Glycogen Metabolism

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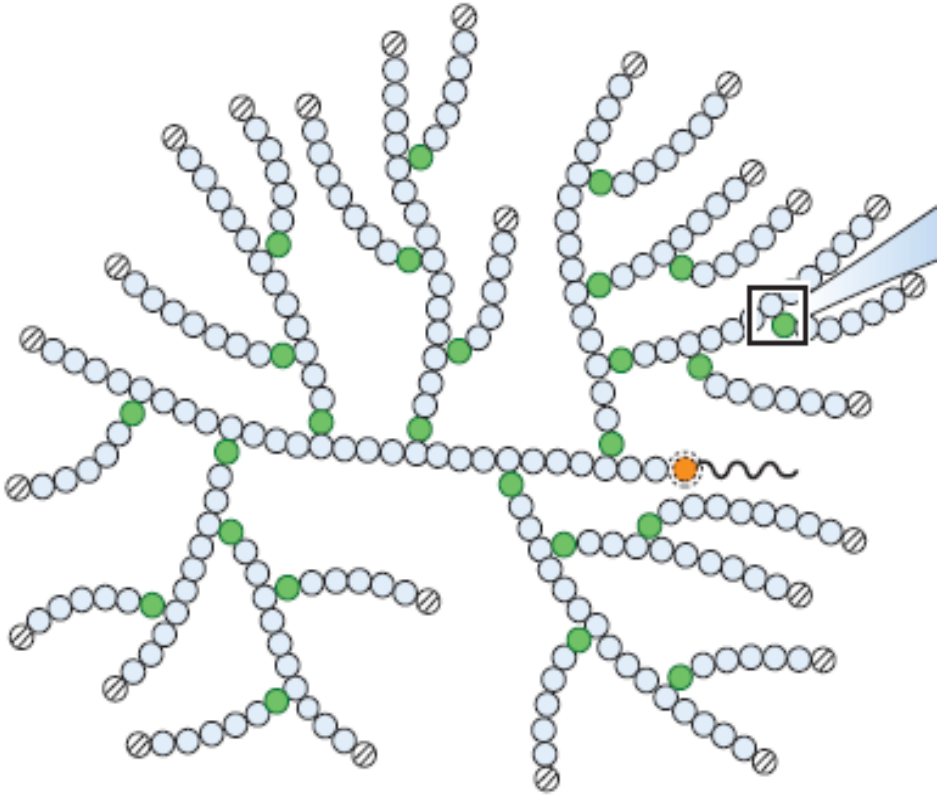
Textbook

Lippincott’s Illustrated reviews: Biochemistry

Sources of Blood Glucose

- Diet
  - Starch, mono and disaccharides, glucose
  - Sporadic, depend on diet
- Gluconeogenesis
  - Sustained synthesis
  - Slow in responding to falling blood glucose level
- Glycogen
  - Storage form of glucose
  - Rapid response
  - Limited amount
  - Important energy source for exercising muscle

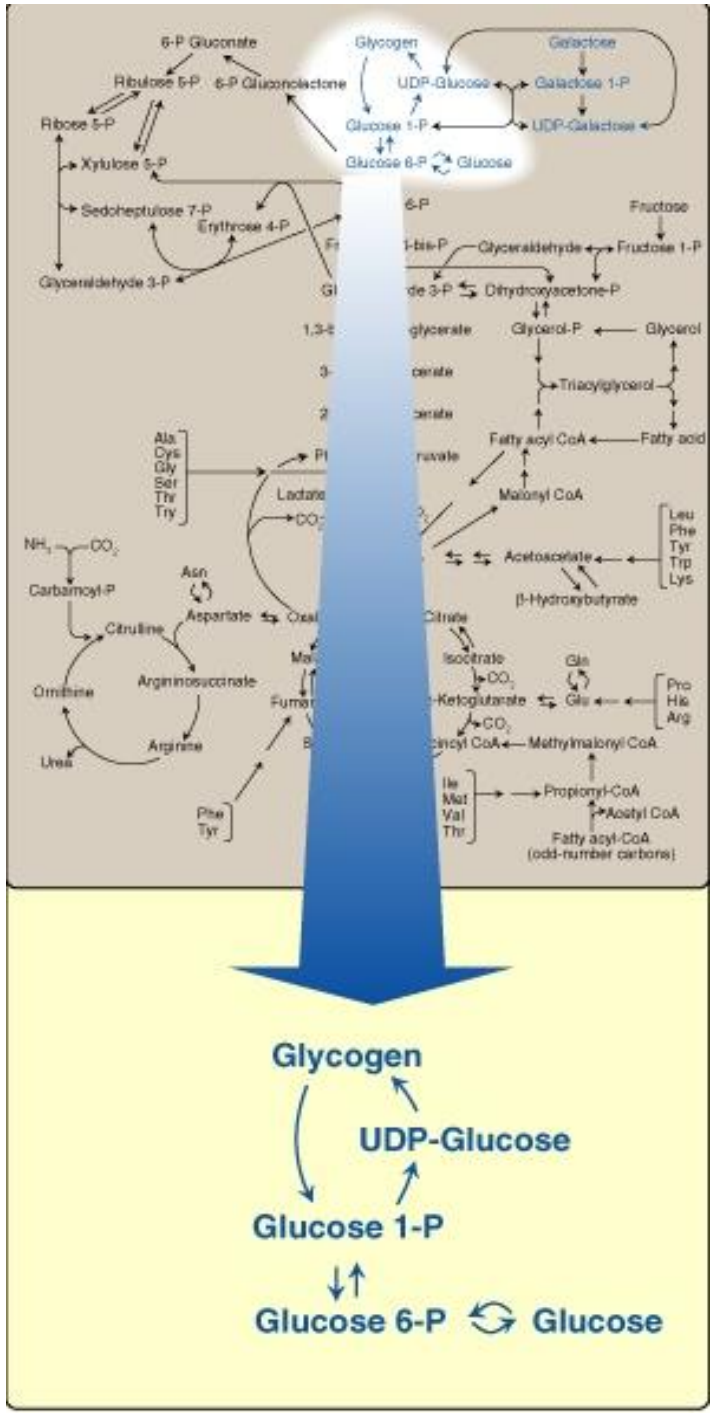
Glycogen Structure

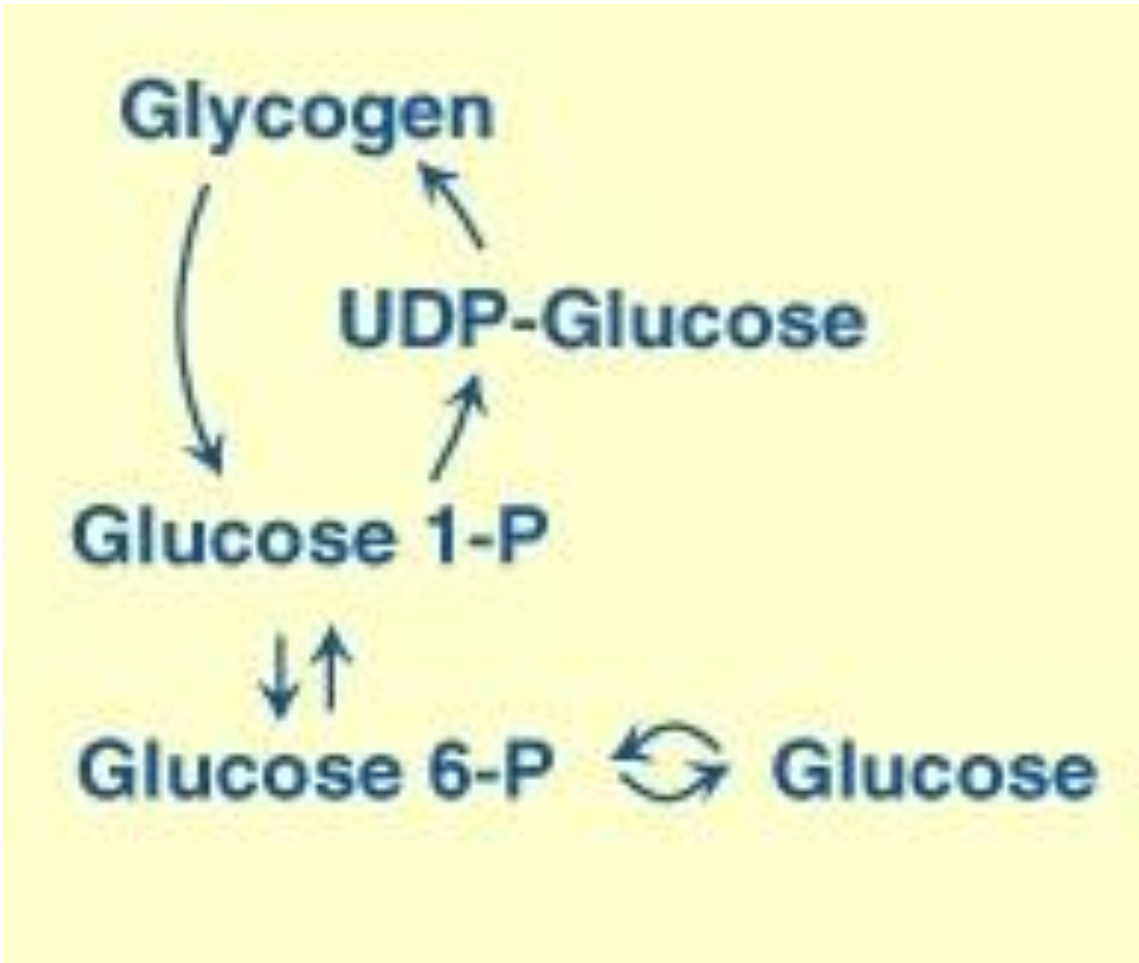


* Extensively branched homopolysaccharide

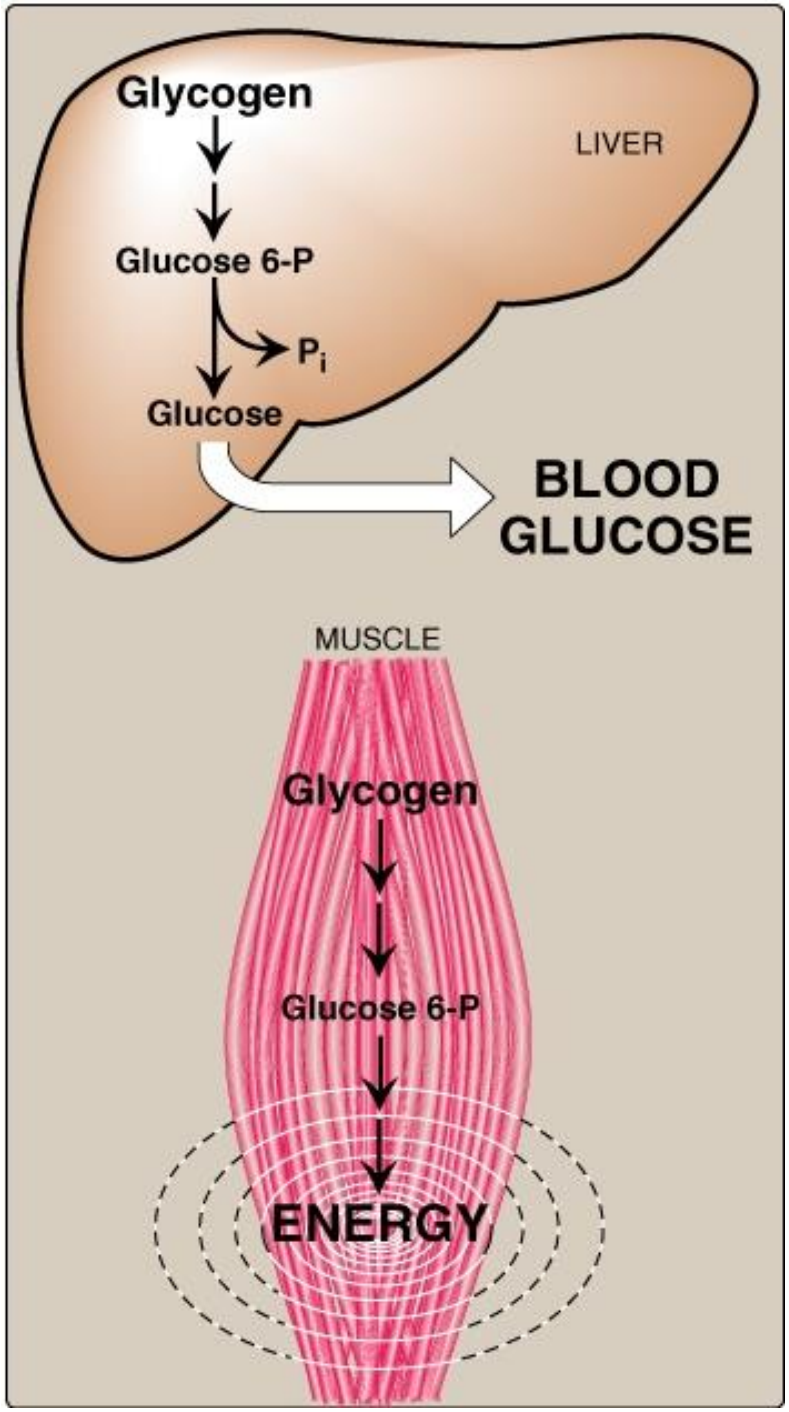
* One molecule consists of hundreds of thousands of glucose units

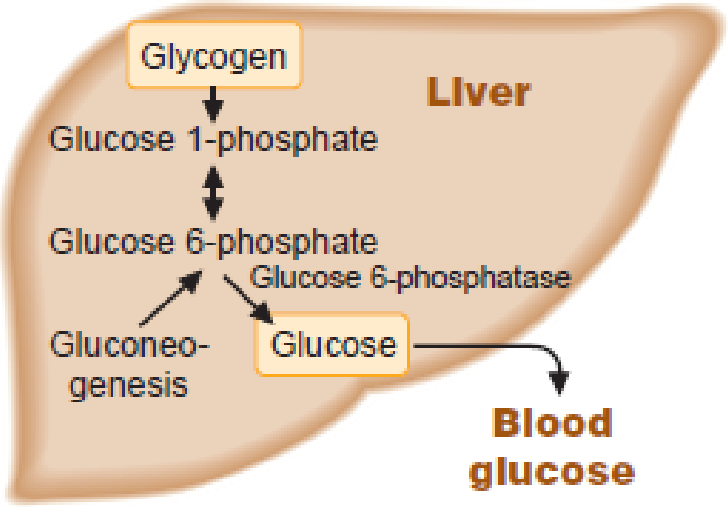
Glycogen synthesis & degradation

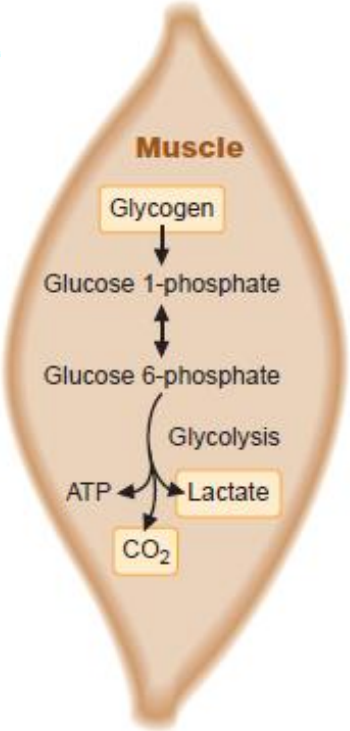




Fates of Glucose that results from glycogen degradation



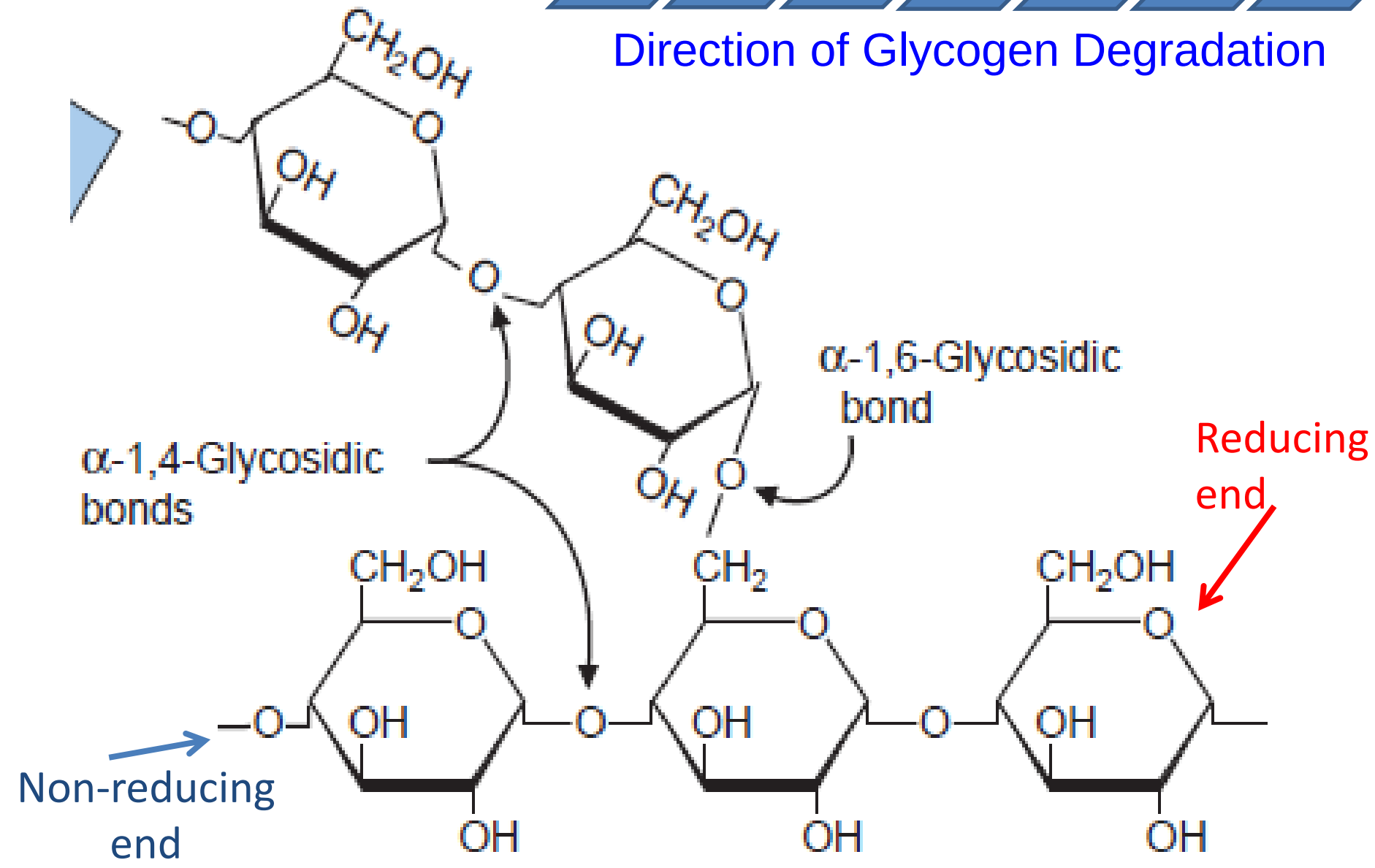


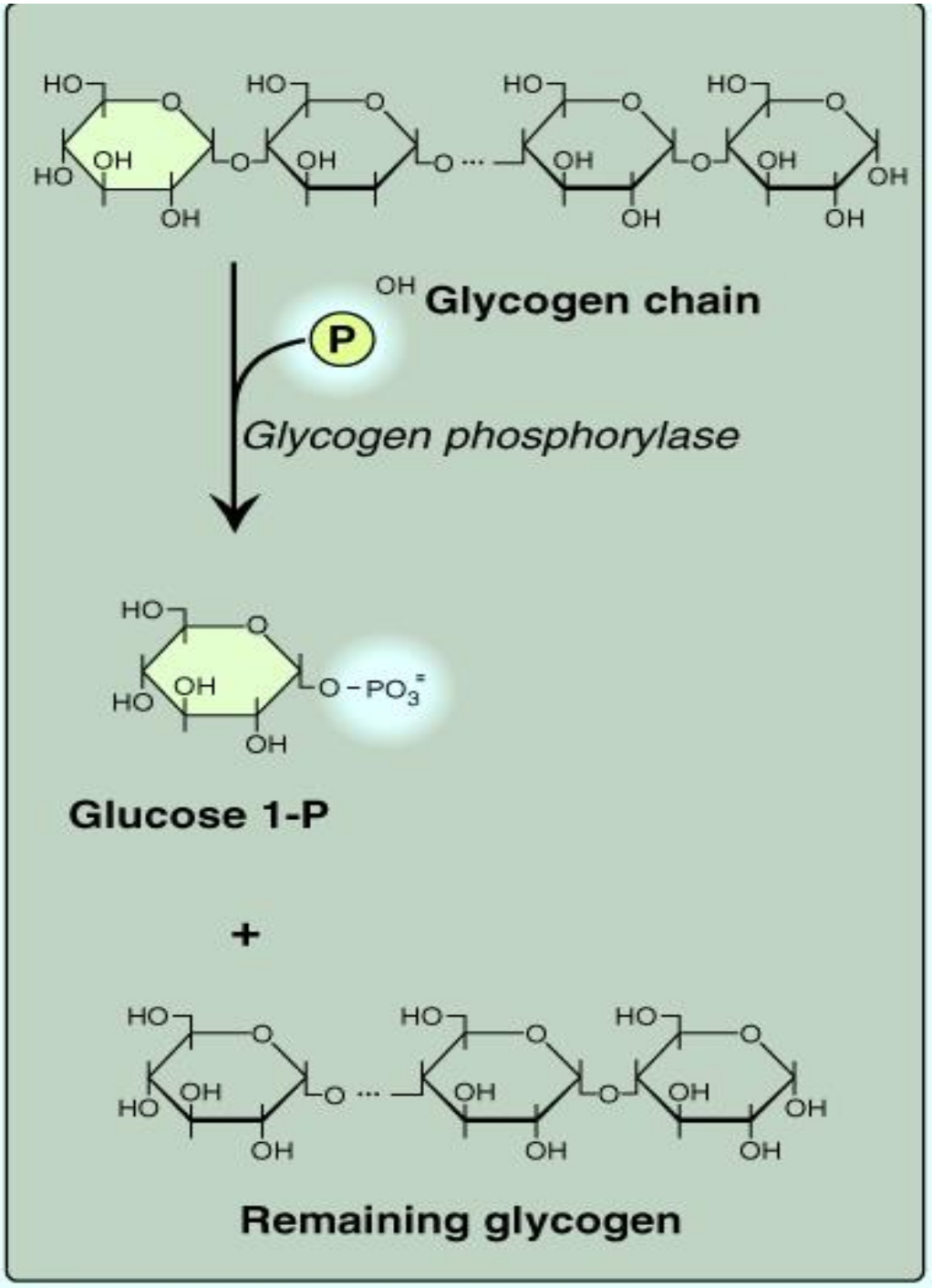


Glycogen Degradation

- Liver glycogen stores increase during the well-fed state and are depleted during fasting
- Muscle glycogen is not affected by short periods of fasting (a few days) and is only moderately decreased in prolonged fasting (weeks).

Direction of Glycogen Degradation





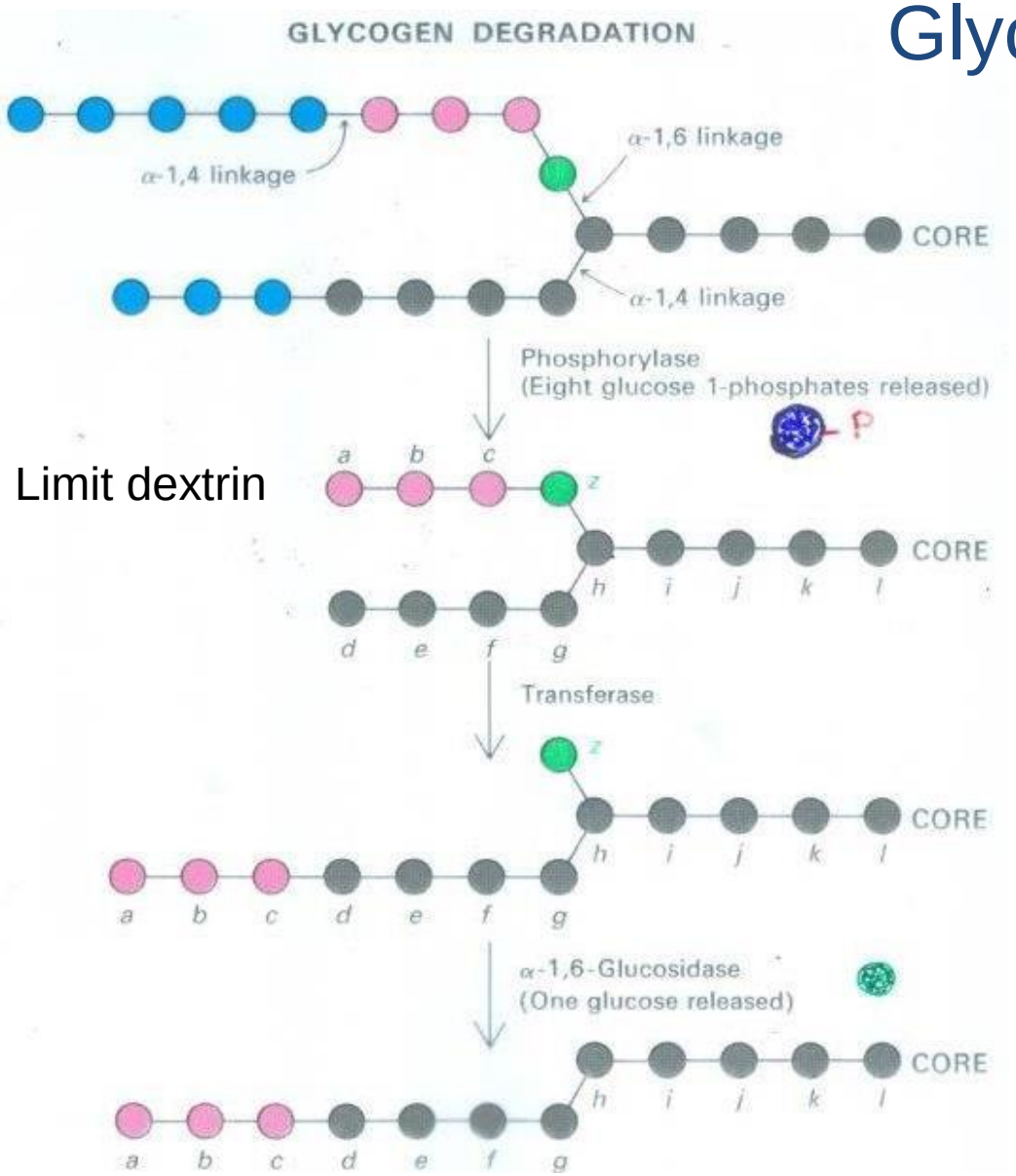
Degradation of glycogen (Glycogenolysis)

Degradation of glycogen
One glucose unit is removed at a time

Starts from the non-reducing ends

Released in the form of glucose 1-phosphate

Glycogen Degradation



Limit dextrin

Debranching enzyme

G-1-P is converted in the cytosol to G-6-P by phosphoglucomutase

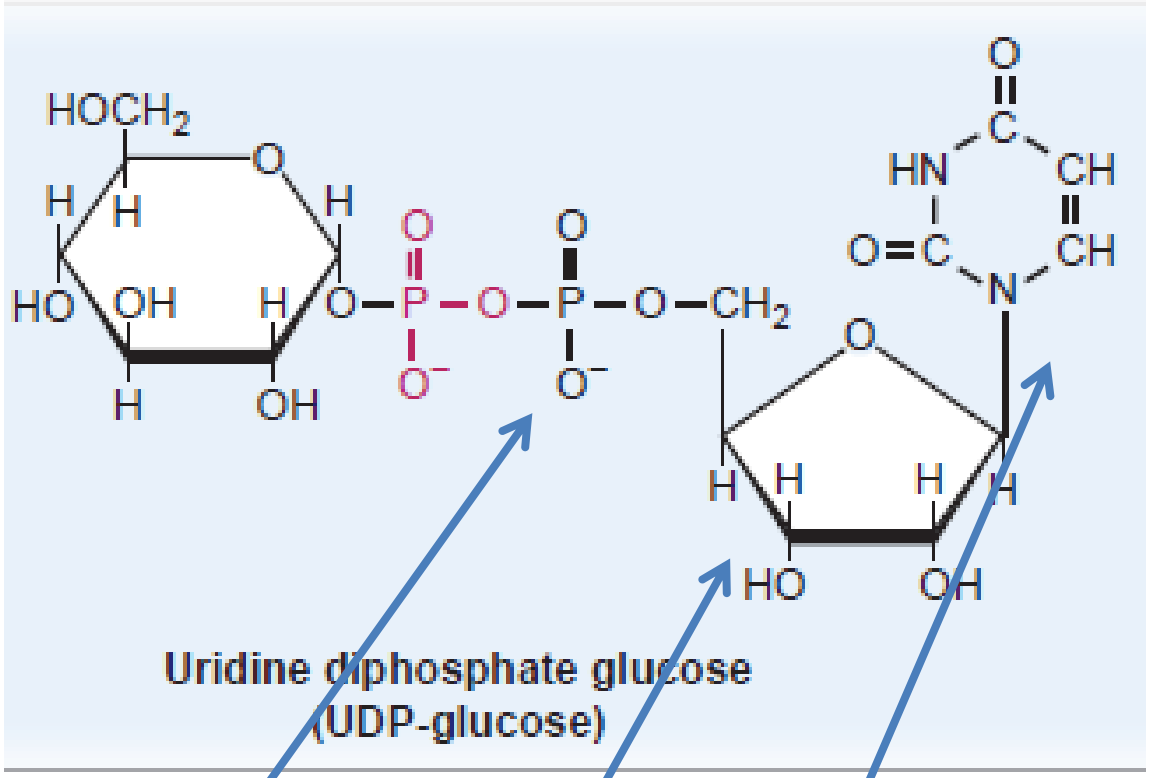
Lysosomal degradation of glycogen

- A small amount (1–3%) of glycogen is degraded by the lysosomal enzyme, α(1–4)-glucosidase (acid maltase).
- The purpose of this pathway is unknown.
- A deficiency of this enzyme causes accumulation of glycogen in vacuoles in the lysosomes (Type II: Pompe disease)

Glycogen Synthesis

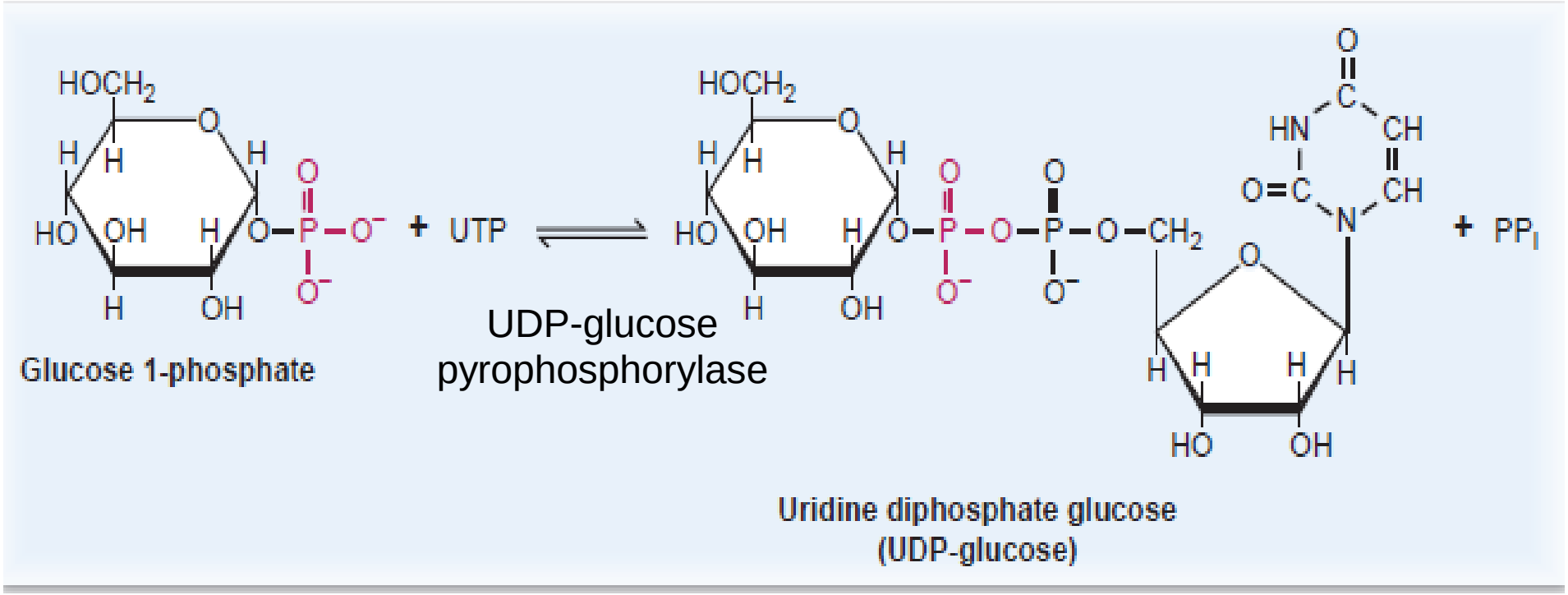
Glycogen is synthesized by adding glucose one by one
UDP-Glucose is the active donor of glucose units

Glycogenesis

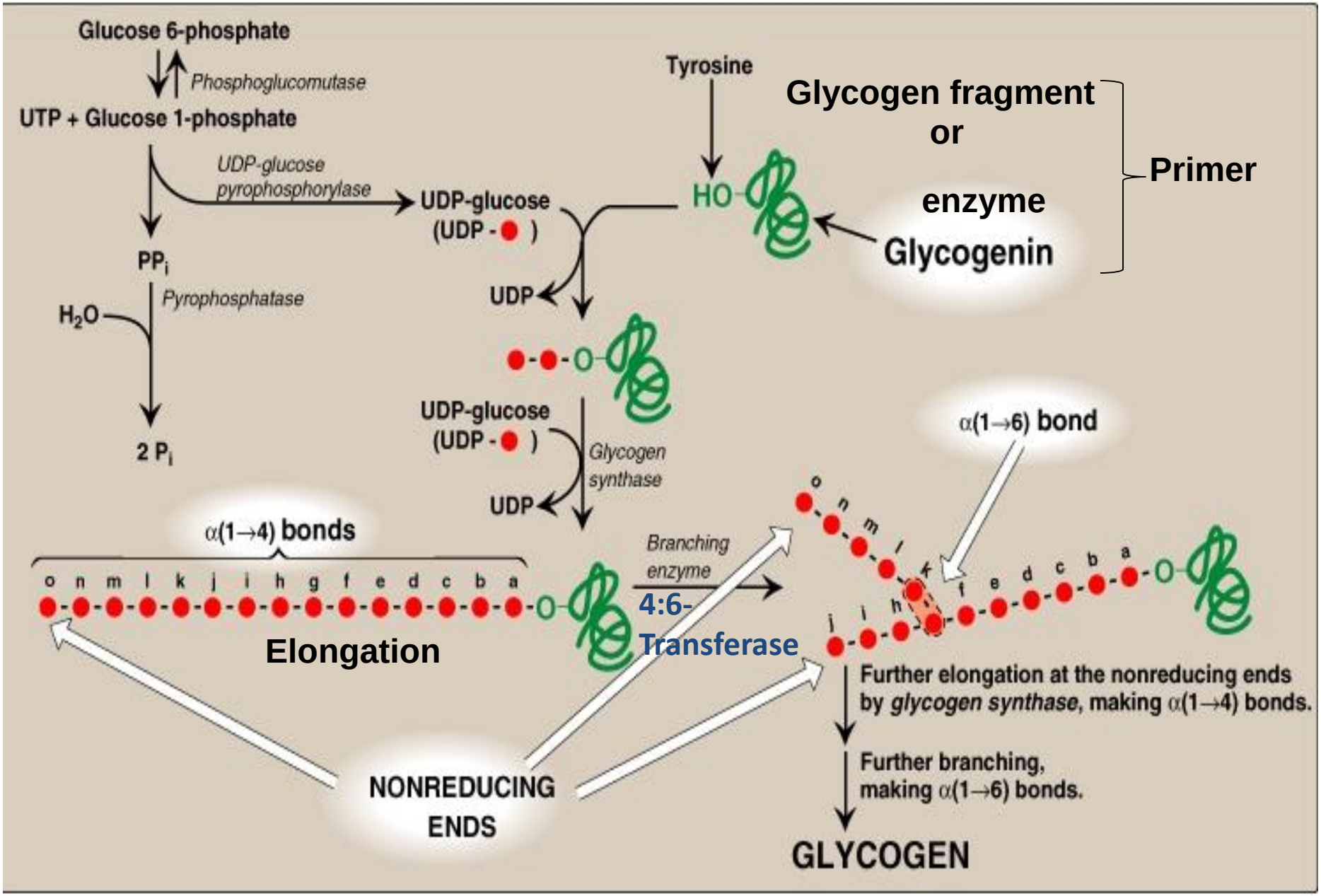


Phosphate Ribose Uracil

Formation of UDP-Glucose



Glycogen Synthesis

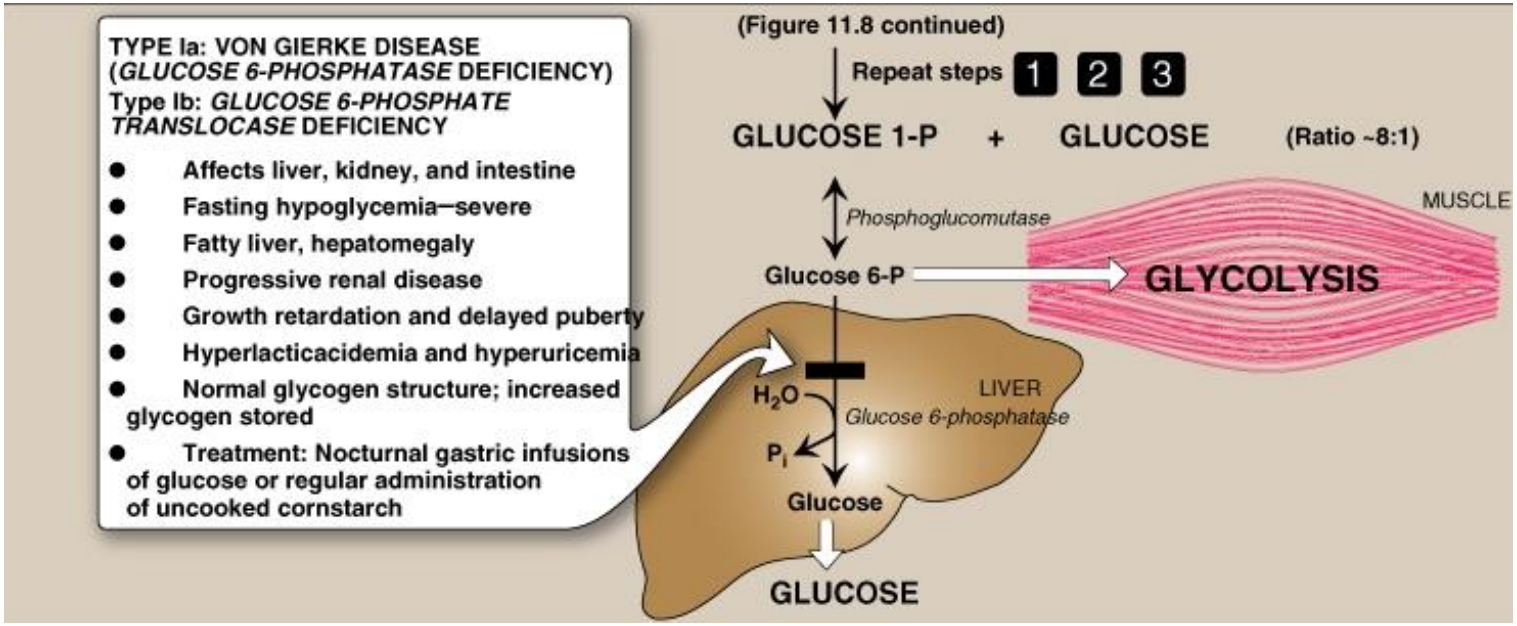


Glycogen Storage Diseases

- Genetic diseases
- Defect in an enzyme required for synthesis or degradation ➔
- Accumulation of excessive amount of abnormal glycogen (synthesis) or normal glycogen (degradation)
- In one or more tissue
- Severity: FATAL in Infancy……. Mild disorder

Glycogen Storage Diseases

- I Glucose-6-phosphatase (von Gierke disease)



- Liver, kidney and intestine.
- Severe fasting hypoglycemia
- Hepatomegaly fatty liver.
- Normal glycogen structure.
- Progressive renal disease.
- Growth retardation.

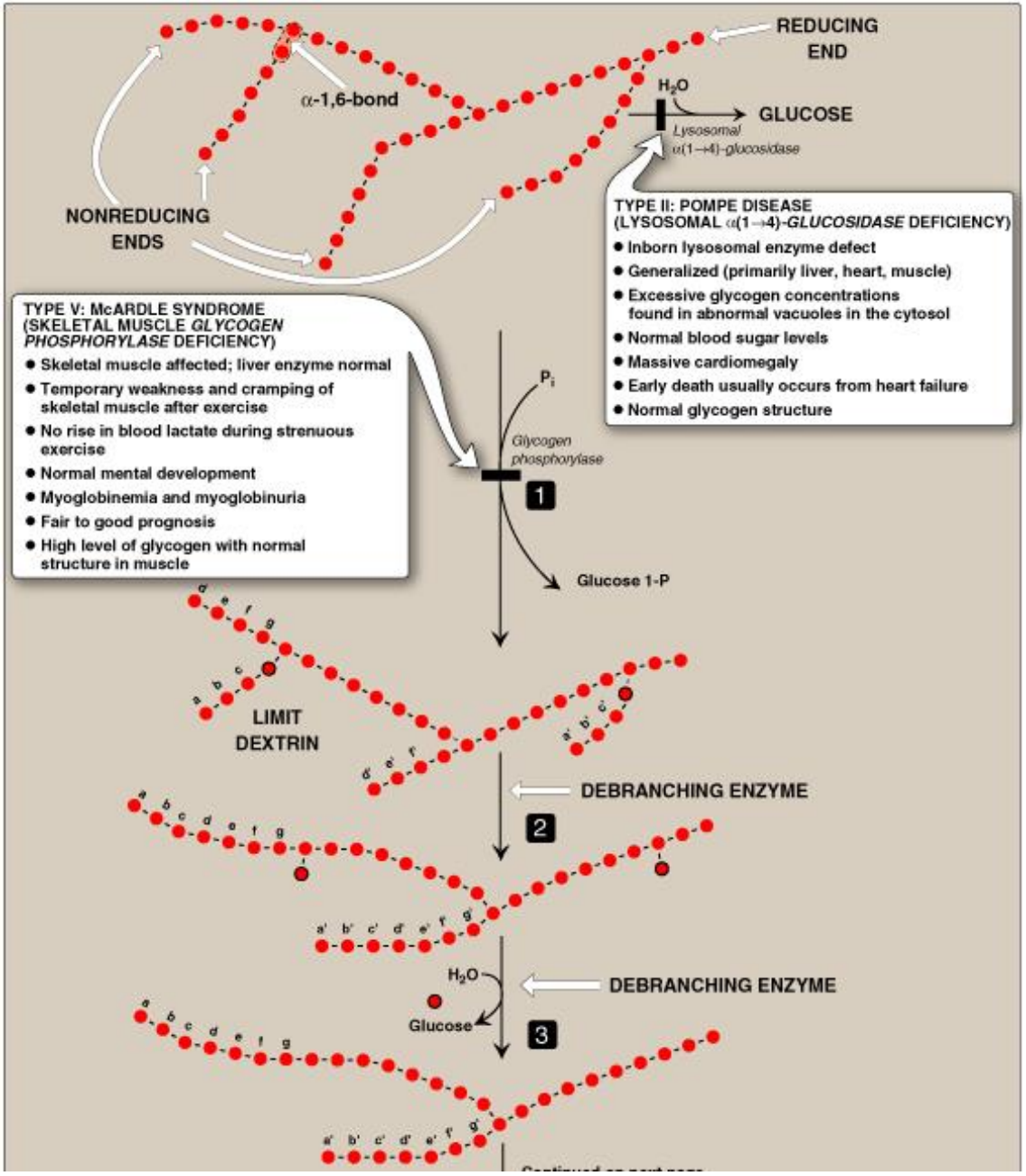
Glycogen Storage Diseases

- V Muscle glycogen phosphorylase (McArdle syndrome)
- Skeletal muscle glycogen phosphorylase deficiency
  - Only muscle is affected;
  - Weakness and cramping of muscle after exercise
  - no increase in [lactate] during exercise

Glycogen Storage Diseases

- II Lysosomes α (1→4) glucosidase ➔ POMPE Disease
- Degradation of glycogen in the lysosomes
- ≈ 3% of glycogen is degraded in the lysosomes
- Affects liver, heart and muscle
- Excessive glycogen in abnormal vacuoles in the lysosomes
- Massive cardiomegaly
- Normal blood sugar, normal glycogen structure
- Early death from heart failure.

Glycogen Storage Diseases



Energy needed for glycogen synthesis

Glucose + ATP $\longrightarrow$ Glucose 6-phosphate + ADP

Glucose 6-phosphate $\rightleftharpoons$ Glucose 1-phosphate

Glucose 1-phosphate UTP $\rightleftharpoons$ UDP-Glucose PP_i

PP_i + H_2O $\longrightarrow$ $2P_i$

UDP-Glucose + $Glycogen_{(n)}$ $\longrightarrow$ UDP + $Glycogen_{(n+1)}$

Glc. + ATP+ UTP+ $Glycogen_{(n)}$ $\longrightarrow$ ADP + UDP +$Glycogen_{(n+1}$

The net reaction in glycogen synthesis and degradation

Glucose 1-phosphate + UTP $\rightleftharpoons$ UDP-Glucose + PP_i

PP_i + H_2O $\longrightarrow$ $2P_i$

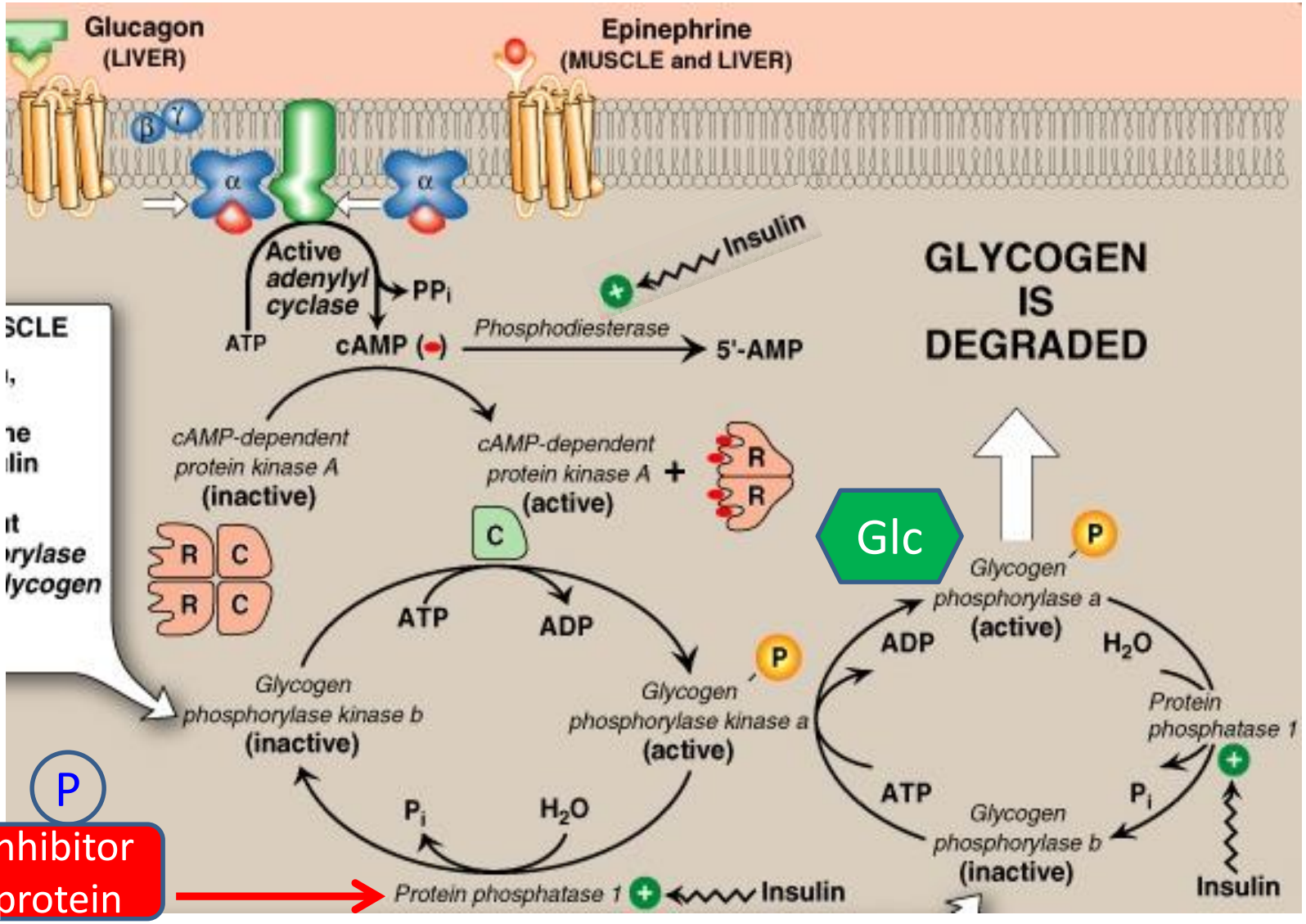
UDP-Glucose + $Glycogen_{(n)}$ $\rightleftharpoons$ UDP + $Glycogen_{(n+1)}$

Glc. 1-phosph. + UTP+$Glycogen_{(n)}$ $\longrightarrow$ UDP +$Glycogen_{(n+1}$

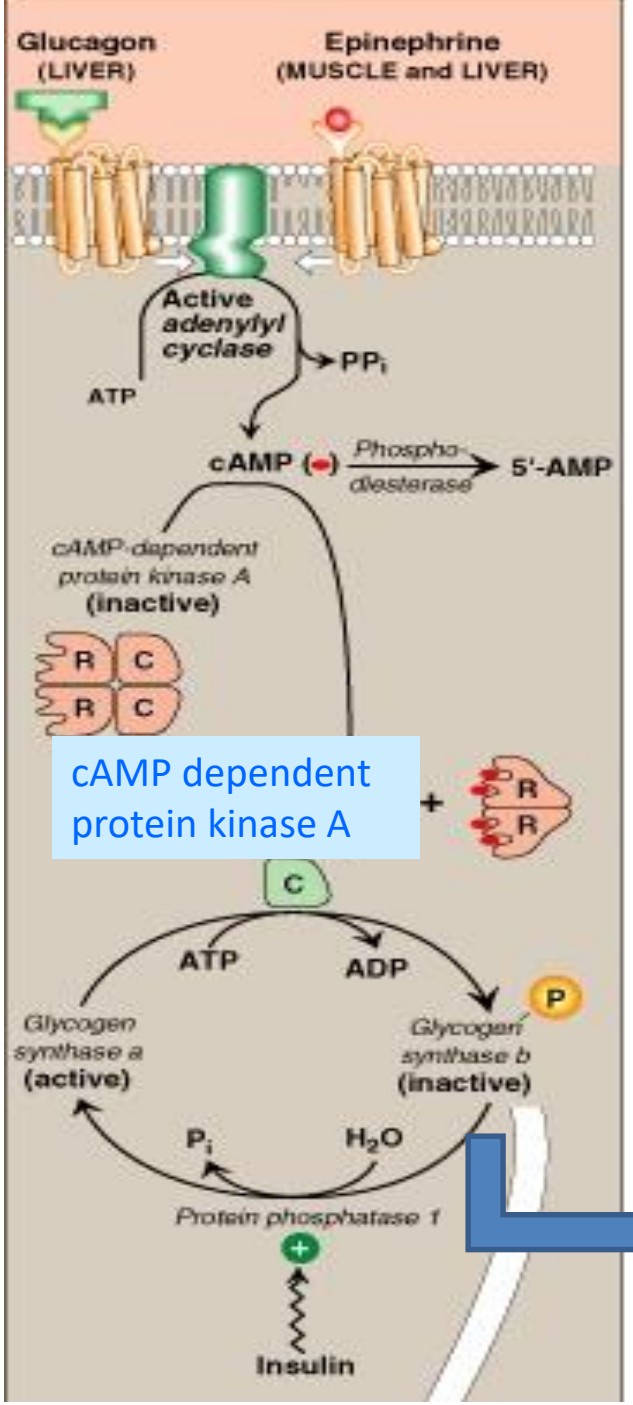
Degradation

$Glycogen_{(n)}$ + P_i $\rightleftharpoons$ $Glycogen_{(n-1)}$ +Glc. 1-phosphate

Hormonal Regulation of Glycogen Metabolism



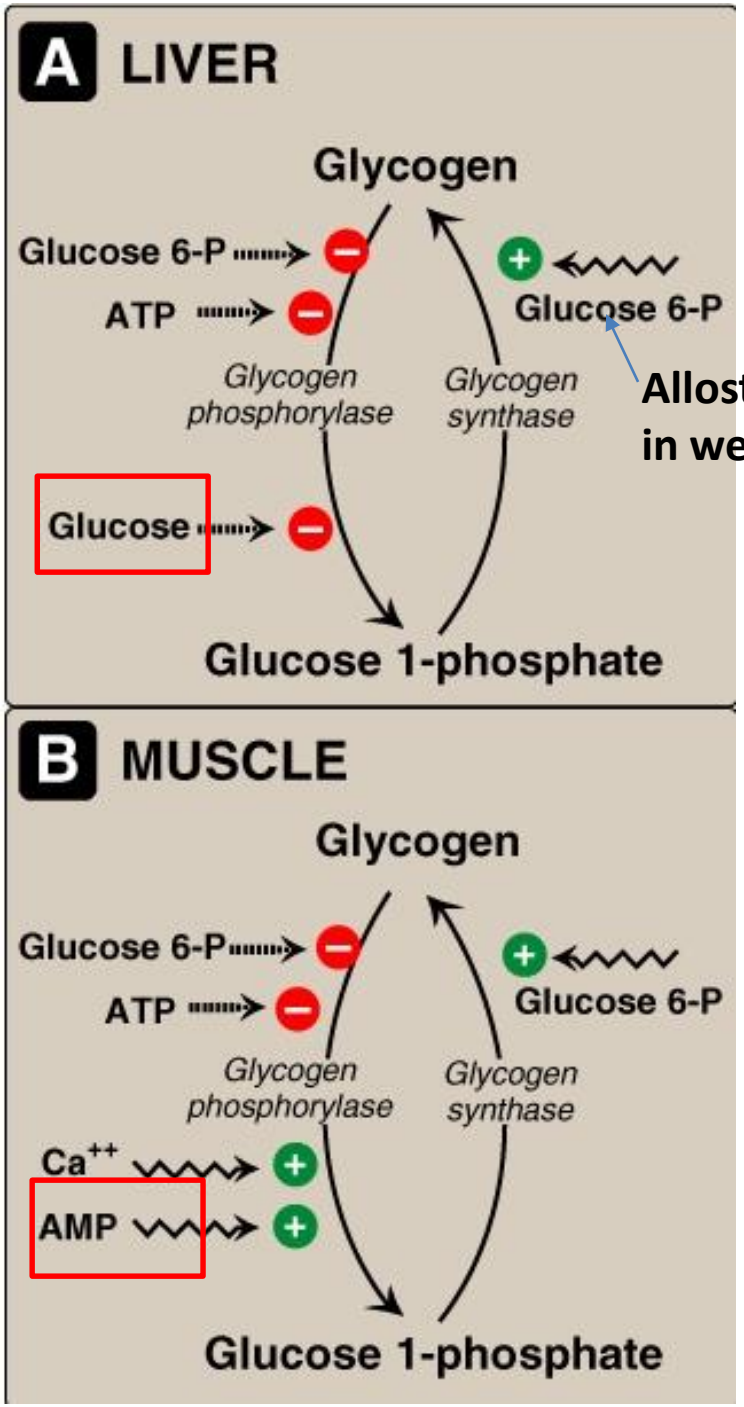
Regulation of Glycogen Synthesis



Phosphorylation at several sites

Inhibition is proportional to the degree of phosphorylation

GLYCOGEN SYNTHESIS IS INHIBITED



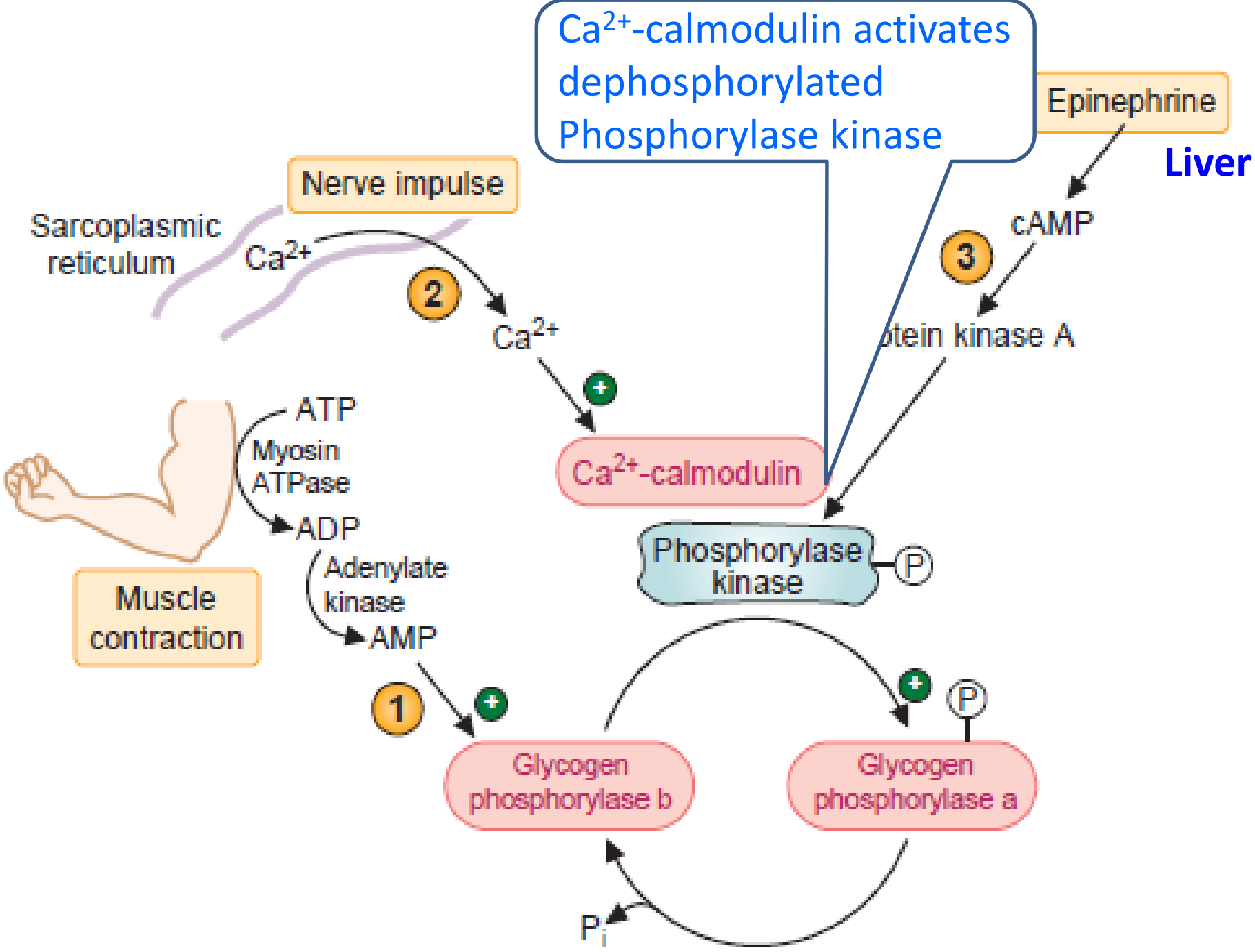
Allosteric Regulation of Glycogen Metabolism

Allosteric activator in well-fed state

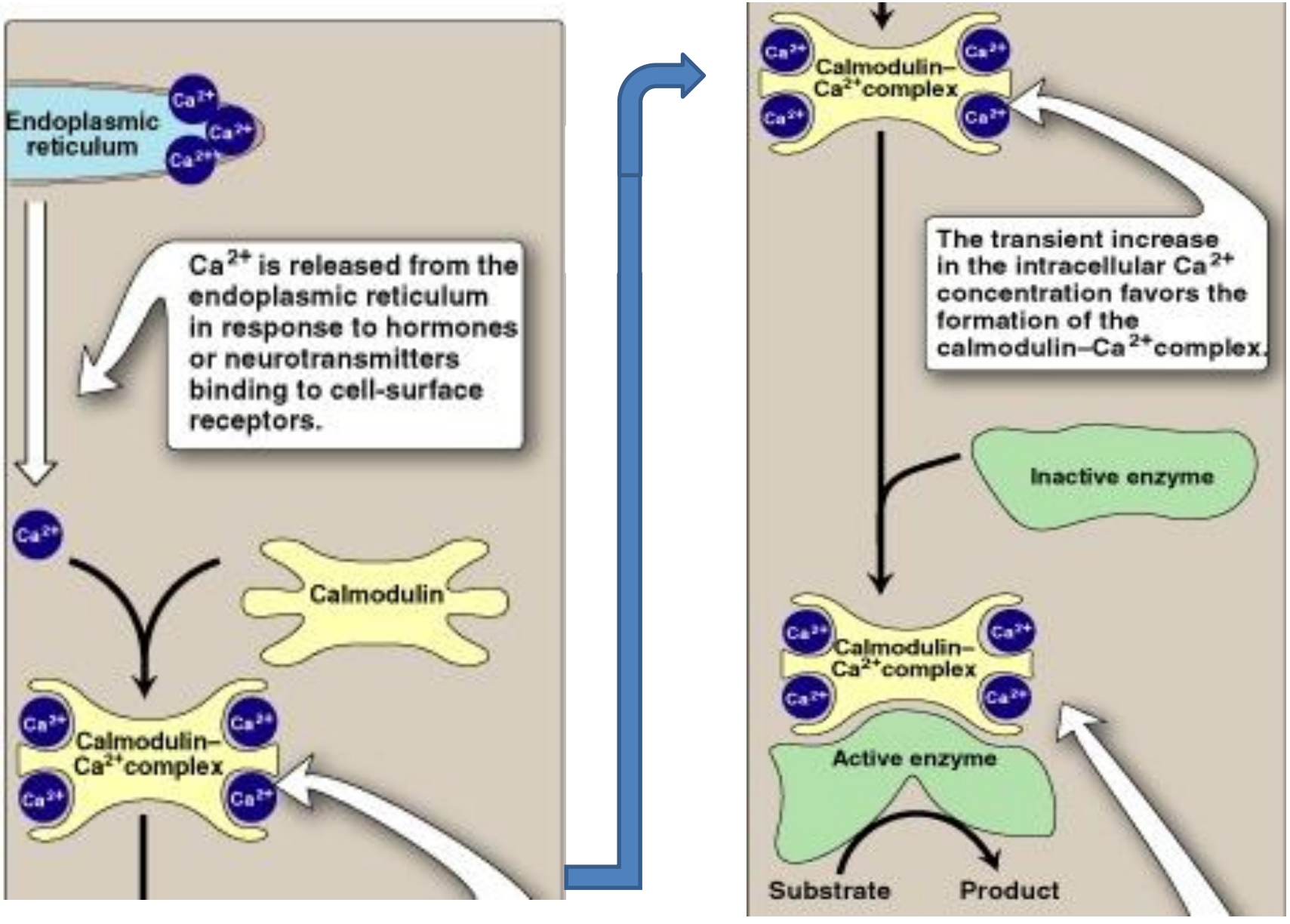
Rapid response to cell's needs

Available substrate and ATP → synthesis

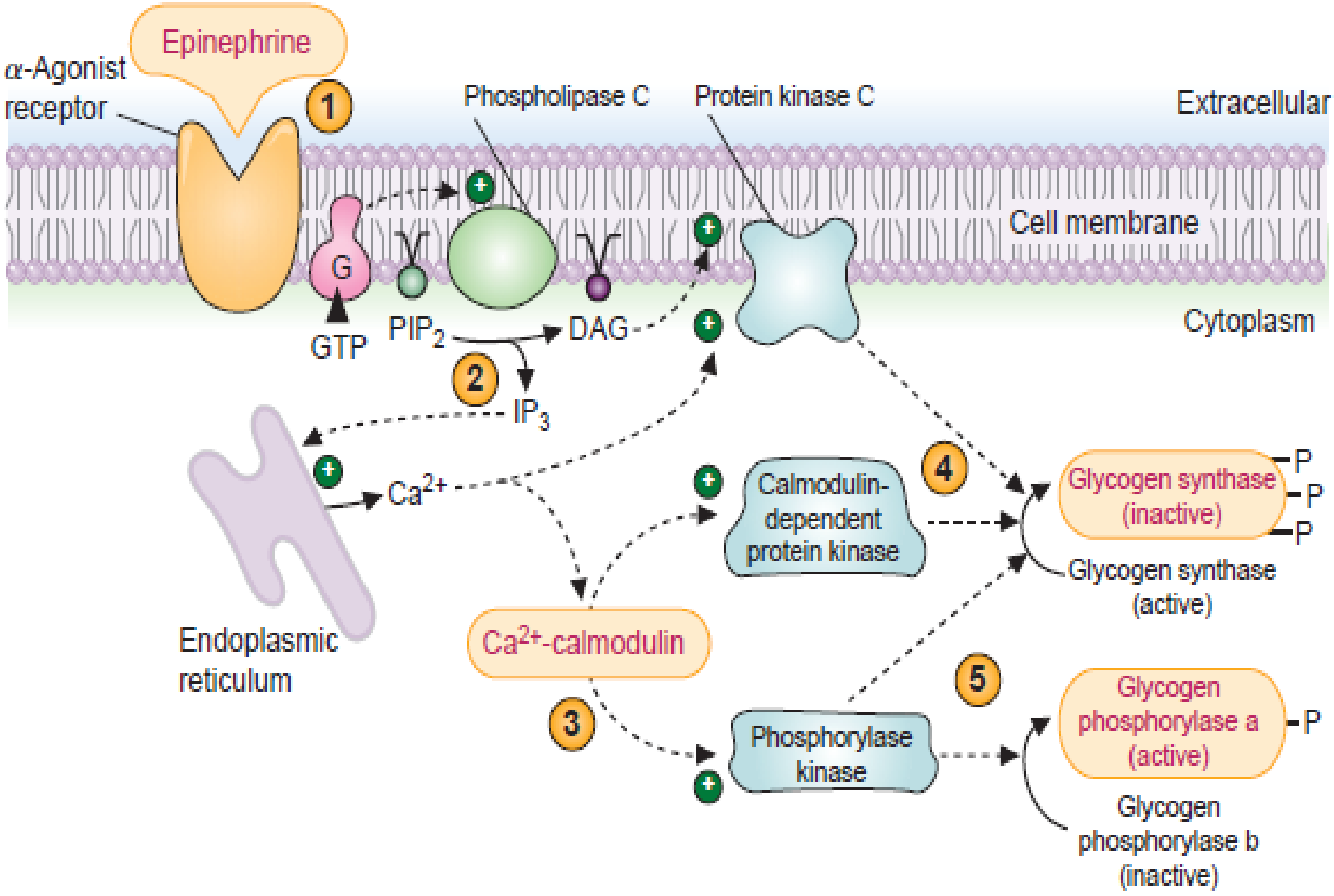
↓↓Glucose and ↓ATP → Glycogenolysis


Ca2+-calmodulin activates dephosphorylated Phosphorylase kinase
Epinephrine
Liver
Nerve impulse
Sarcoplasmic reticulum
Ca2+
2
Ca2+
cAMP
3
tein kinase A
ATP
Myosin ATPase
ADP
Adenylate kinase
AMP
Muscle contraction
Ca2+-calmodulin
Phosphorylase kinase
P
1
Glycogen phosphorylase b
Glycogen phosphorylase a
P
Pi

Ca^{+2} -Calmodulin Complex Function



Calcium Activation of liver phosphorylase Kinase



Glycogen Metabolism Regulation