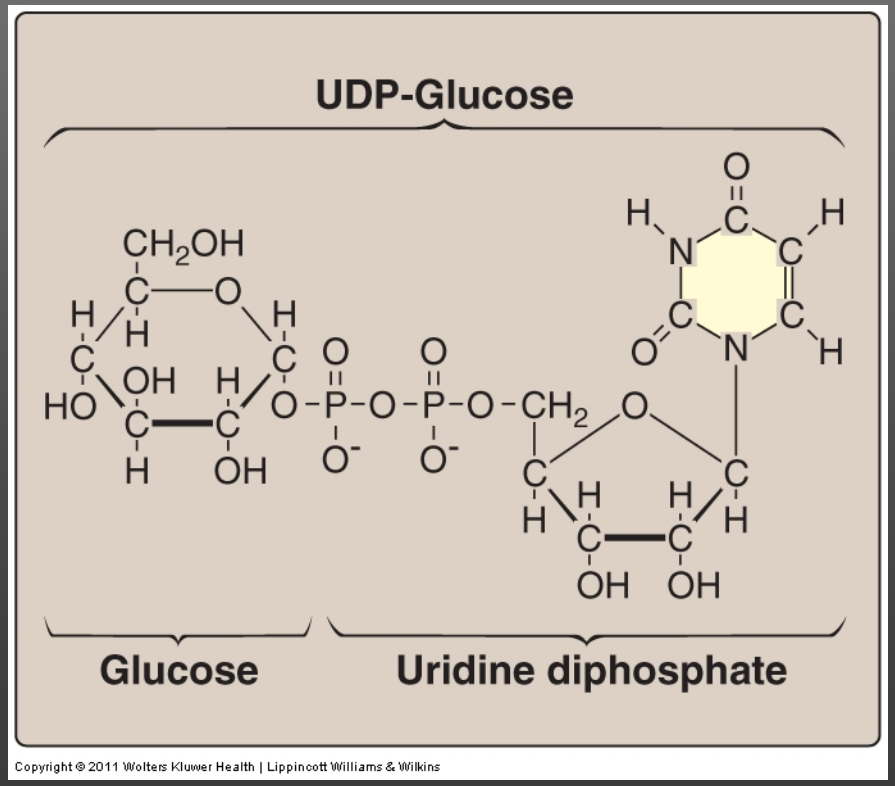


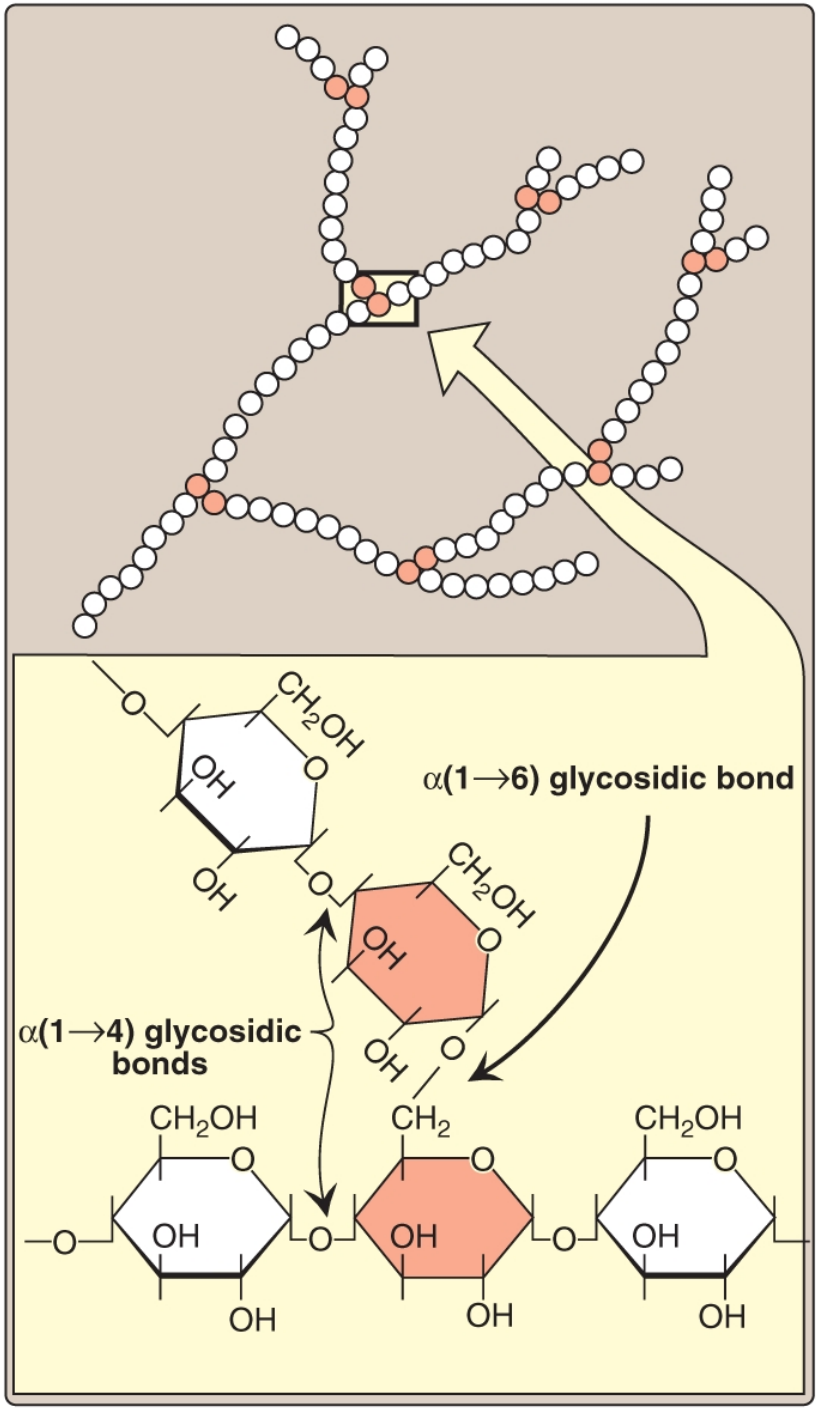
Figure 11.6
Interconversion of glucose 6-phosphate and glucose 1-phosphate by *phosphoglucomutase*.

- Glucose 1P is formed from Glucose 6P by Phosphogluco mutase through the intermediate Glucose 1,6 bisphosphate

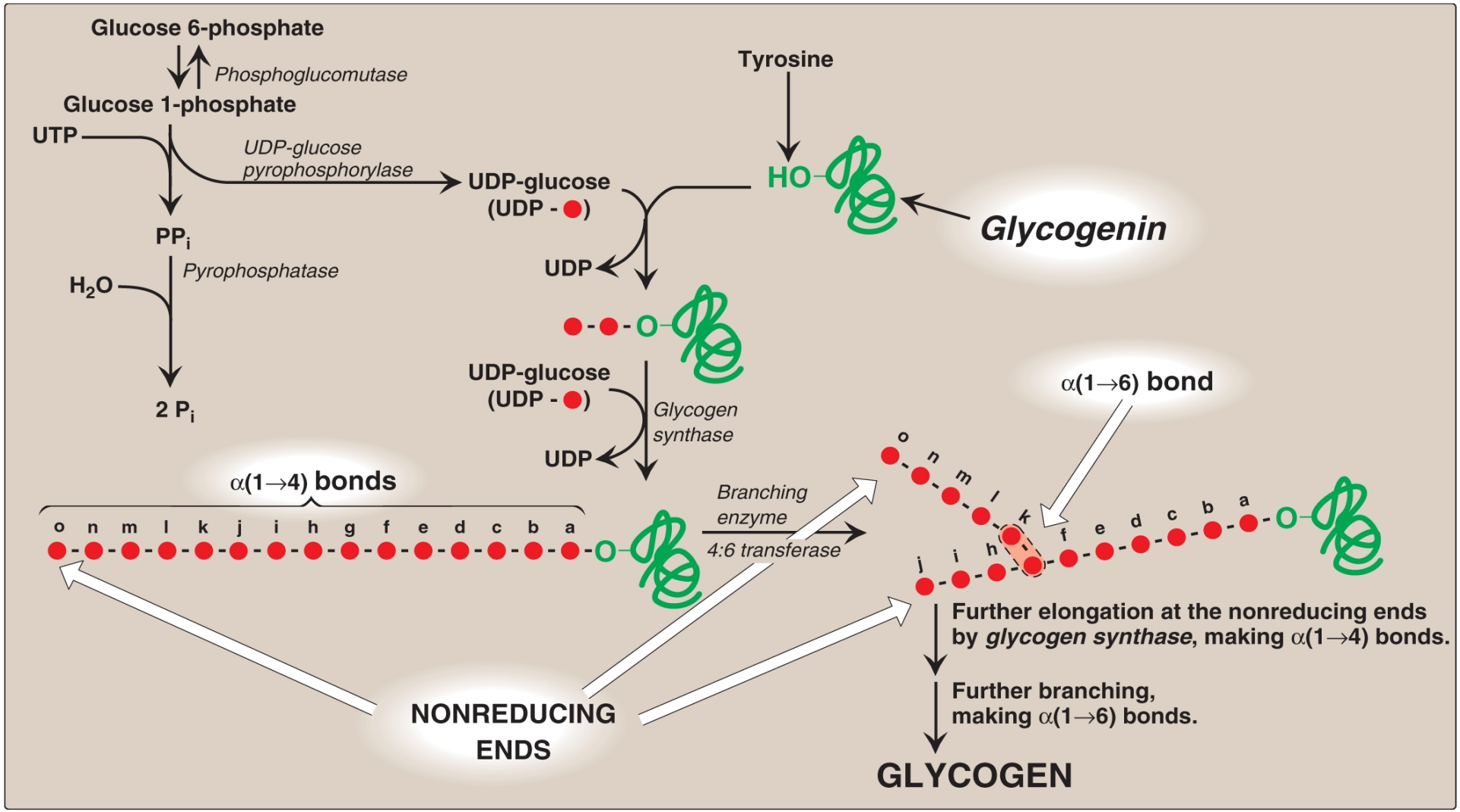

Sugar
Ribose
Base
Sugar phosphate
NTP
NDP-sugar
pyrophosphorylase
Pyrophosphate (PP_i)
Sugar nucleotide
(NDP-sugar)
inorganic
pyrophosphatase
2
Phosphate (P_i)
Net reaction: Sugar phosphate + NTP ⟶ NDP-sugar + $2P_i$


UDP-glucose
Uracil
glycogen synthase
UDP
Nonreducing end of a glycogen chain with n residues (n > 4)
New nonreducing end
Elongated glycogen with n + 1 residues





Glycogen is synthesized from molecules of α-D-glucose. It occurs in the cytosol requiring energy from ATP and UTP. Notice the α-1-4 and α-1-6 bond in the structure.



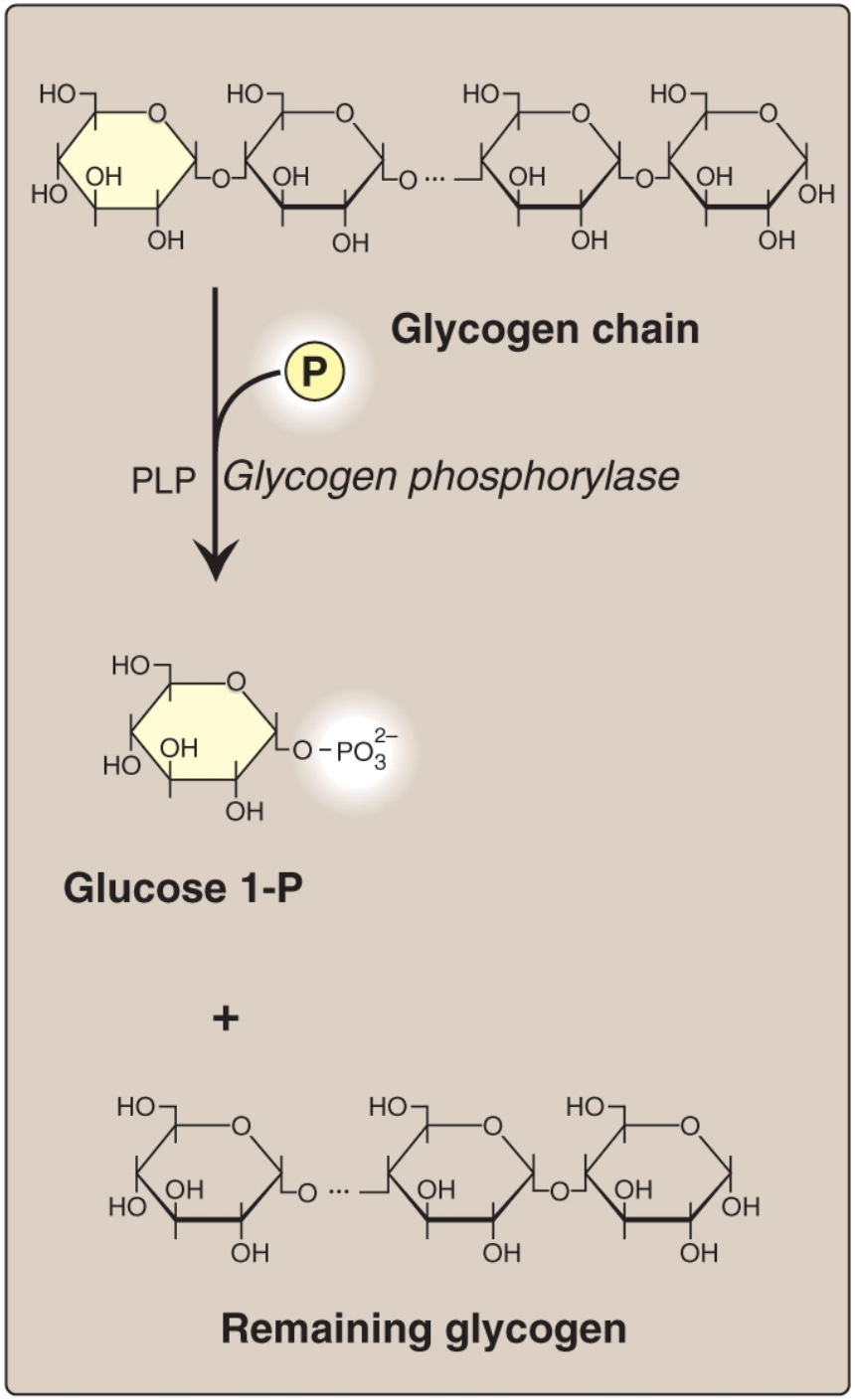
Glycogen synthase is responsible of the α-1-4 linkage but can only add on to existing chains. In the absence of glycogen fragments the glycogenin protein can serve as the initial donor for the elongation. It begins on the hydroxyl group of a tyrosine. The bond is from the carbon 4 of the glycosyl residue to the hydroxyl carbon 1 of activated glucose by glycogen synthase. UDP is released.

The advantages of glycogen not being linear in animals (increase surface area, reduces volume, increases solubility, increases number of nonreducing ends) this accelerate the rates at which glycogen synthesis and degradation can occur .

Branching by glucosyl 4:6 transferase (branching enzyme) this enzyme transfers a chain of five to eight glucosyl residues from the nonreducing end. It attaches it to a α-1-6. Glycogen synthase can then continue adding glucose and branches (branching enzyme) to the glycogen fragment.

Degradation of Glycogen

The primary product of glycogen degradation is glucose 1-Phosphate from the α-1-4 and glucose from the α-1-6 bond.



Glycogen phosphorylase cleaves the α-1-4 glycosidic bond at the nonreducing ends. Contains pyridoxal phosphate as coenzyme. It degrades the glycogen chain until four glucosyl units remain resulting in a structure called limit dextrin. Then branches are removed by two enzyme activities. Glucosyl (4:4) transferase which removes the outer three of the four glucosyl residues and transfers them to the adjacent non-reducing end thus a α-1-4 bond is broken and another made. The second enzyme that breaks the α-1-6 remaining bond on the branch is amylo α-(1-6)-glucosidase which releases the free glucose. Both of these enzyme activities are domains of a single polypeptide the debranching enzyme.

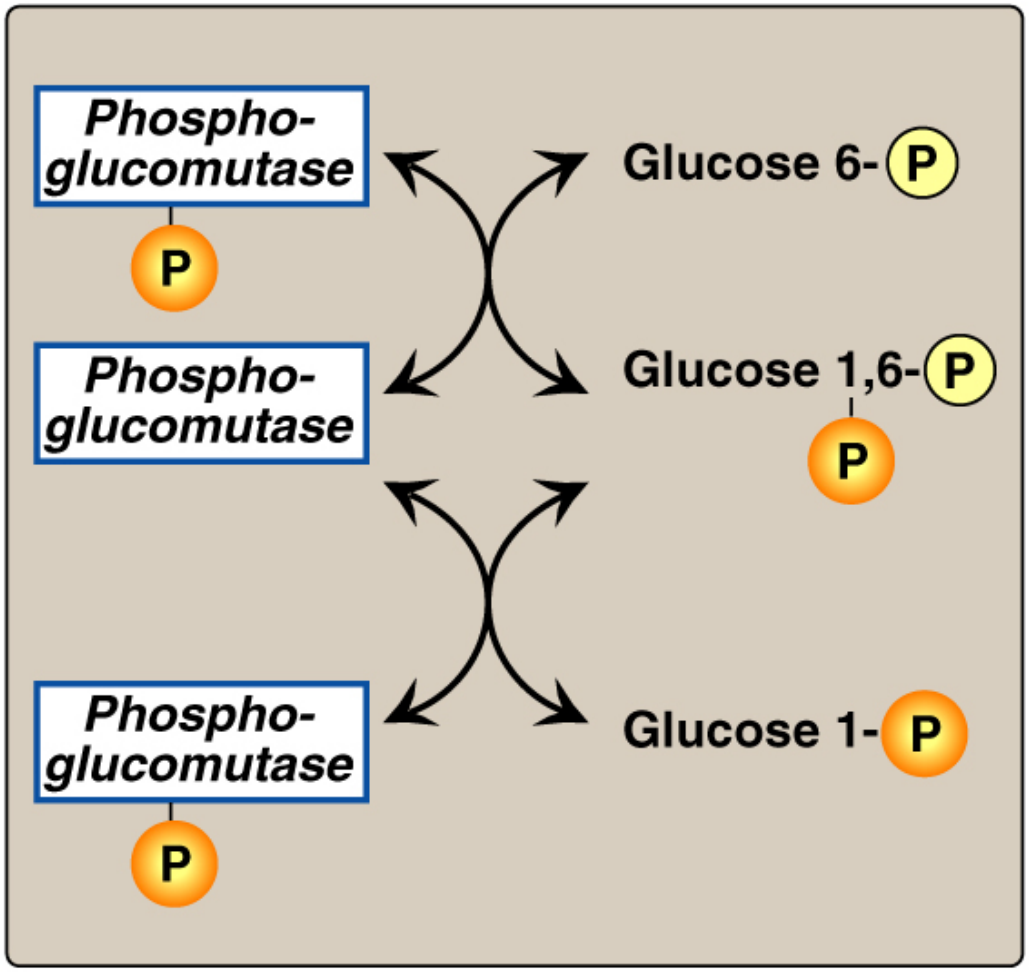
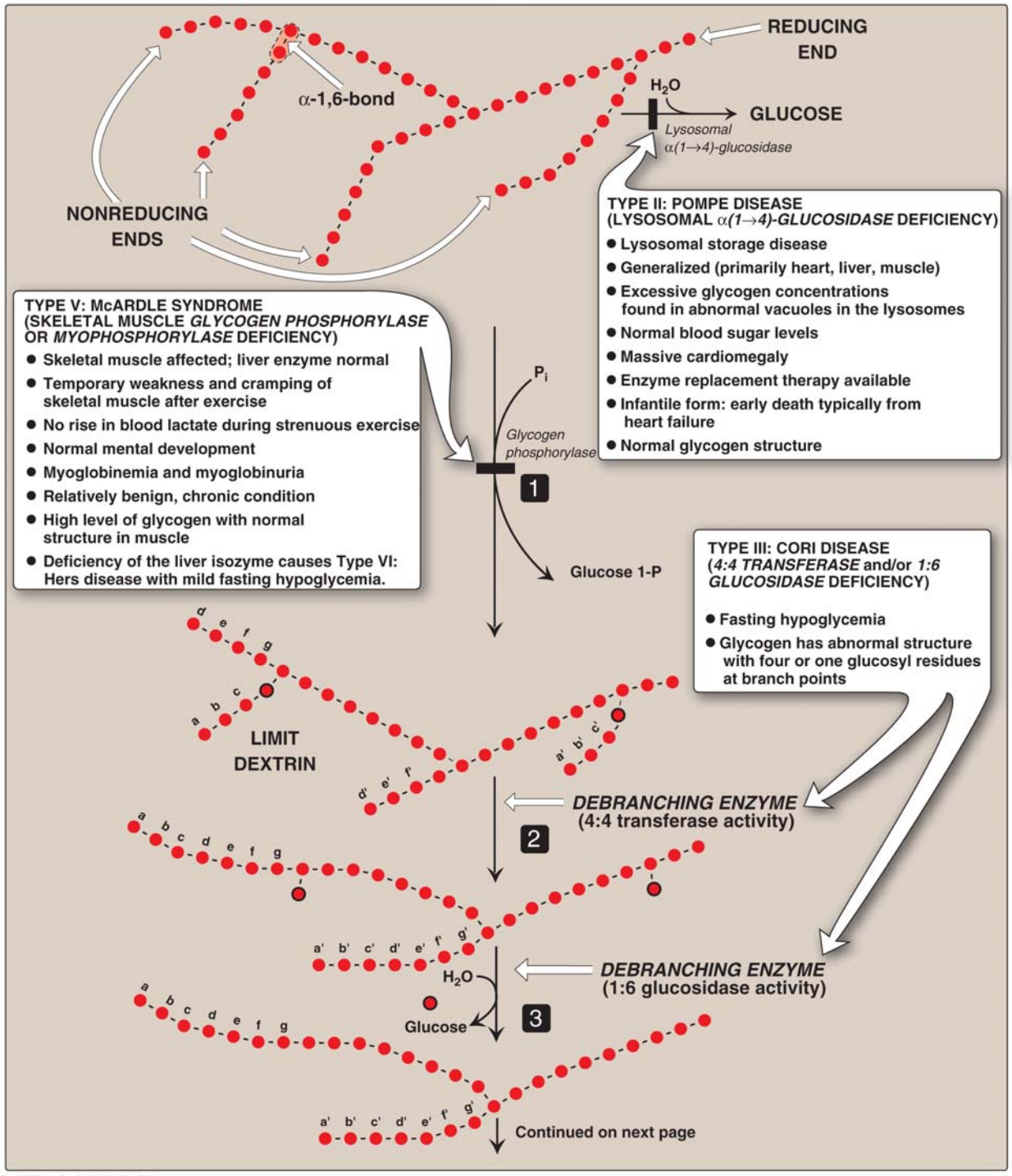


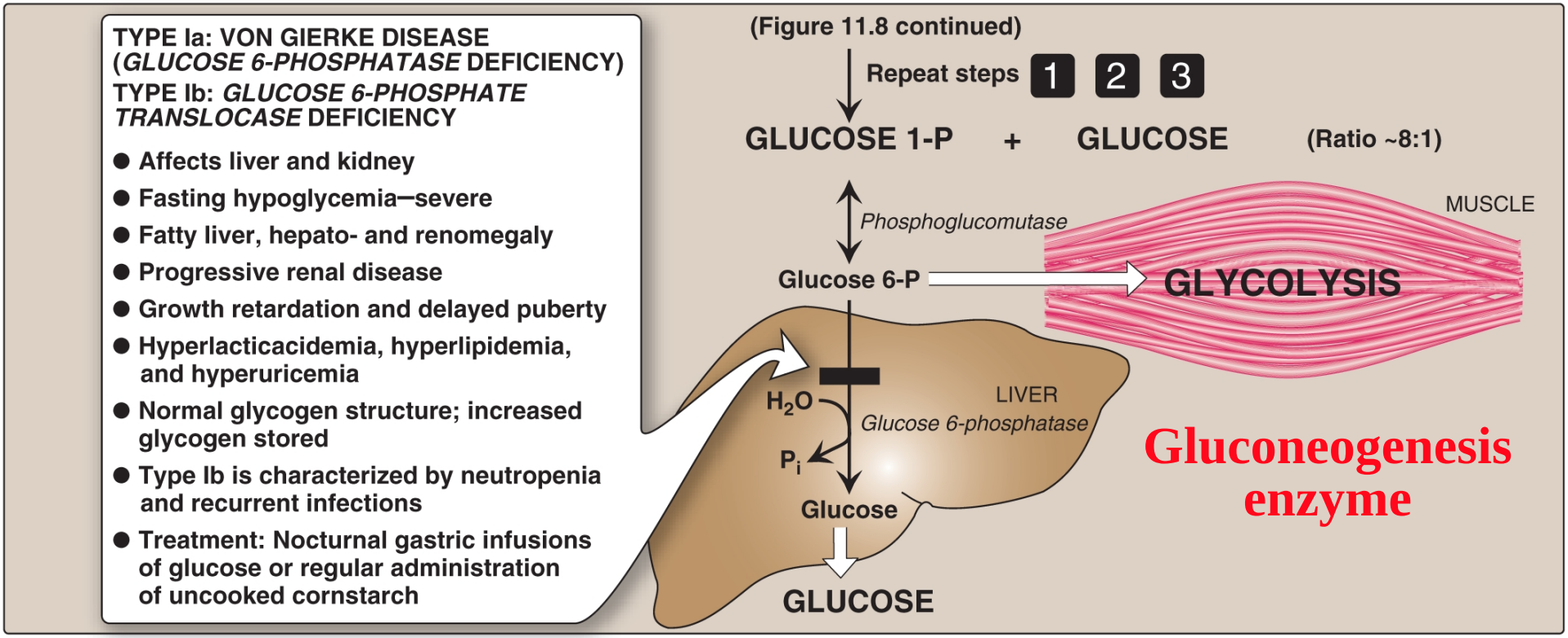
Figure 11.6
Interconversion of glucose 6-phosphate and glucose 1-phosphate by *phosphoglucomutase*.

Glucose 1-P produced by glycogen phosphorylase is then converted to Glucose 6-P (phosphoglucomutase) by passing through the intermediate Glucose 1-6 bisphosphate This is a reversible reaction. G6P is then translocated to the ER where it is converted to Glucose by Glucose 6 phosphatase. It is transported to the cytosol and then to the blood until gluconogenesis is activated. In muscle G6P cannot be dephosphorylated (- G6Phosphatase).

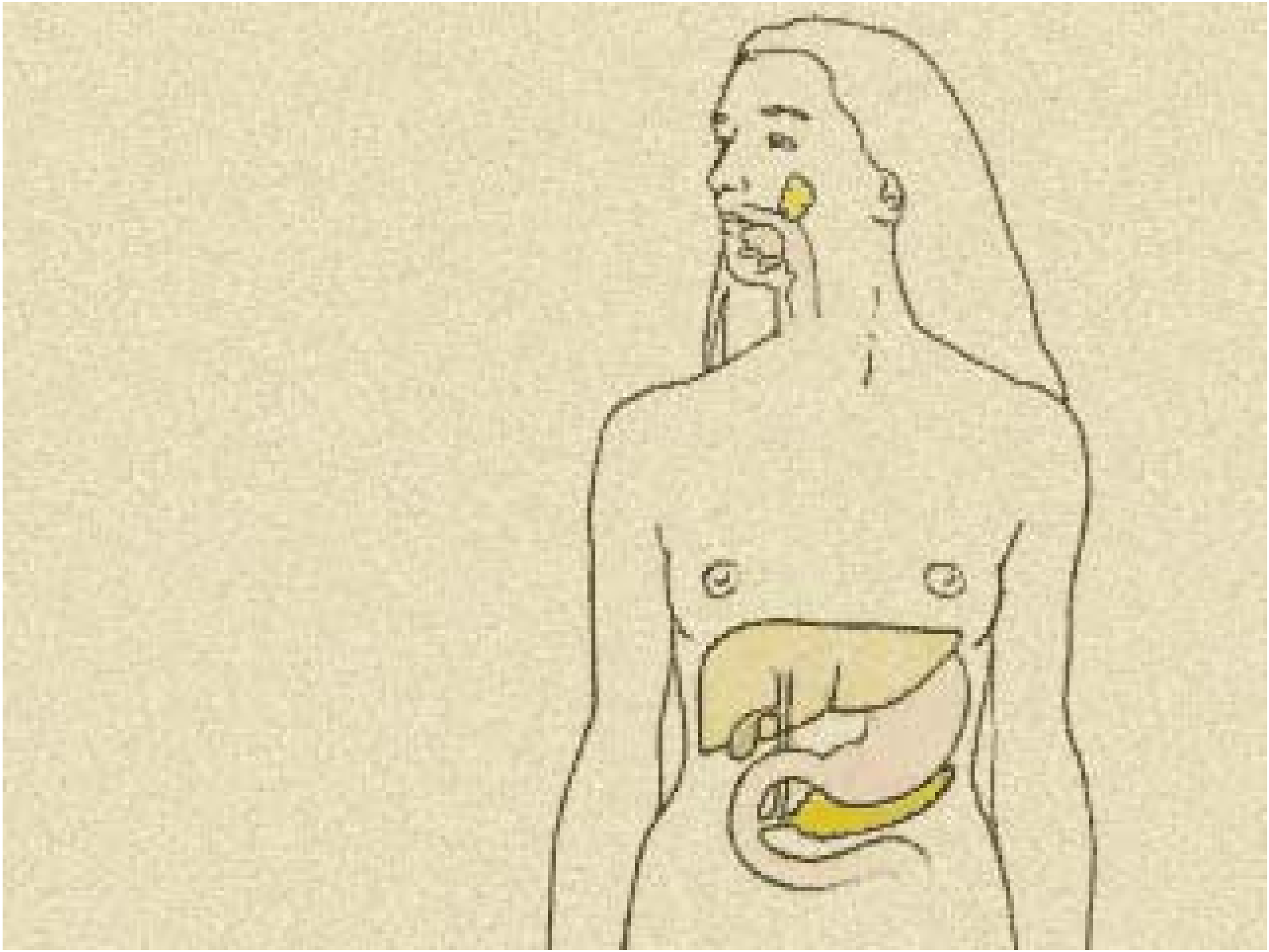


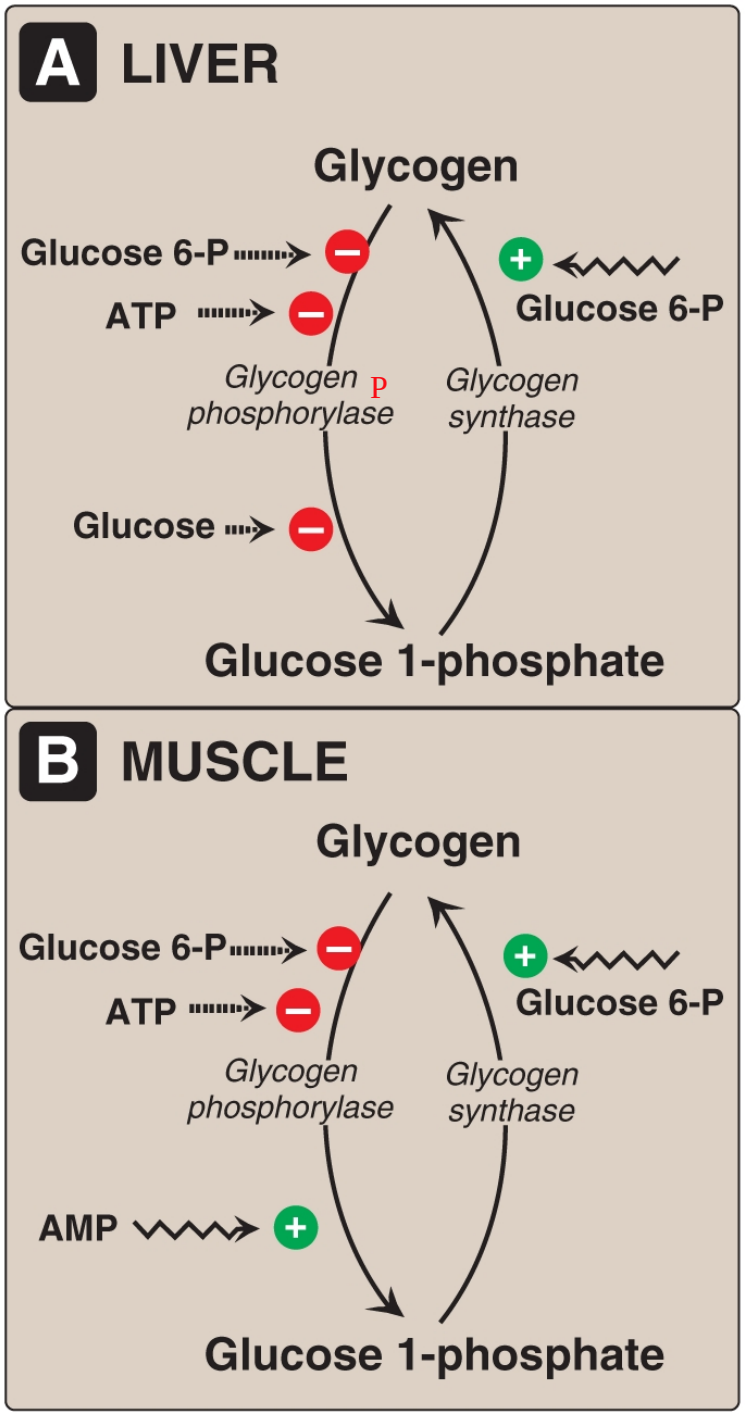
Summary glycogen degradation 1. Starts at the non-reducing end (1) by glycogen phosphorylase until 4 units are left (limit dextrin (2)) 2. Debranching enzyme activity a) removes the 3 units and transfers to adjacent nonreducing ends (3) by glycosyl 4:4 transferase α-1-4 bond broken and α-1-4 made. (continues next slide)

Glycogen storage disease type II (Pompe's disease) deficiency in the lysosomal enzyme α-1-4 glucosidase (acid maltase) accumulation of glycogen in vacuoles

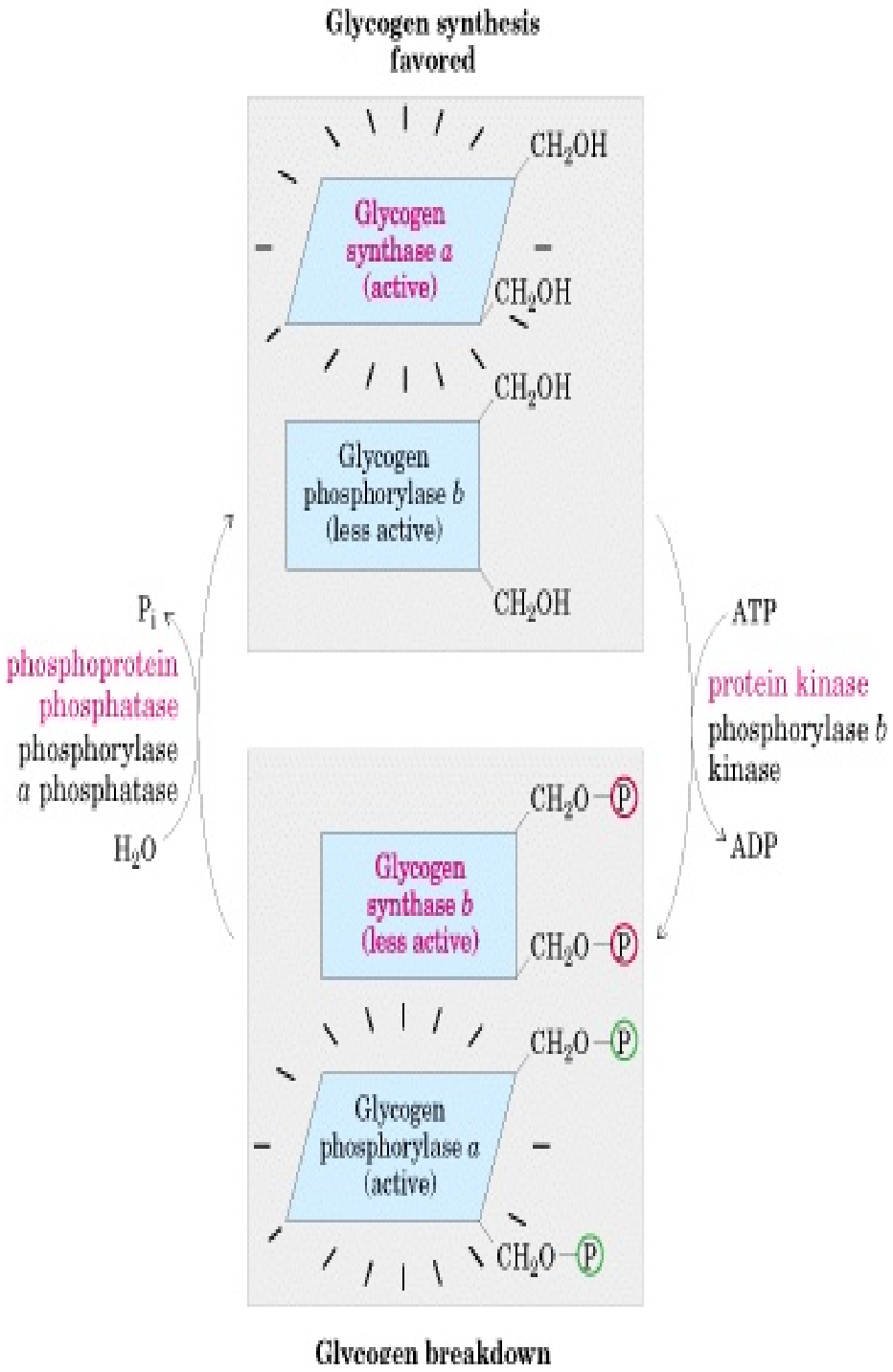


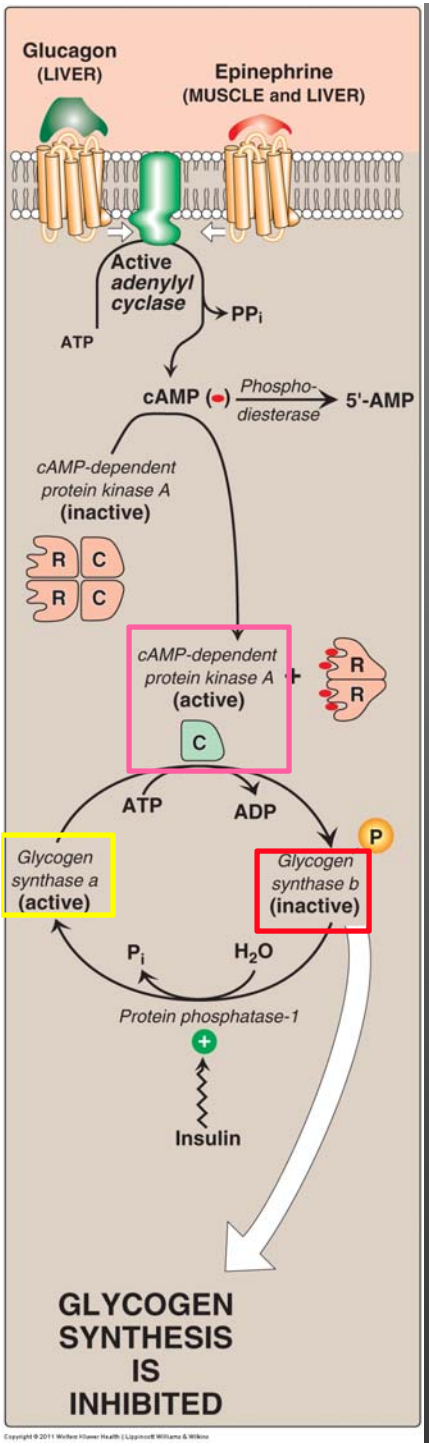
Then the α-1-6 bond is removed by the amylo (1-6) glycosylase activity of the debranching enzyme (3) This is repeated until degradation is completed and glucose 1-P and eventually glucose is the final product. Immediate Glucose levels are maintained and energy demands are fulfilled. Liver functions to restore Glucose level muscle to produce energy since it lacks (- G-6phosphatase)





Regulation of Glycogen Synthesis The synthesis and degradation of glycogen are tightly regulated. Glycogen synthase and glycogen phosphorylase are allosterically controlled and are hormonally regulated. Glycogen synthesis is stimulated when energy levels and substrate availability are high. Glycogen degradation is increasedwhen energy levels and available glucose supplies are low. In muscle, contraction requires ATP hence AMP is accumulated. Ca^{2+} is released due to depolarization of nerve impulses. Ca^{2+} binds to calmodulin (a subunit of phosphorylase kinase) and activates this enzyme (glycogen phosphorylase).


Glycogen synthesis favored
CH2OH
Glycogen synthase a (active)
CH2OH
CH2OH
Glycogen phosphorylase b (less active)
CH2OH
Pi
phosphoprotein phosphatase
phosphorylase a phosphatase
H2O
ATP
protein kinase
phosphorylase b kinase
ADP
CH2O—P
Glycogen synthase b (less active)
CH2O—P
CH2O—P
Glycogen phosphorylase a (active)
CH2O—P
Glycogen breakdown



Inhibition of glycogen synthase . There are two forms of this enzyme, the activated a and inactive b (phosphorylated) form. The enzyme can be phosphorylated at various sites on the enzyme, the higher the degree of phosphorylation the greater its inactivity. This phosphorylation process is catalyzed by a protein kinase that is cAMP dependent. Glucagon and epinephrine induce adenylate cyclase which in turn activate cyclic AMP dependent kinases (see figure). Epinephrine activates degradation and inhibits synthesis in muscle.

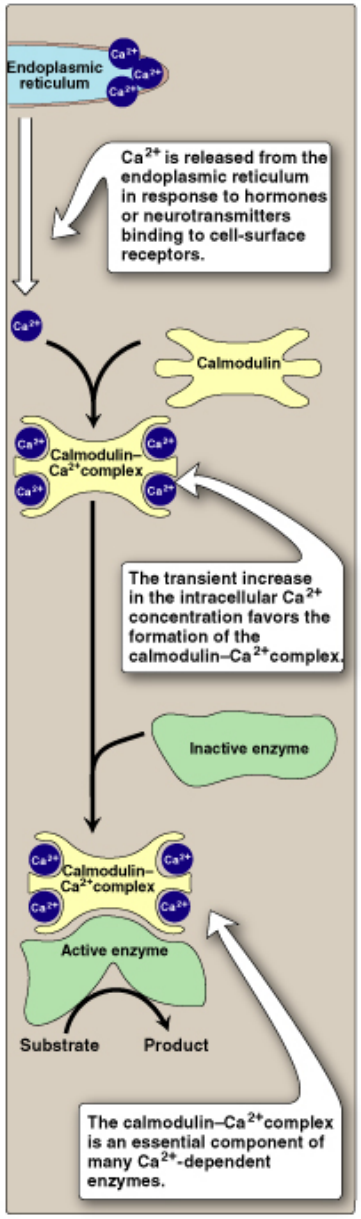


Figure 11.10
Calmodulin mediates many effects of intracellular calcium.

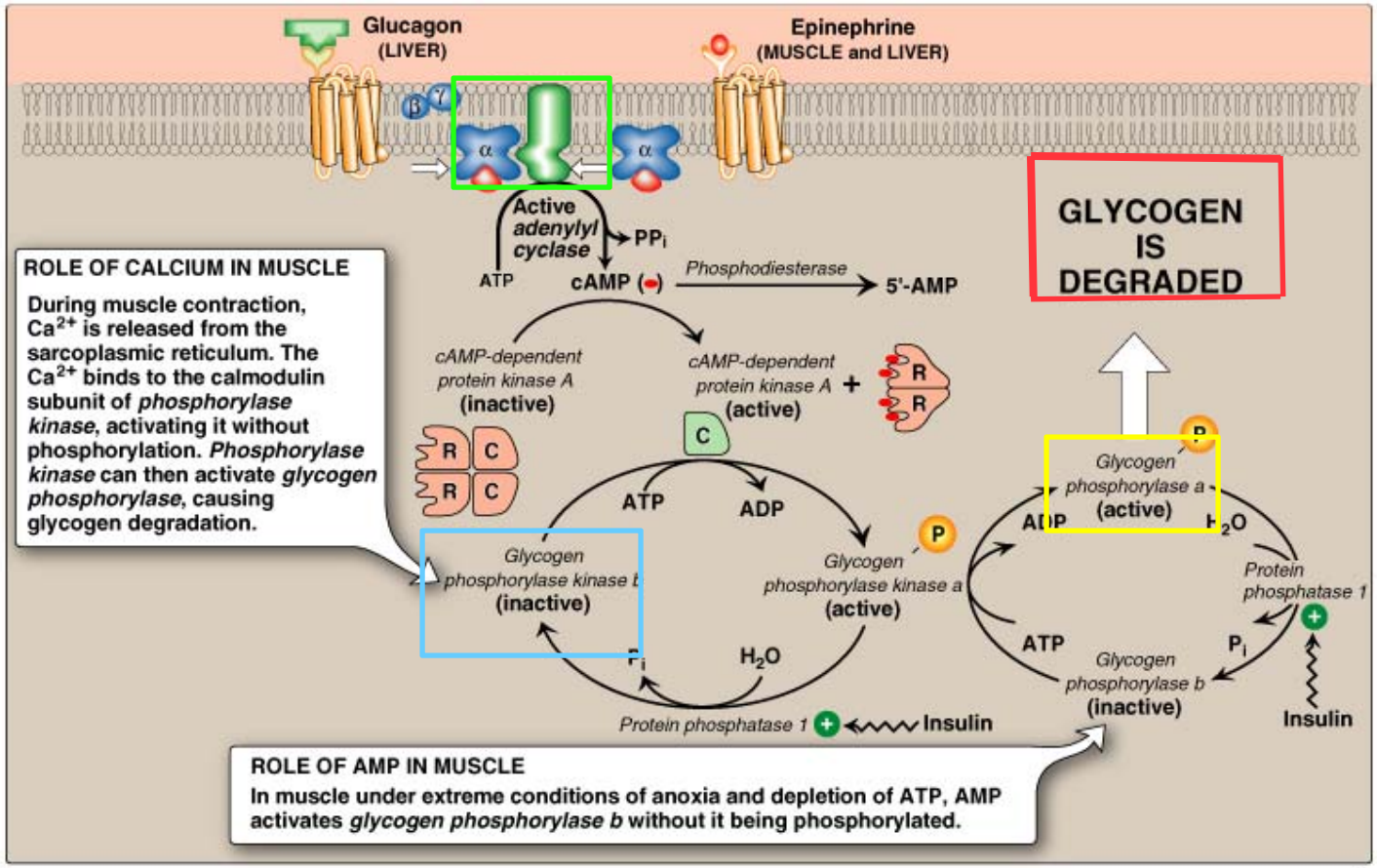


Figure 11.11

Stimulation and inhibition of glycogen degradation.

Activation of glycogen phosphorylase by means of glycogen phosphorylase kinase through cAMP, Glucagon and epinephrine activating adenylate cyclase. When glucose is in sufficient concentration

it will bind to glycogen phosphorylase a making it a more suitable substrate for protein phosphatase 1 and converting glycogen phosphorylase b.

Summary

1. Glycogen synthesis and degradation are regulated by the same hormonal signals. Elevated insulin level results in increased glycogen synthesis whereas glucagon and epinephrine cause increase glycogen degradation.

2. Cyclic cAMP increases in the presence of glucagon and epinephrine increasing glycogen degradation while insulin decreases cAMP.

3. Key enzymes are phosphorylated by a family of kinases activating one glycogen phosphorylase a and inhibiting others glycogen synthase.

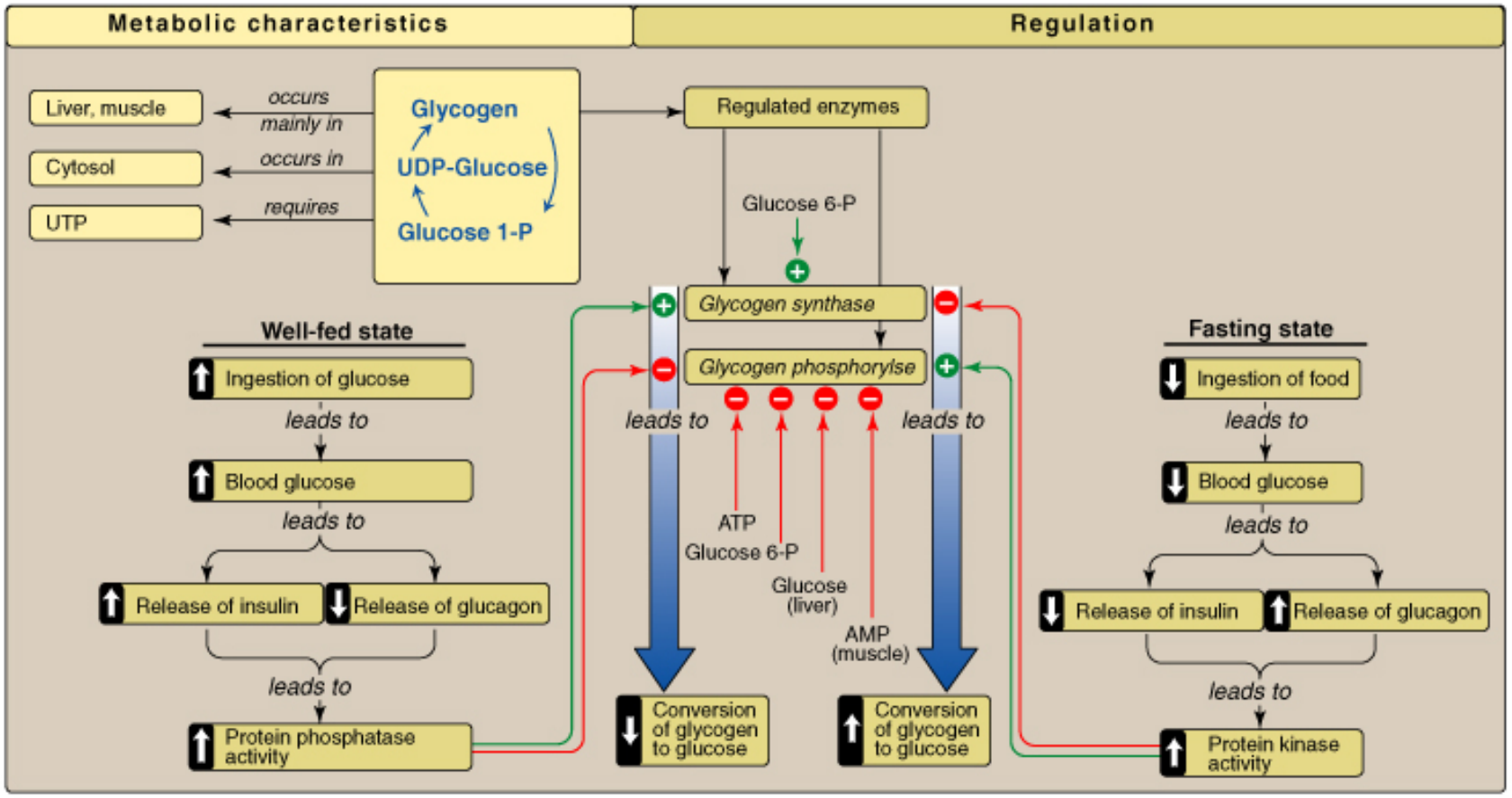


Figure 11.13

Key concept map for glycogen metabolism in liver.

DUDAS?