Glycogenesis and Glycogenolysis

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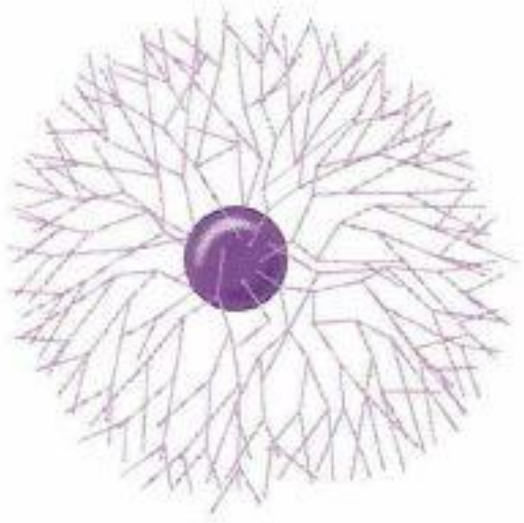
Introduction

- **Glycogen is the major storage form of glucose in animal, corresponding to starch in plants.**
- **It is a large polymer of α-D-glucose**
- **Stored as granules in cytosol**
- **Glycosidic BONDS**

1. **α-1,4 and**
2. **α-1,6.(for branching)**



LIVER vs Muscle

- **Approx. 100 g (liver) and 400g (muscle)**
- **Although liver content of glycogen is greater than that of muscle,**
- **However, because of muscle greater mass,**
- **it contains about three to four times as much glycogen as does liver**
- **other tissues, including cardiac muscle and the kidney, store smaller quantities.**

USE

❑Liver glycogen (Unselfish)

- **Maintain the blood glucose level, particularly between the meals**
- **After 12–18 hours of fasting, the liver glycogen is almost totally depleted.**
- **Stores increase during well fed stage and depleted during fasting.**

❑Muscle glycogen (selfish)

- **Serve as fuel reserve for the supply of ATP during muscle contraction.**
- **Immediate source of glycolysis with in itself**

HOW???

Highly branched

↓

Large number of sites for glycogenolysis

↓

Rapid release of many glucose -1- phosphate
(muscle) and glucose (liver)

↓

Glycoslysis

↓

Energy release

Glycogenesis: synthesis of glycogen from glucose

- Takes place in cytosol
- Requires UTP

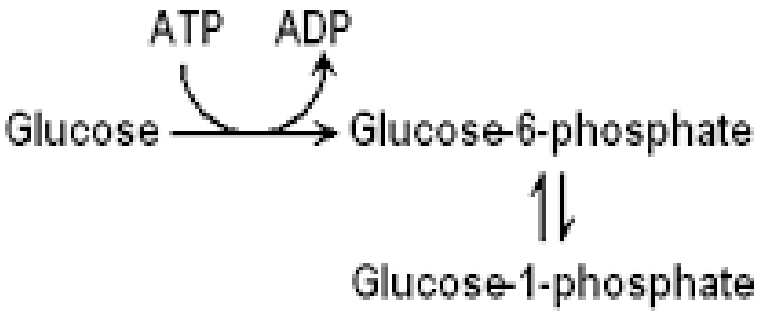
Steps of glycogenesis
Glucose converted to glucose 1 phosphate
Synthesis of UDP-glucose
Requirement of primer to initiate glycogenesis called glycogenin
Glycogen synthesis by glycogen synthase
Formation of branches

Glucose converted to glucose -1 - phosphate

- **Glucose is phosphorylated to glucose 6-phosphate,**
- **Catalyzed by**

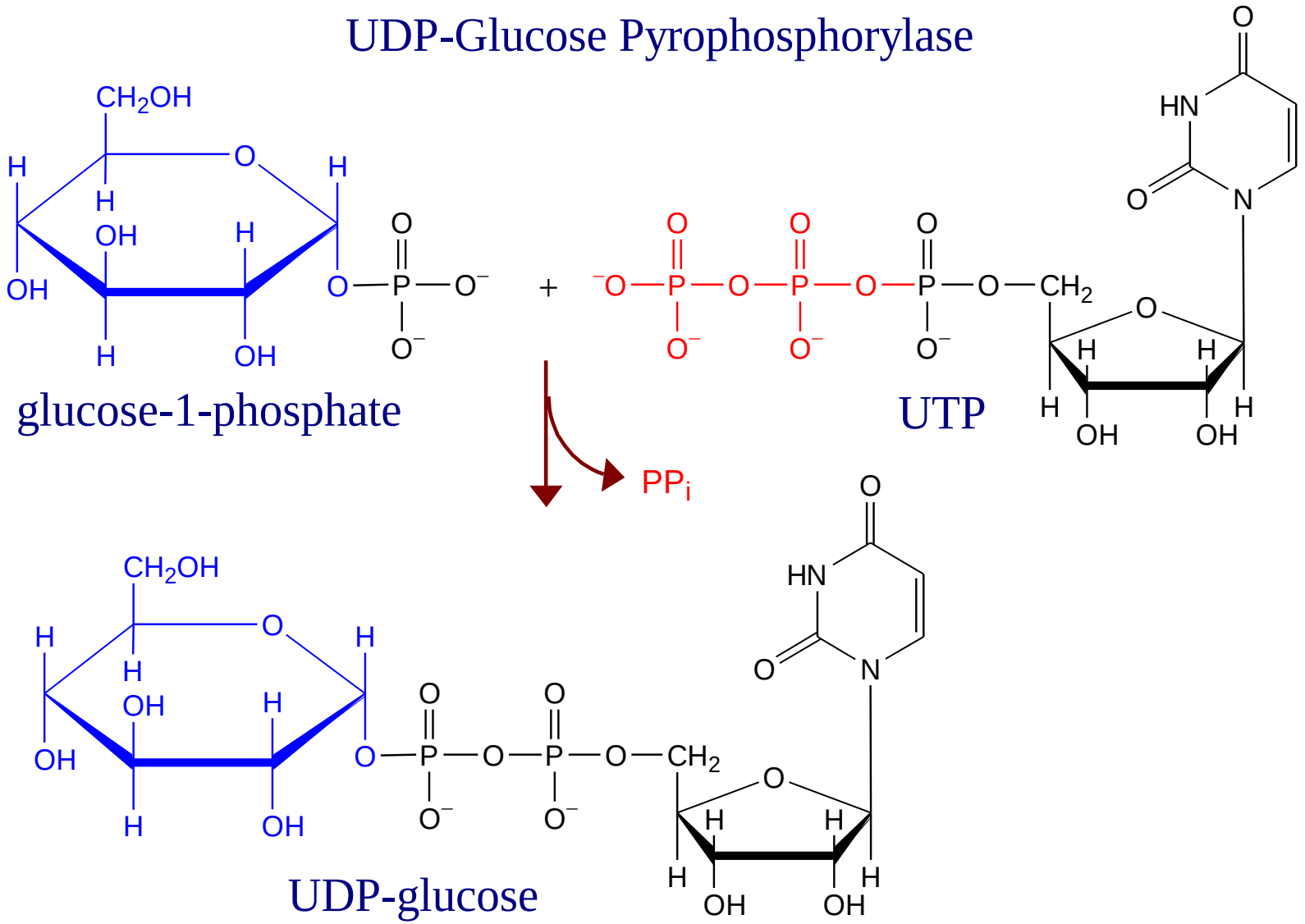
1. **Hexokinase in muscle**
2. **Glucokinase in liver**

- **Glucose 6-phosphate is converted to glucose 1-phosphate by phosphoglucomutase**

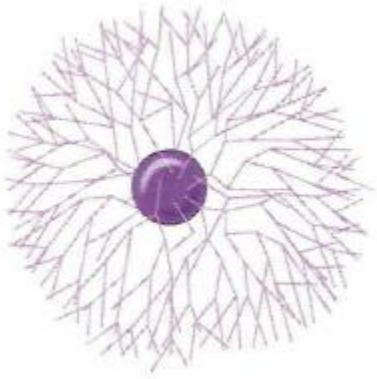


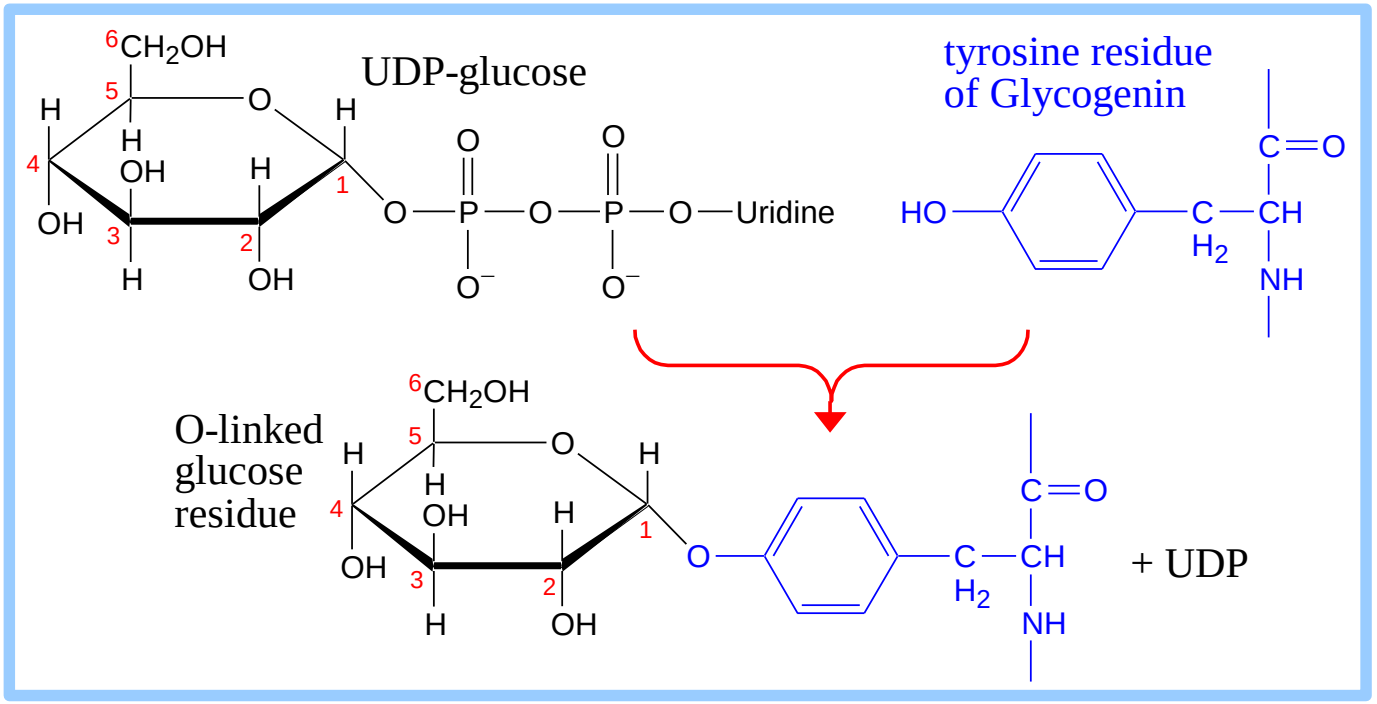
Synthesis of UDP-glucose

UDP-Glucose Pyrophosphorylase



Glycogenin protein and primer

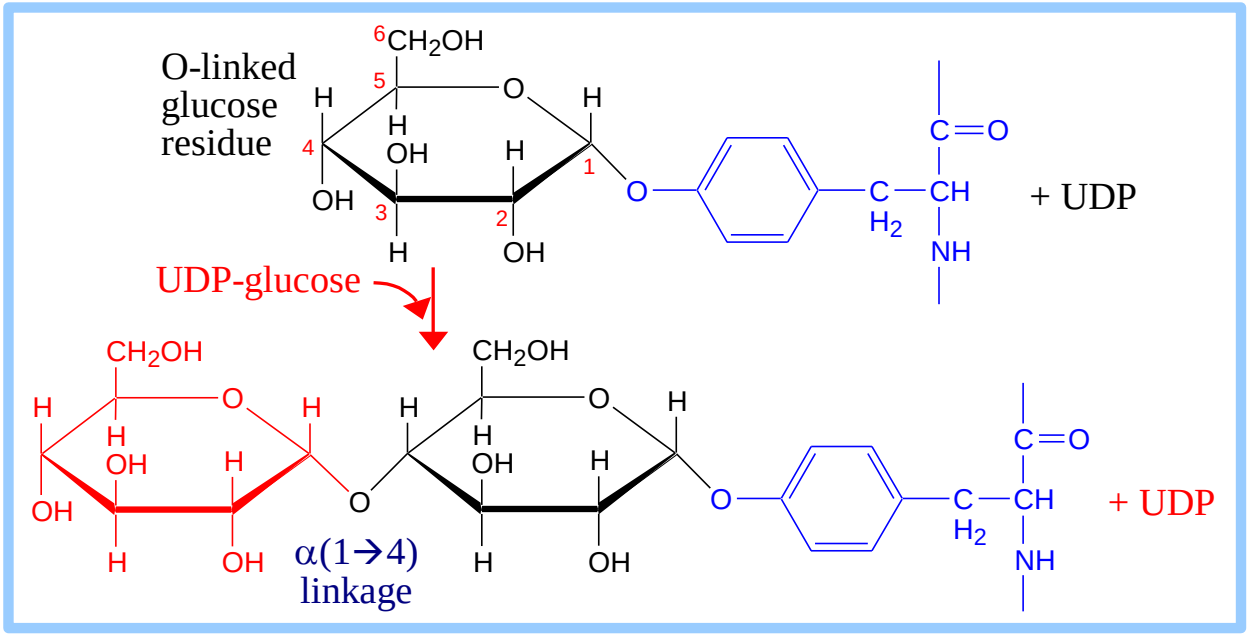




A glycosidic bond is formed between the anomeric C_1 of the glucose moiety derived from UDP-glucose and the hydroxyl oxygen of a tyrosine side-chain of Glycogenin.

UDP is released as a product.

Autoglycosylation



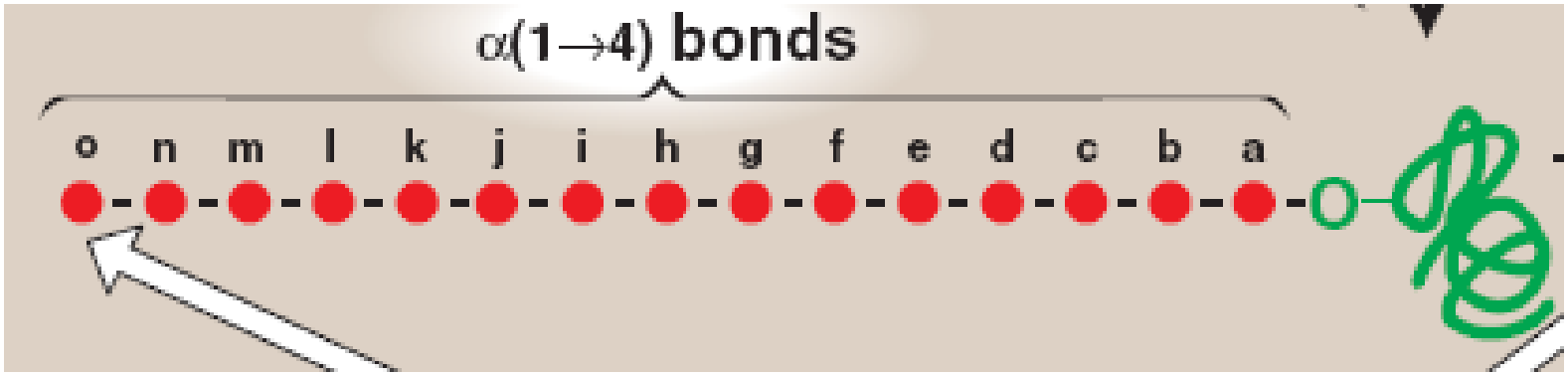
Glycogenin catalyzes glucosylation at C_4 of the attached glucose to yield an O-linked disaccharide with α(1,4) glycosidic linkage.

This is repeated until a short linear glucose polymer up to seven glucose residues (glycogen primer) is built up on Glycogenin.

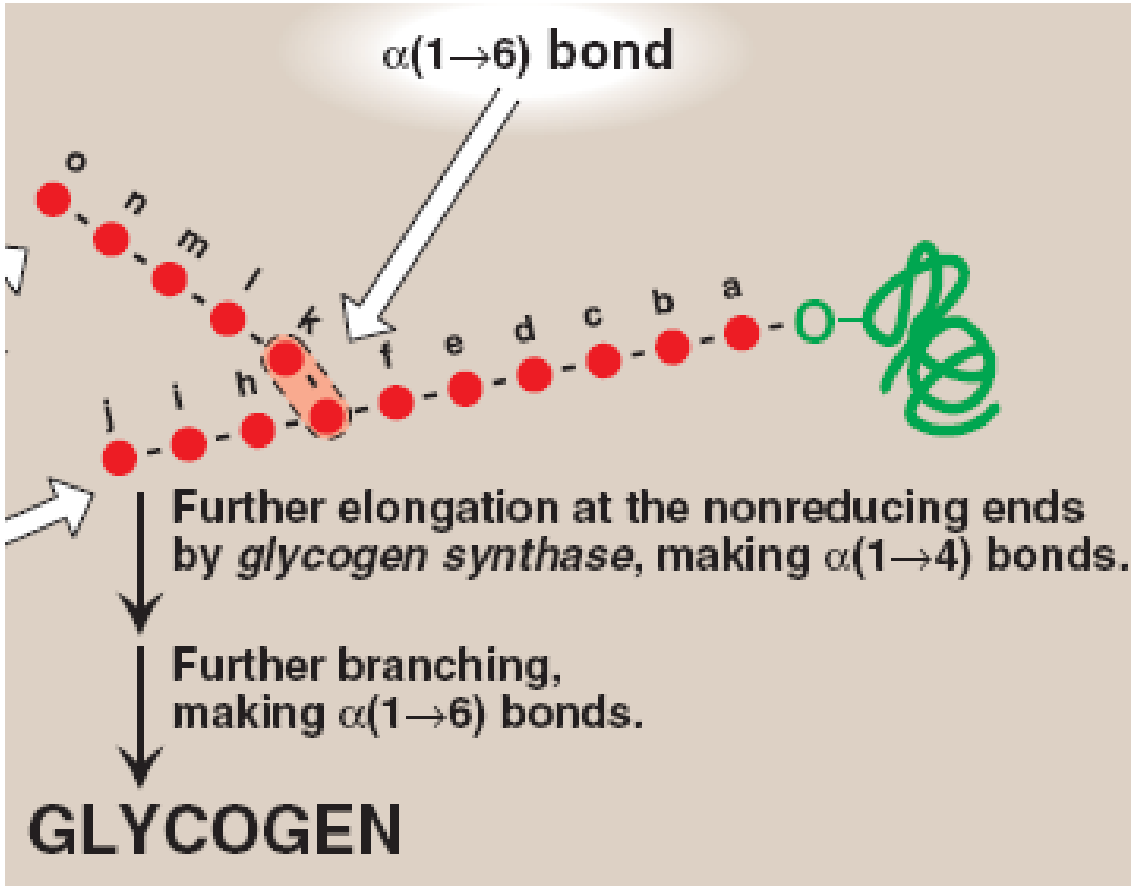
Glycogen synthesis by glycogen synthase

Glycogen Synthase catalyzes transfer of the glucose moiety of UDP-glucose to the hydroxyl at C_4 of the terminal residue of a glycogen chain to form an **α(1 → 4)** glycosidic linkage:

$$\text{glycogen}_{(n\ \text{residues})} + \text{UDP-glucose} \rightarrow \text{glycogen}_{(n+1\ \text{residues})} + \text{UDP}$$

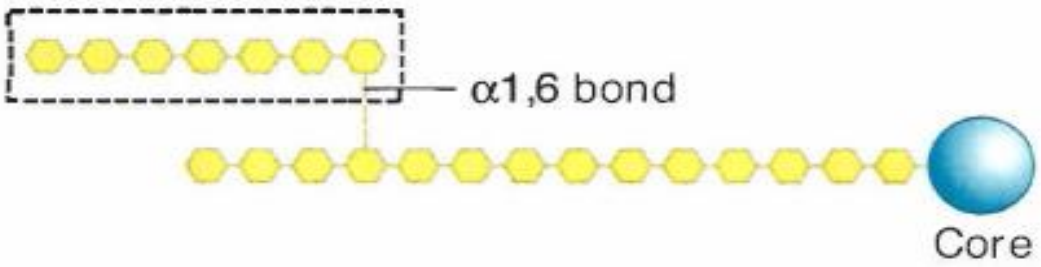


Formation of branches



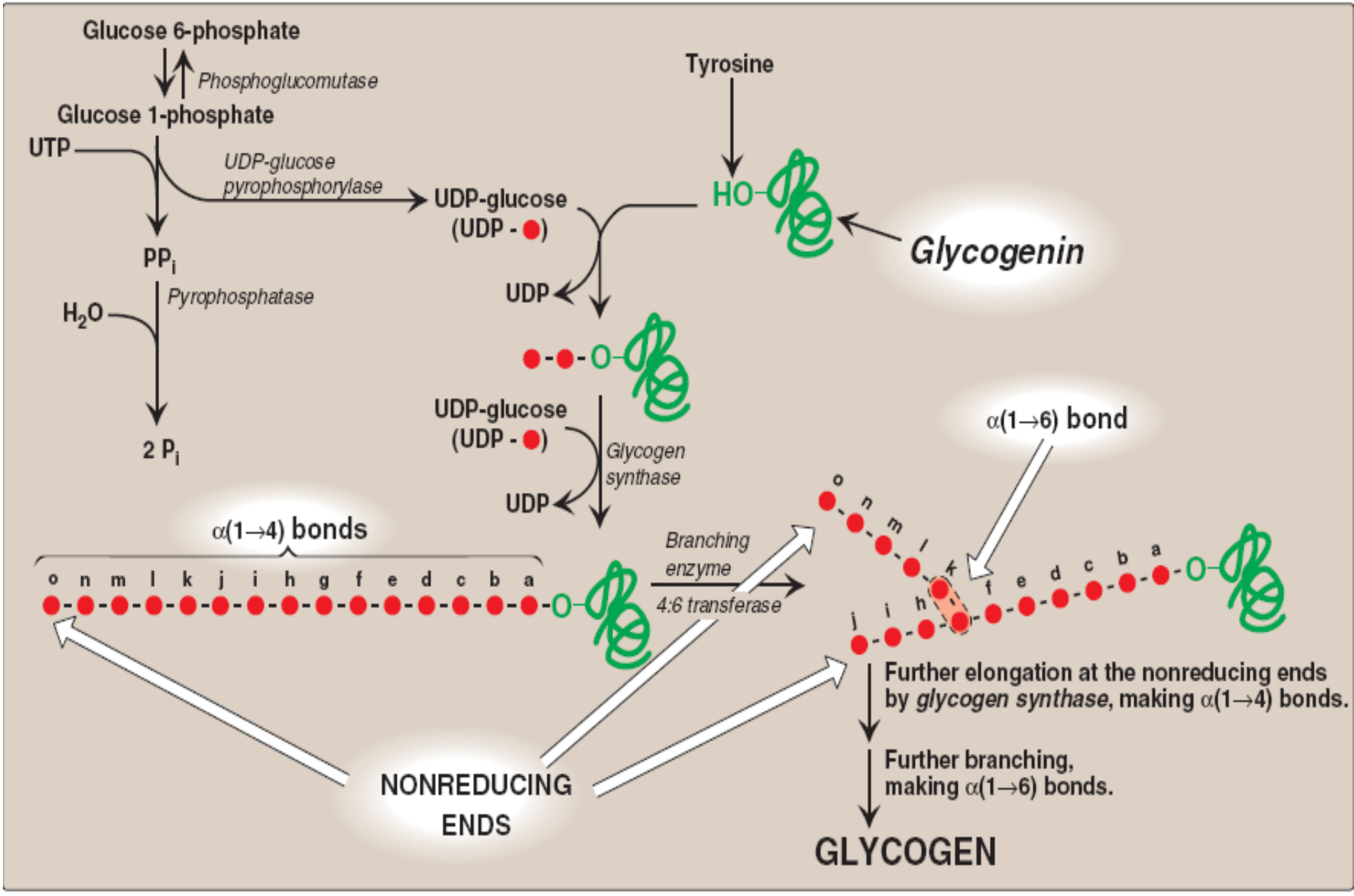
Branching Enzyme (Glycosyl α1,4:α1,6 Transferase)

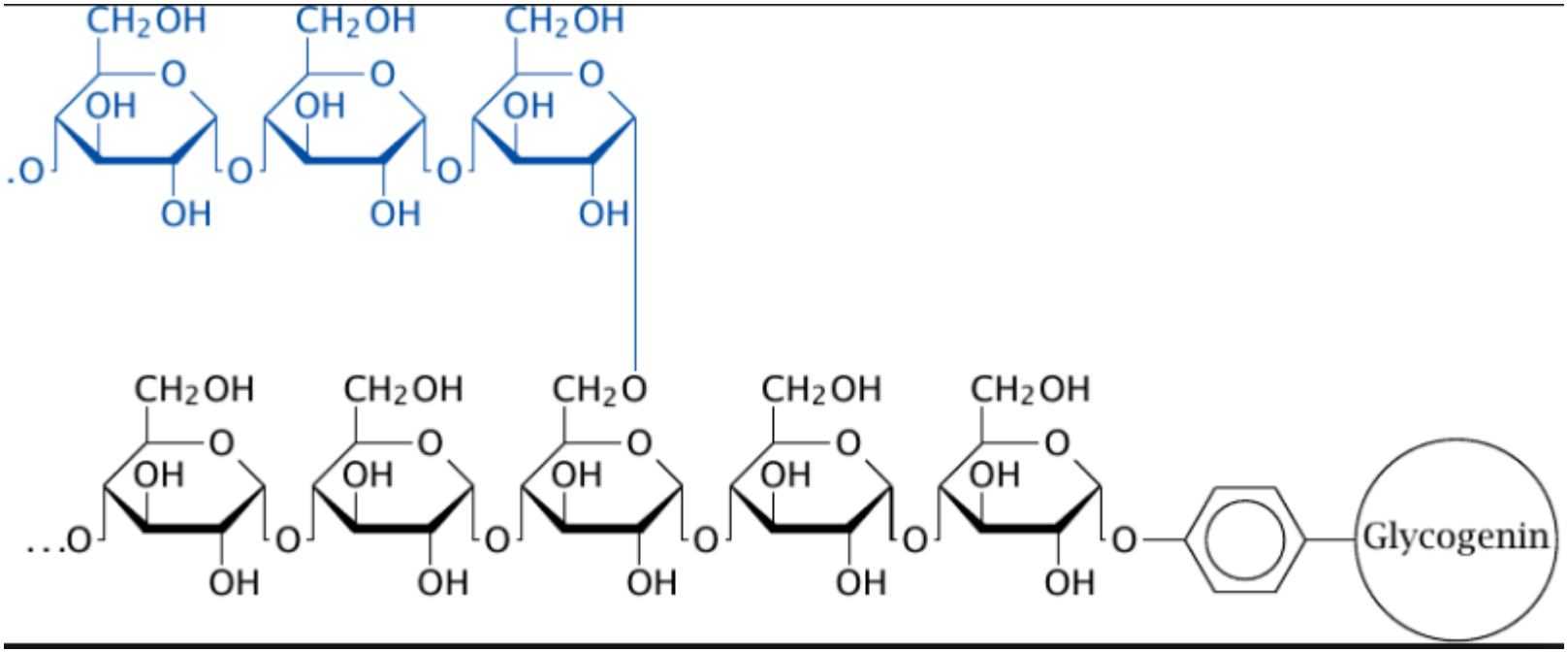
1. Glycogen synthase makes a linear α1,4-linked polyglucose chain (⬭⬭⬭⬭⬭).
2. Branching enzyme hydrolyzes an α1,4 bond.

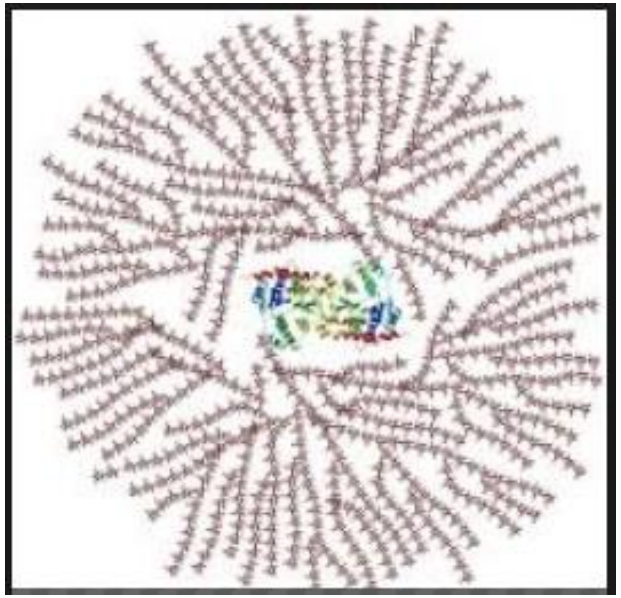


3. Transfers the oligoglucose unit and attaches it with an α1,6 bond to create a branch.
4. Glycogen synthase extends both branches.

Figure I-14-3. Branching Enzyme


Glucose 6-phosphate
Phosphoglucomutase
Glucose 1-phosphate
UTP
UDP-glucose pyrophosphorylase
PPi
H2O
Pyrophosphatase
2 Pi
UDP-glucose (UDP - ●)
UDP
Tyrosine
HO
Glycogenin
UDP-glucose (UDP - ●)
UDP
Glycogen synthase
α(1→4) bonds
o n m l k j i h g f e d c b a
Branching enzyme
4:6 transferase
α(1→6) bond
Further elongation at the nonreducing ends by glycogen synthase, making α(1→4) bonds.
Further branching, making α(1→6) bonds.
NONREDUCING ENDS
GLYCOGEN


CH2OH
O
OH
O
CH2O
Glycogenin



Glycogenolysis

- **The degradation of the stored glycogen in the liver and muscle is called glycogenolysis.**

Steps in Glycogenolysis
Action of glycogen phosphorylase to remove terminal glycosyl residue
Formation of limit dextrin
Action of debranching enzyme
Conversion of glucose 1 phosphate to glucose 6 phosphate
G-6-p to glucose by G-6-phosphatase which is absent in muscle

ACTION OF GLYCOGEN PHOSPHORYLASE AND LIMIT DEXTRIN

Glycogen Phosp

phosphorolytic **clea**

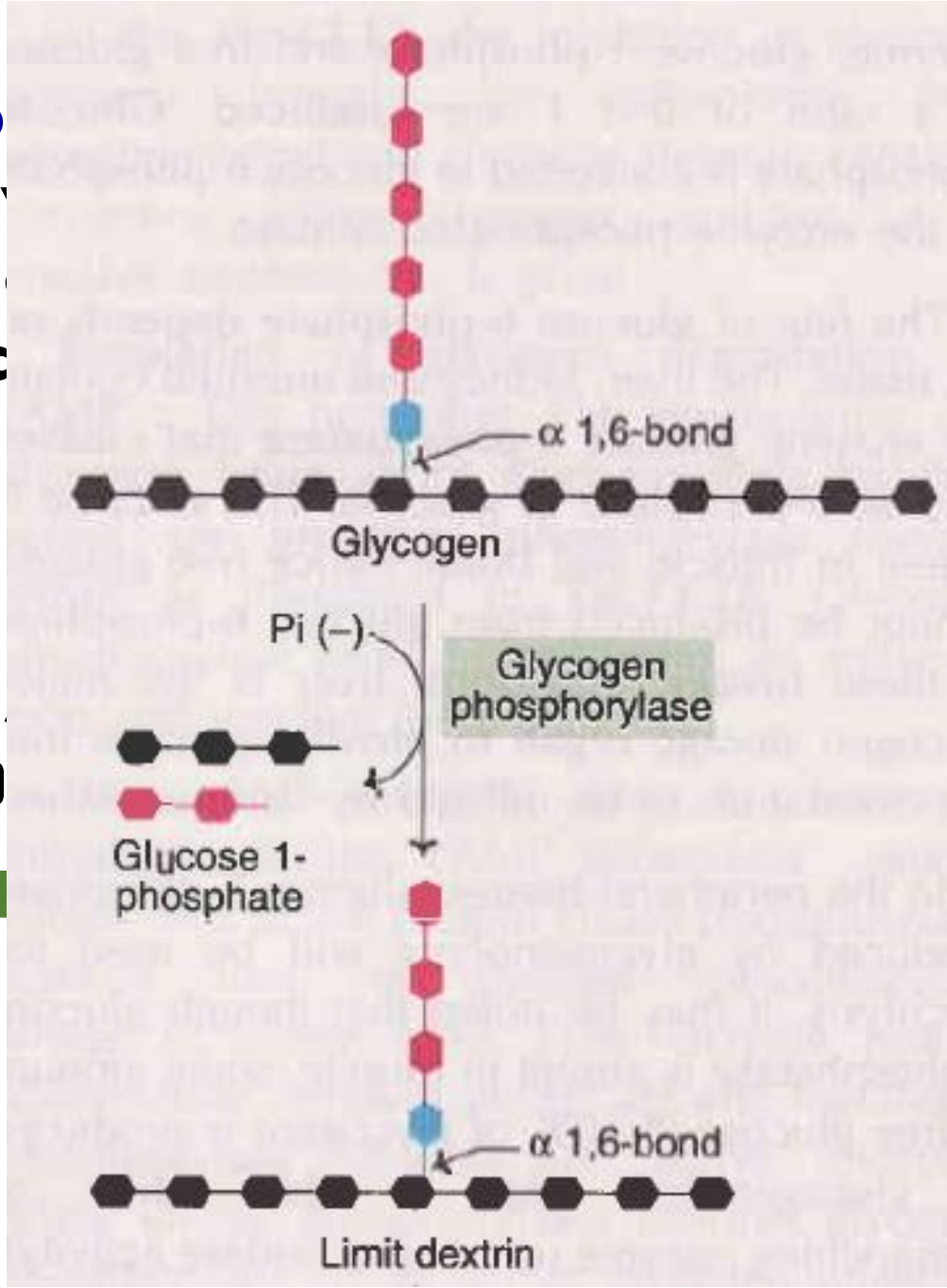
glycosidic linkages

glucose-1-phosphate c

cleave α(1→4) linkage

residues of an α(1→6)

This is called a "Limit



Action of debranching enzyme

Debranching enzyme is a bi-functional enzyme having two independent active sites of a single polypeptide chain

Debranching Enzyme (Glucosyl α1,4: α1,4 Transferase and α1,6 Glucosidase)

Debranching enzyme deconstructs the branches in glycogen that have been exposed by glycogen phosphorylase. The two-step process by which this occurs is diagrammed in Figure I-14-4. Debranching enzyme:

- Breaks an α1,4 bond adjacent to the branch point and moves the small oligoglucose chain released to the exposed end of the other chain
- Forms a new α1,4 bond
- Hydrolyzes the α1,6 bond, releasing the single residue at the branch point as free glucose. This represents the only free glucose produced directly in glycogenolysis.

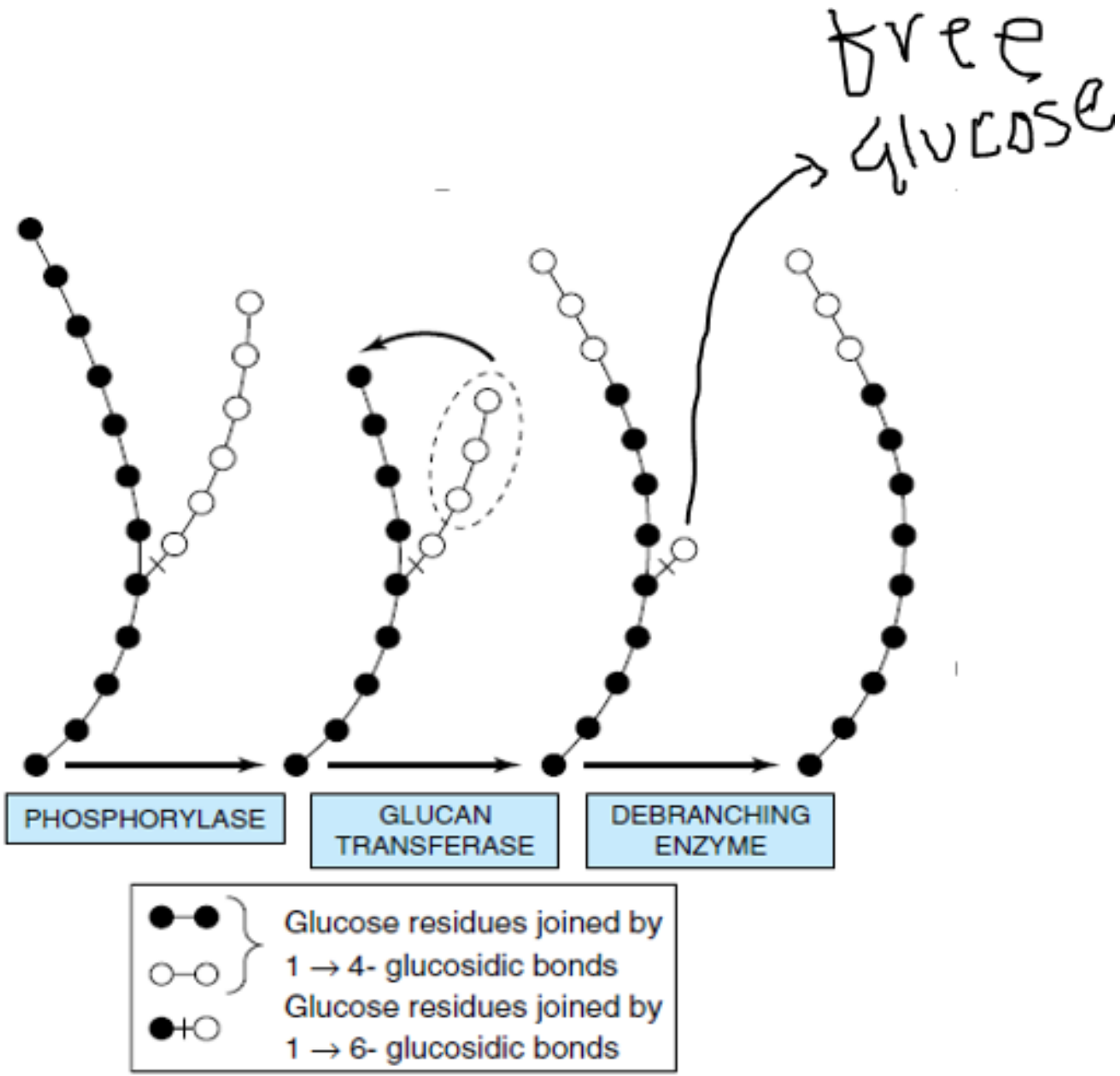
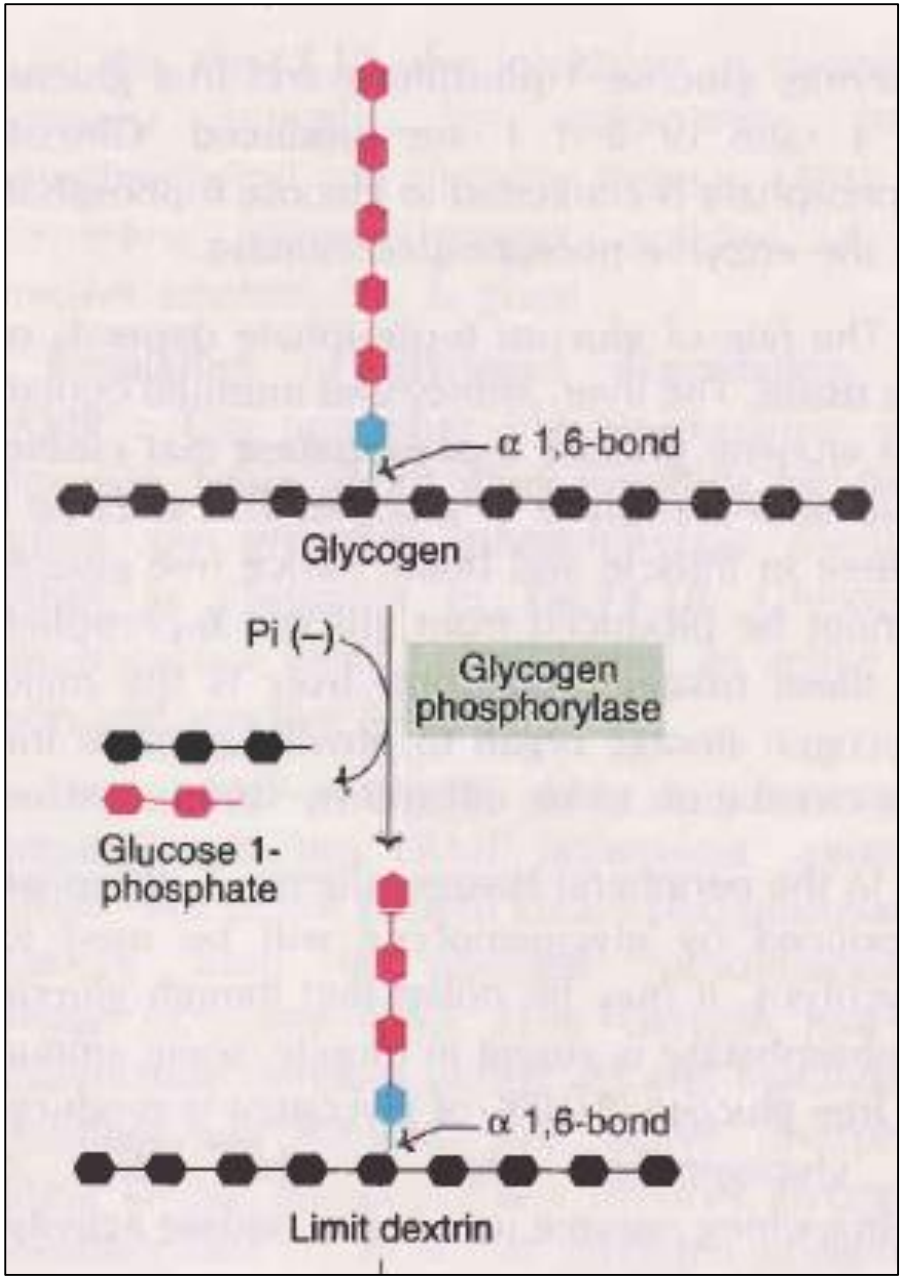
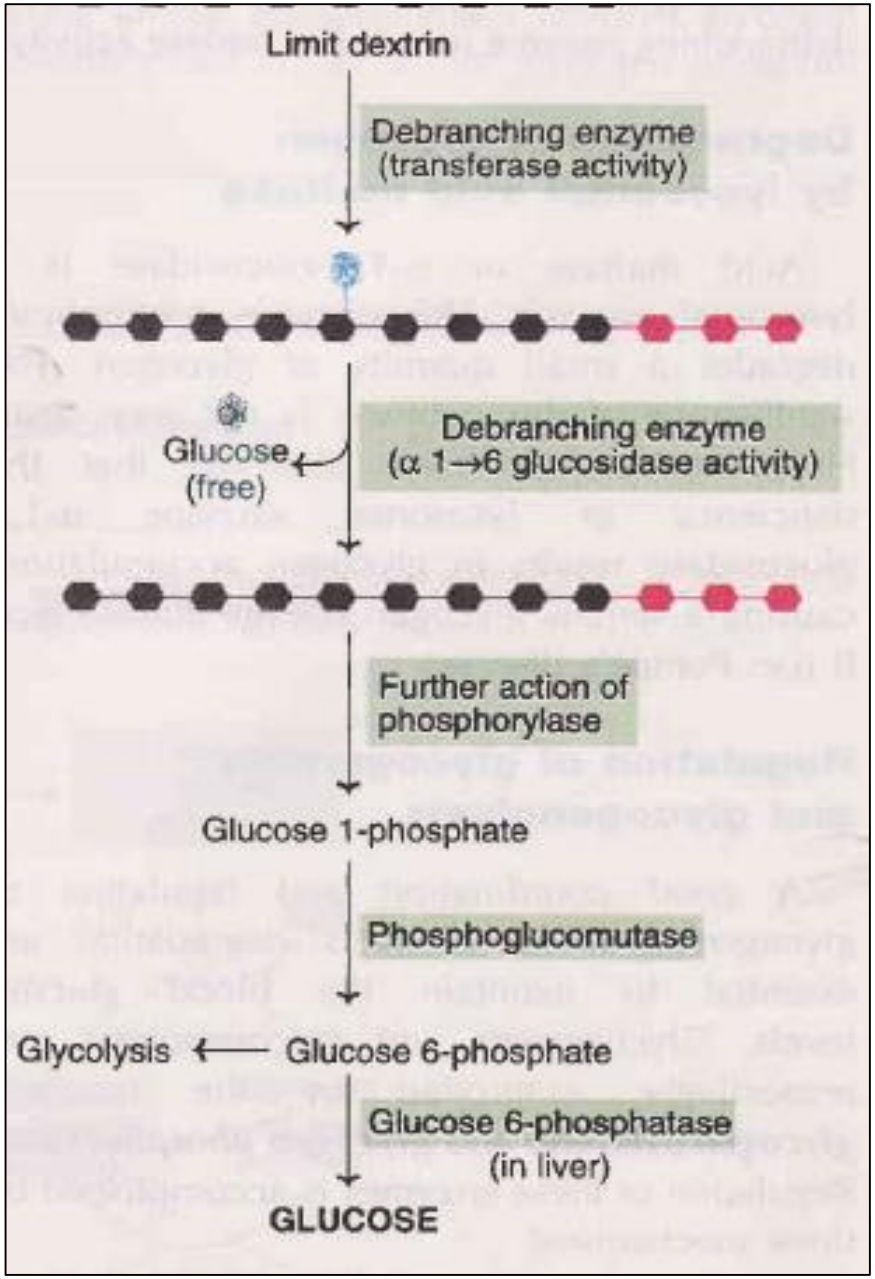
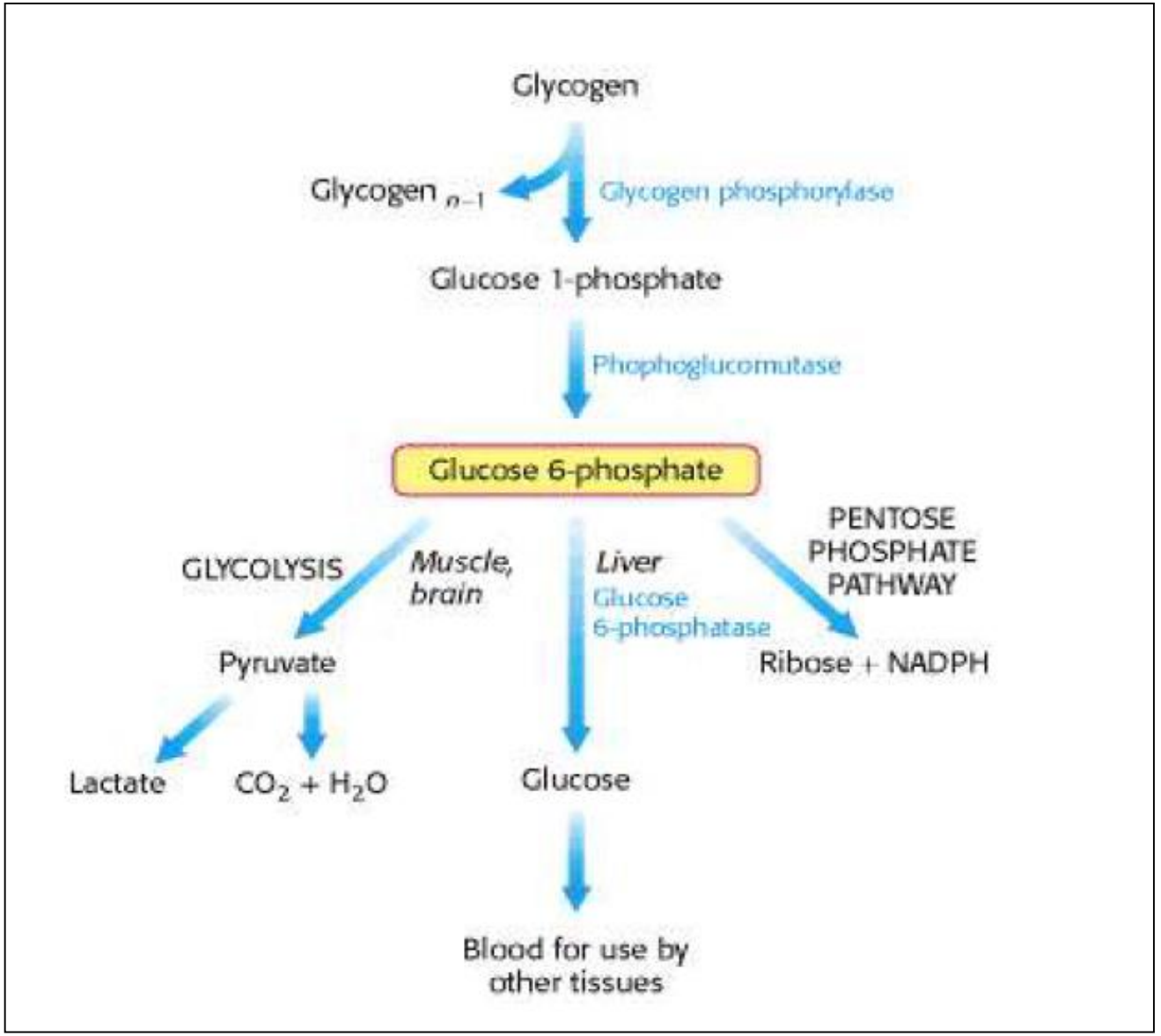


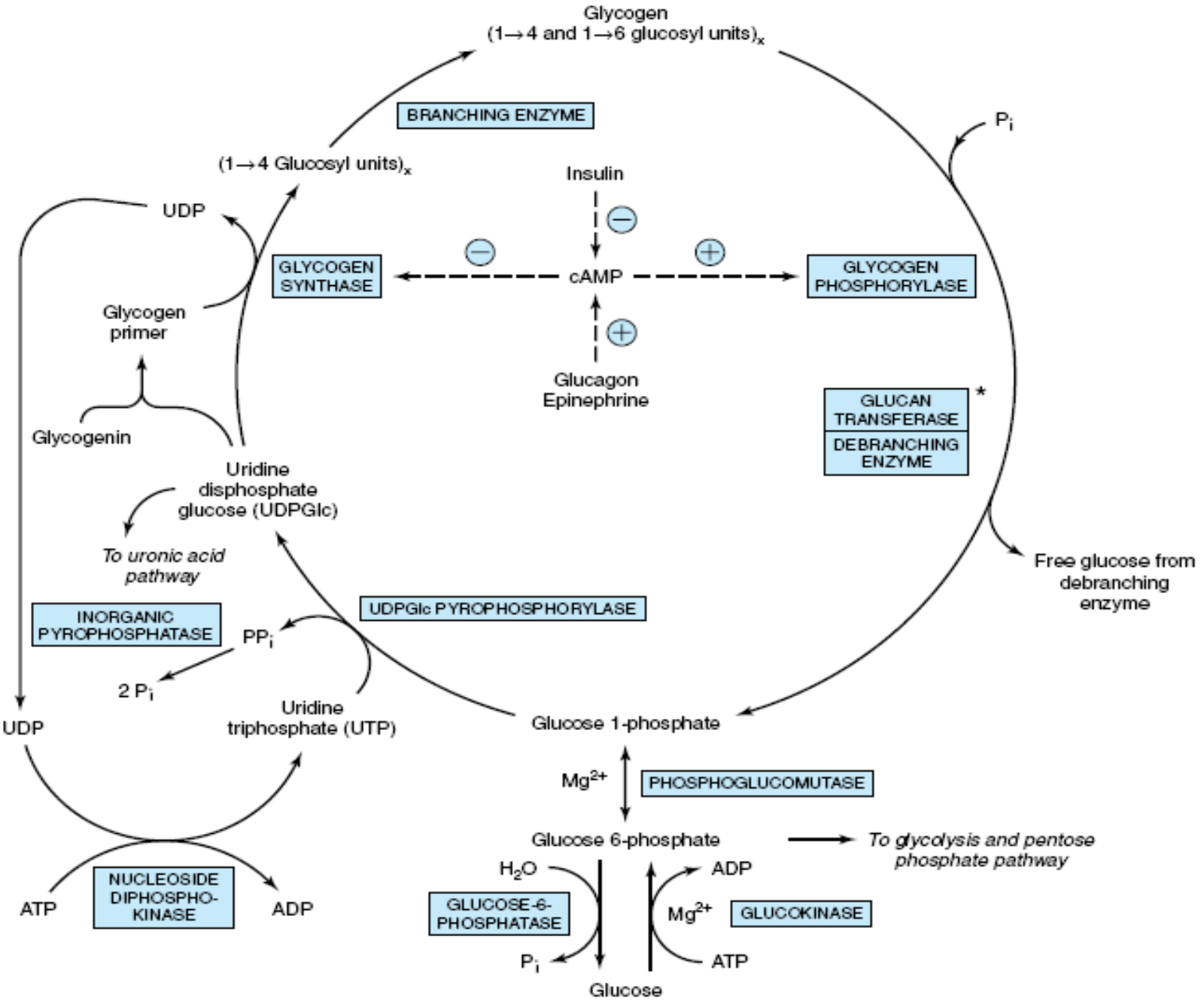
Figure 18–4. Steps in glycogenolysis.


α 1,6-bond
Glycogen
Pi (–)
Glycogen phosphorylase
Glucose 1-phosphate
α 1,6-bond
Limit dextrin


Limit dextrin
Debranching enzyme (transferase activity)
Glucose (free)
Debranching enzyme (α 1→6 glucosidase activity)
Further action of phosphorylase
Glucose 1-phosphate
Phosphoglucomutase
Glycolysis
Glucose 6-phosphate
Glucose 6-phosphatase (in liver)
GLUCOSE

Fate of glucose 6 phosphate




Glycogen
(1→4 and 1→6 glucosyl units)x
BRANCHING ENZYME
(1→4 Glucosyl units)x
Pi
Insulin
UDP
GLYCOGEN SYNTHASE
cAMP
GLYCOGEN PHOSPHORYLASE
Glycogen primer
Glucagon
Epinephrine
GLUCAN TRANSFERASE
*
DEBRANCHING ENZYME
Glycogenin
Uridine disphosphate glucose (UDPGlc)
To uronic acid pathway
Free glucose from debranching enzyme
INORGANIC PYROPHOSPHATASE
PPi
UDPGlc PYROPHOSPHORYLASE
2 Pi
UDP
Uridine triphosphate (UTP)
Glucose 1-phosphate
Mg2+
PHOSPHOGLUCOMUTASE
Glucose 6-phosphate
To glycolysis and pentose phosphate pathway
H2O
ADP
GLUCOSE-6-PHOSPHATASE
Mg2+
GLUCOKINASE
Pi
ATP
Glucose
ATP
NUCLEOSIDE DIPHOSPHO-KINASE
ADP

Regulation of two enzymes

Table I-14-1. Comparison of Glycogen Synthase in Liver and Muscle

Glycogen Synthase	Liver	Skeletal Muscle
Activated by	Insulin	Insulin
Inhibited by	Glucagon Epinephrine	Epinephrine

Table I-14-2. Comparison of Glycogen Phosphorylase in Liver and Muscle

Glycogen Phosphorylase	Liver	Skeletal Muscle
Activated by	Epinephrine Glucagon	Epinephrine AMP Ca^{2+} (through calmodulin)
Inhibited by	Insulin	Insulin ATP

- **to maintain the blood glucose levels.**
- **controlled by the enzymes glycogen synthase and glycogen phosphorylase.**

- **three mechanisms**

1) Allosteric regulation (substrate and energy signal)

2) Hormonal regulation

3) influence of calcium

Allosteric regulation of glycogen metabolism

- **Glycogen synthase and glycogen phosphorylase respond to the levels of metabolites and energy signals of the cell.**

- **Glycogenesis is stimulated when substrate availability and energy levels are high**

- **whereas glycogenolysis is increased when glucose and energy levels are low.**

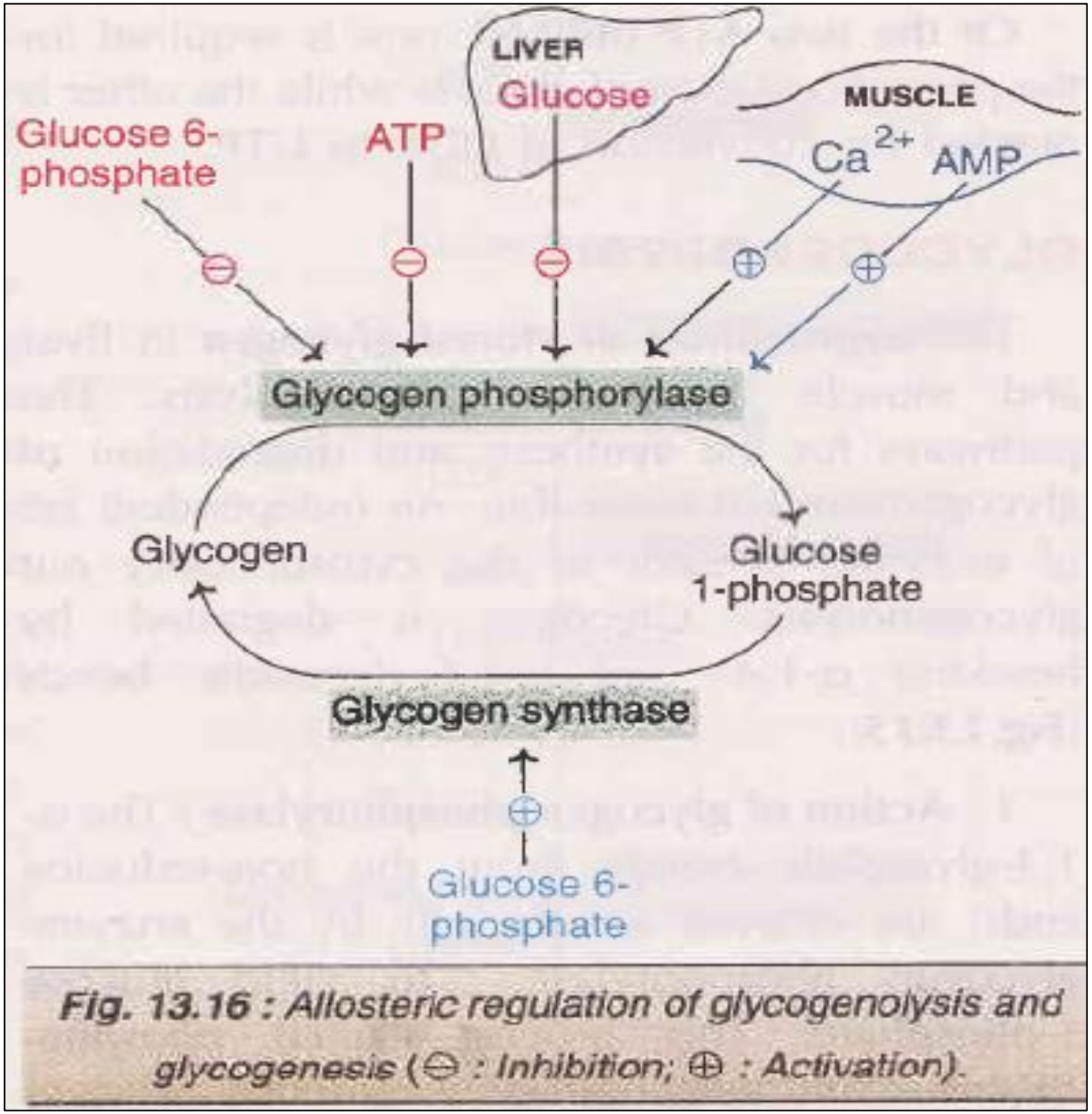
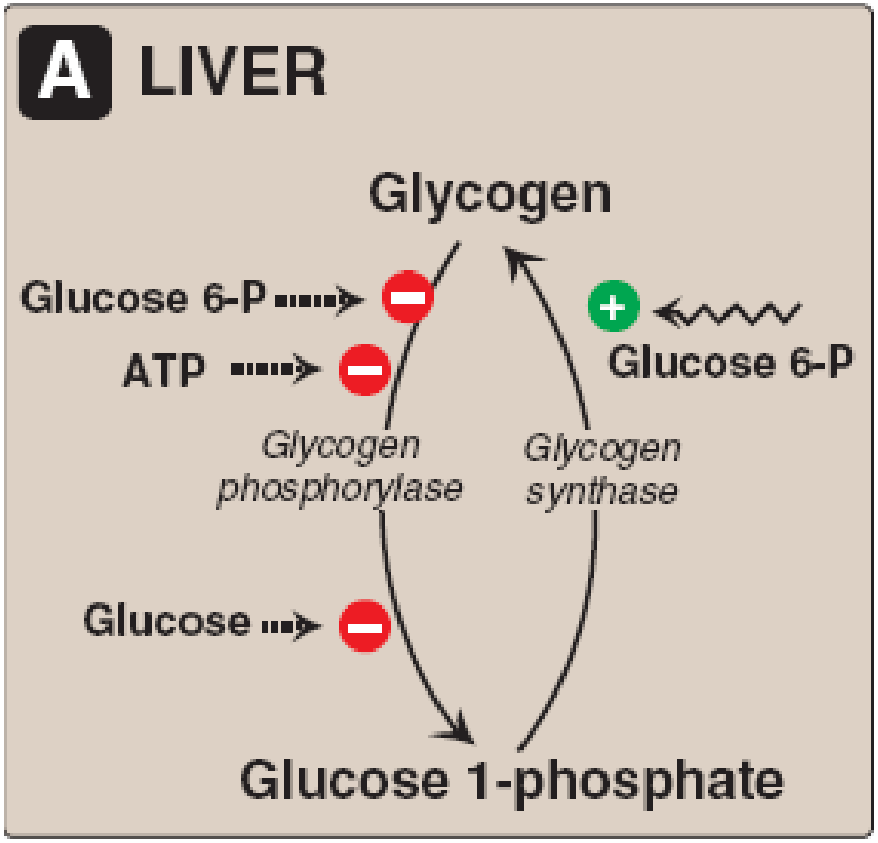
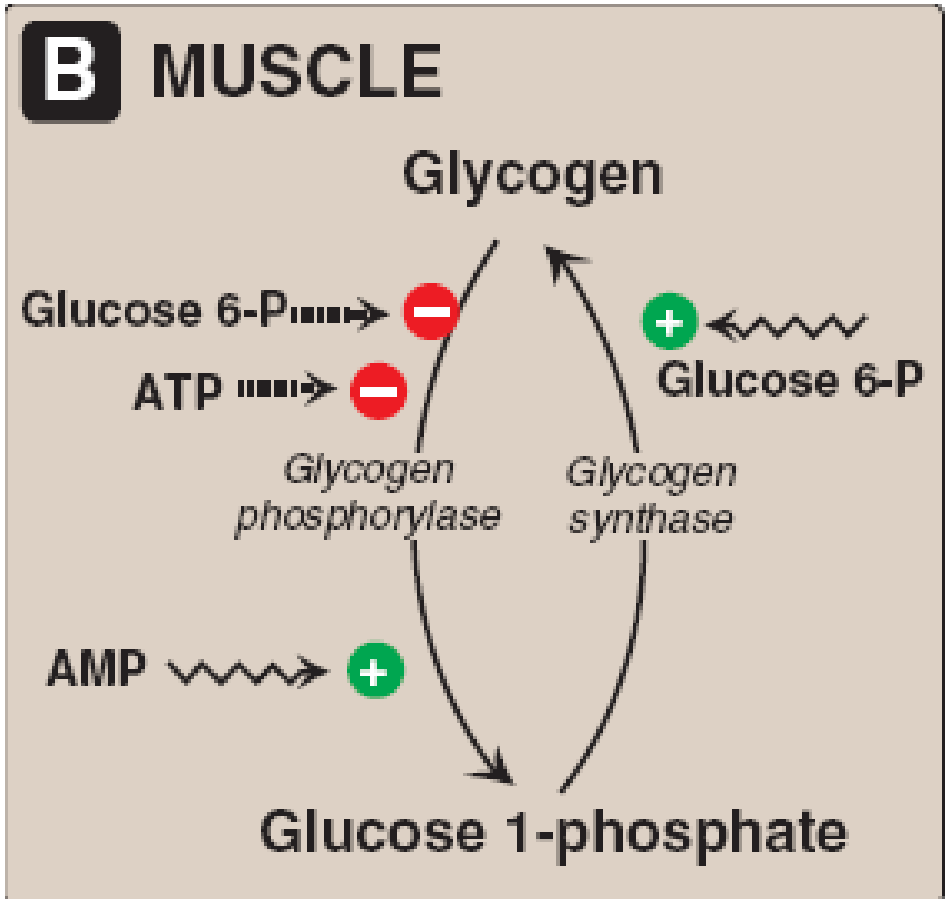


Fig. 13.16 : Allosteric regulation of glycogenolysis and glycogenesis (⊖ : Inhibition; ⊕ : Activation).


A LIVER
Glycogen
Glucose 6-P
ATP
Glucose 6-P
Glycogen phosphorylase
Glycogen synthase
Glucose
Glucose 1-phosphate


B MUSCLE
Glycogen
Glucose 6-P
ATP
Glucose 6-P
Glycogen phosphorylase
Glycogen synthase
AMP
Glucose 1-phosphate

Activation of glycogen degradation by calcium

- When the muscle contracts, Ca^{2+} ions are released from the sarcoplasmic reticulum
- Ca^{2+} binds to calmodulin- calcium modulating protein
- directly activates Glycogen phosphorylase kinase without the involvement of cAMP-dependent protein kinase.

HORMONAL REGULATION

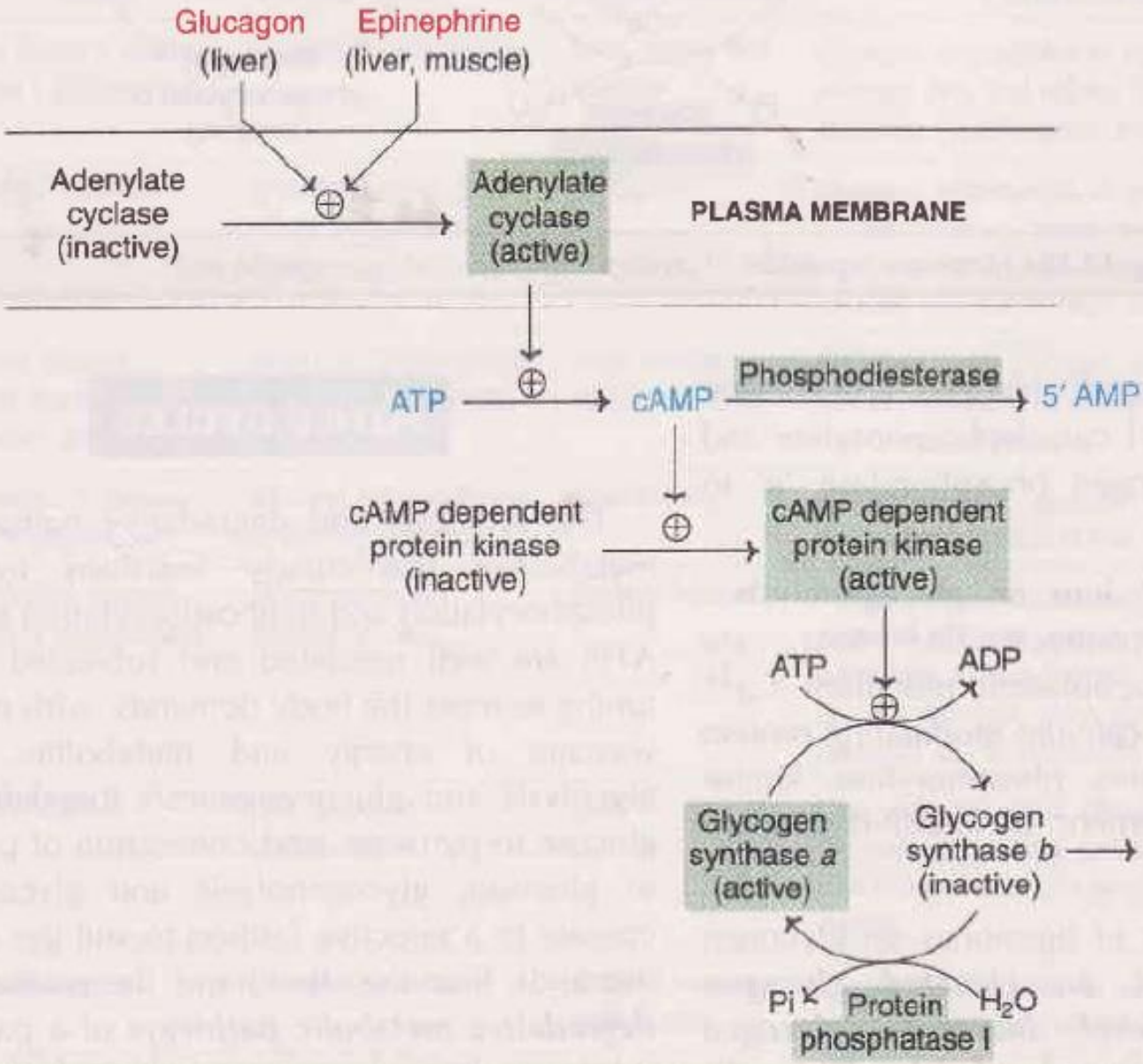


***Fig. 13.17** : Hormonal regulation of glycogen synthesis (glycogenesis).*

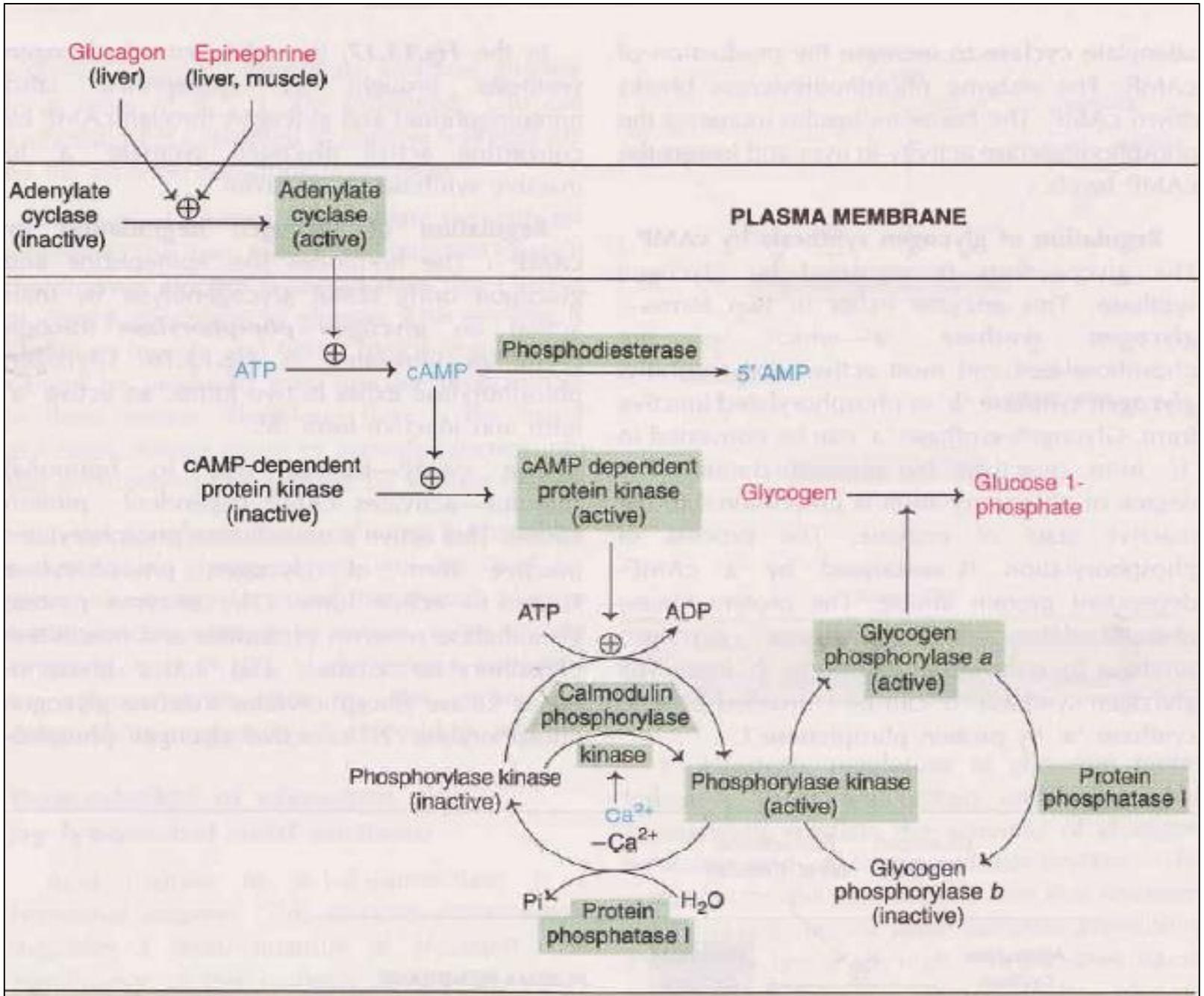


Fig. 13.18 : *Hormonal regulation of glycogen degradation (glycogenolysis).*

Thank You