Glycogen metabolism and Glycogen storage diseases

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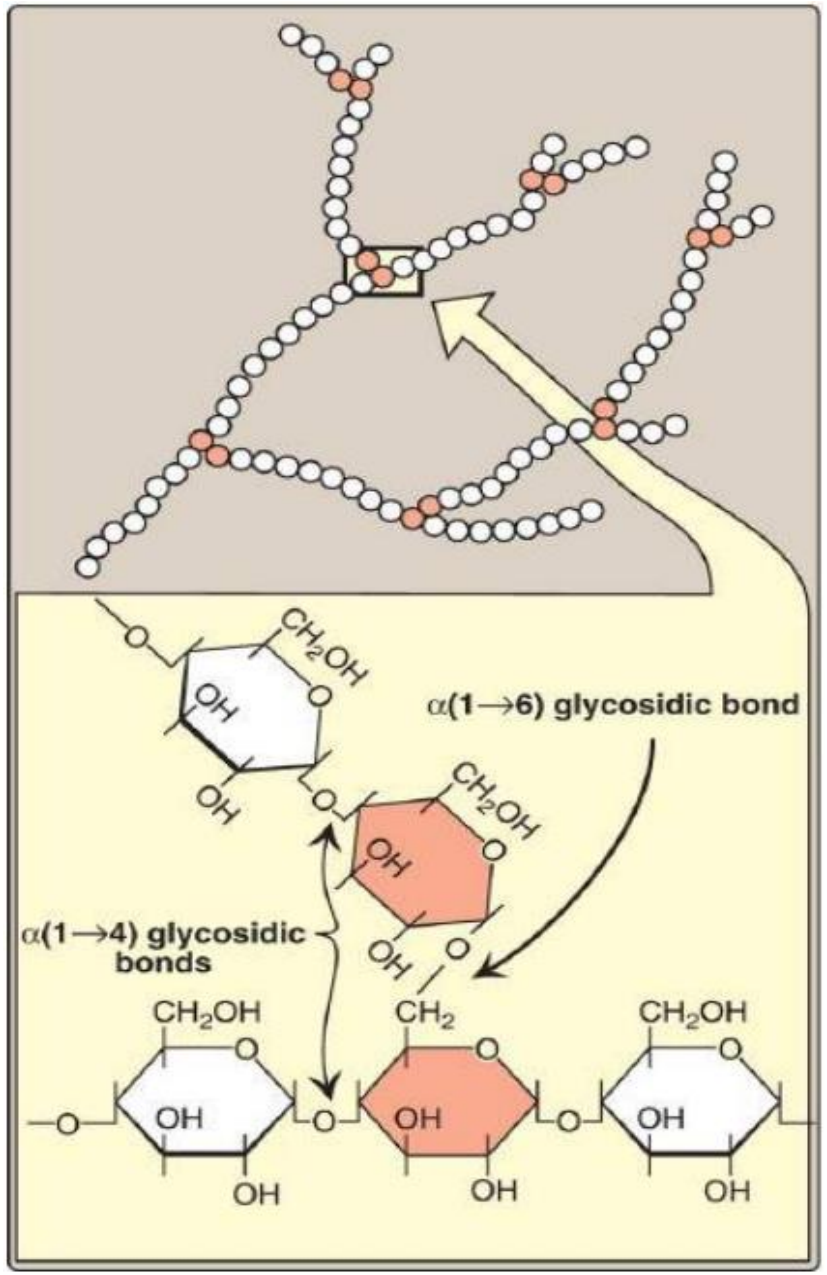
Glycogen metabolism

Glycogenesis: Synthesis of glycogen

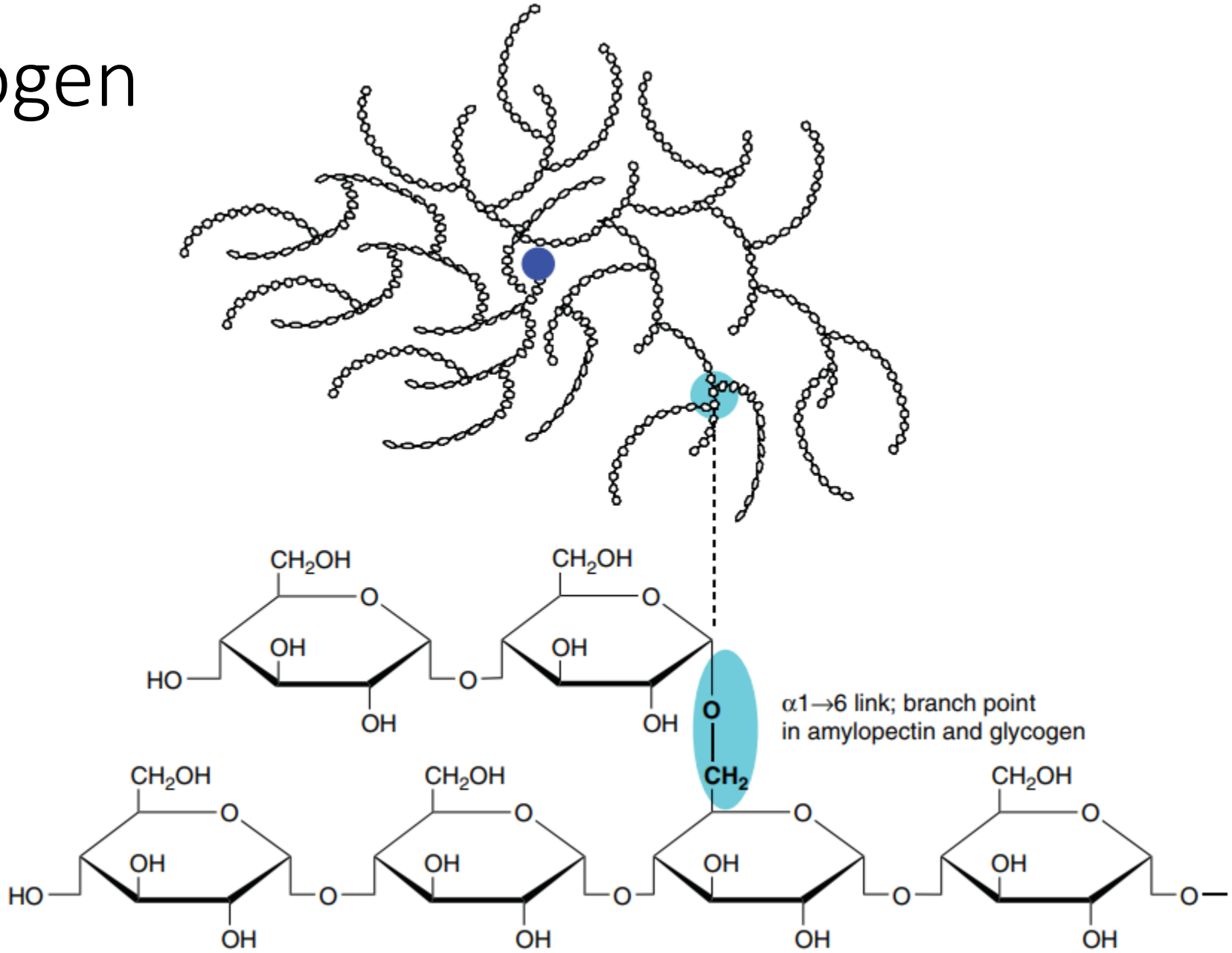
Glycogenolysis: Breakdown of glycogen

Glycogen

- **Storage** form of glucose.
- Stored mainly in liver and muscle.
- Branched polymer of glucose residues
- Yield glucose on breakdown.
- Glucose in glycogen are linked linearly:
  - by α-1,4-glycosidic bonds.
- Branches at about every tenth residue are created by α-1,6-glycosidic bonds

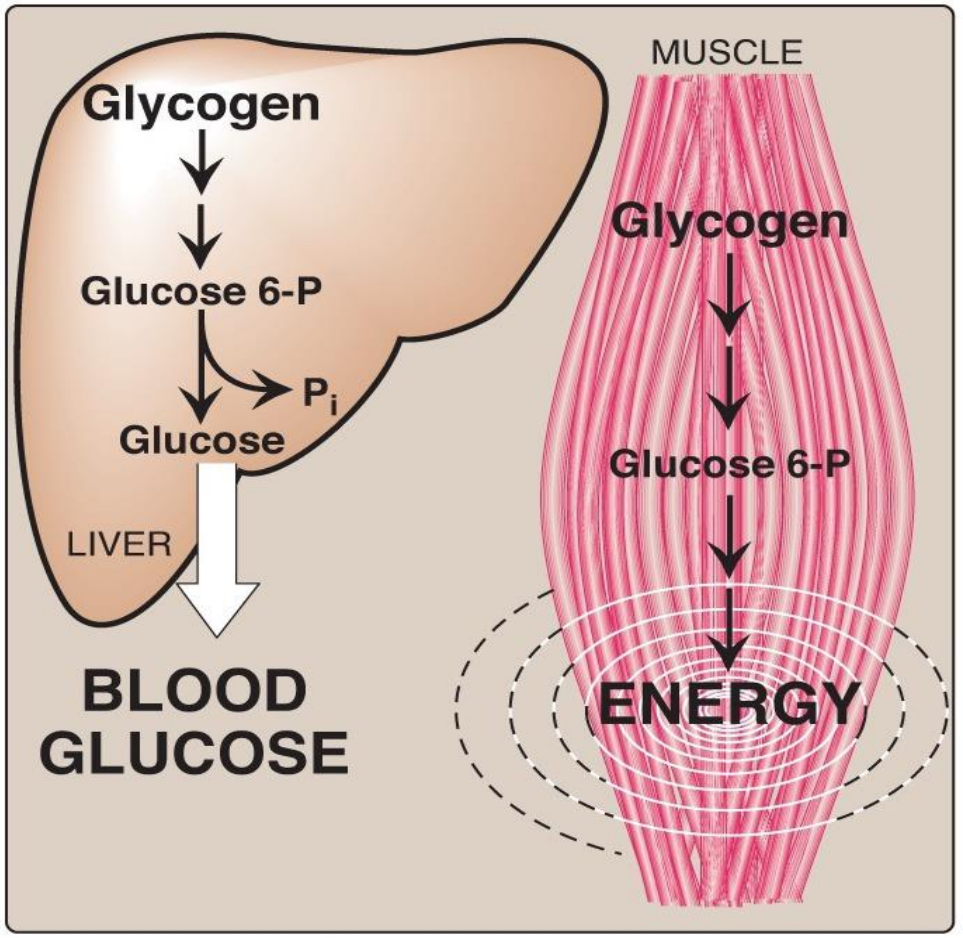


Glycogen


CH2OH
O
OH
HO
OH
O
CH2OH
O
OH
OH
O
CH2
α1→6 link; branch point
in amylopectin and glycogen

Glycogenesis

- Polymerization of glucose into glycogen
- Mainly occurs in muscle and liver.
- Liver glycogen functions to store and export glucose to maintain blood glucose levels.
- Muscle glycogen provides a readily available source of glucose for glycolysis.

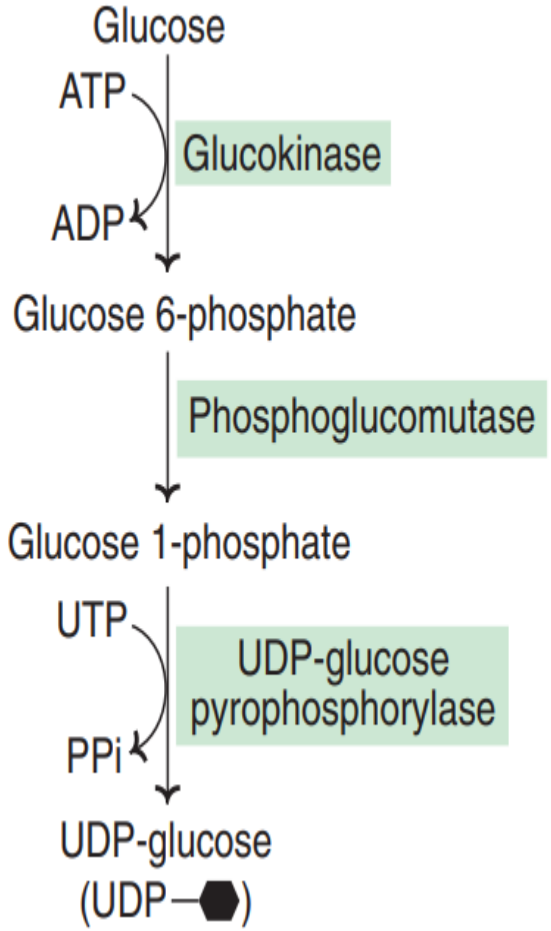


Steps of Glycogenesis

- Activation of Glucose
- Initiation of glycogen synthesis
- Elongation of glycogen chain
- Glycogen branching (formation of glycogen branching)

Activation of Glucose

- Synthesis of glycogen from glucose is carried out by the enzyme **Glycogen synthase**.
- UDP-glucose, the glucose donor, is an activated form of glucose.
- UDP-glucose is formed from glucose-1-phosphate by UDPGlc-pyro-phosphorylase.
- Phosphoglucomutase catalyzes the conversion of glucose 6-phosphate to glucose 1-phosphate.



Initiation of glycogen synthesis

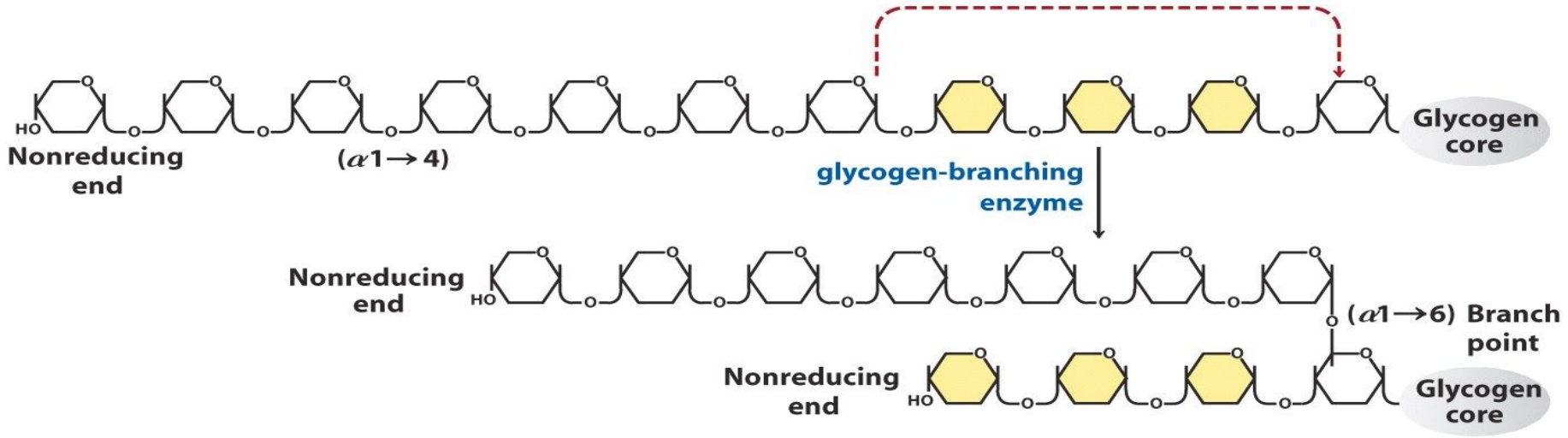
- Glycogenin- (37-kDa) protein is present at the core of the glycogen granule acts as an initiator of glycogen synthesis.
- Specific tyrosine residue of glycogenin gets glucosylated by UDPGlc.
- Glycogenin catalyzes the transfer of a further seven glucose residues from UDPGlc, in 1 → 4 linkage, to form a glycogen primer.
- Glycogen primer is the substrate for glycogen synthase.

Elongation of glycogen chain

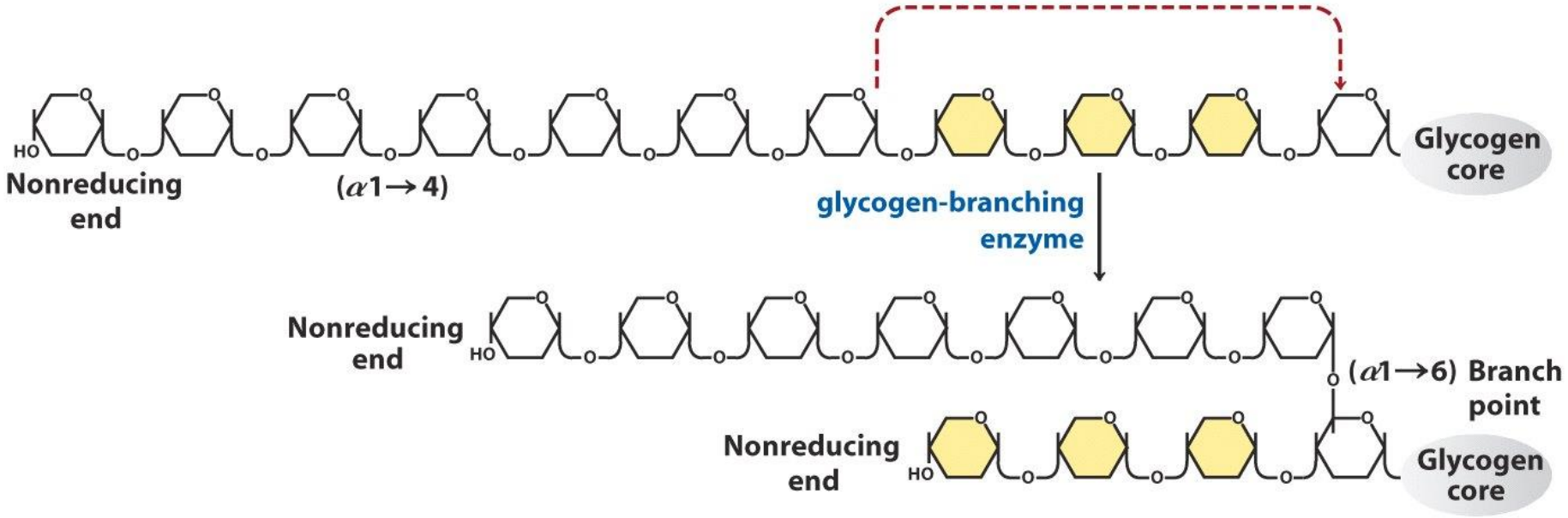
- Glycogen synthase catalyzes the formation of a glycoside bond between C-1 of the glucose of UDPGlc and C-4 of a terminal glucose residue of glycogen primer, liberating uridine diphosphate (UDP)
- Addition of a glucose residue to a glycogen chain occurs at the nonreducing, outer end of the molecule.
- Elongation of glycogen chain occurs with successive 1 → 4 linkages.

Formation of branches in glycogen

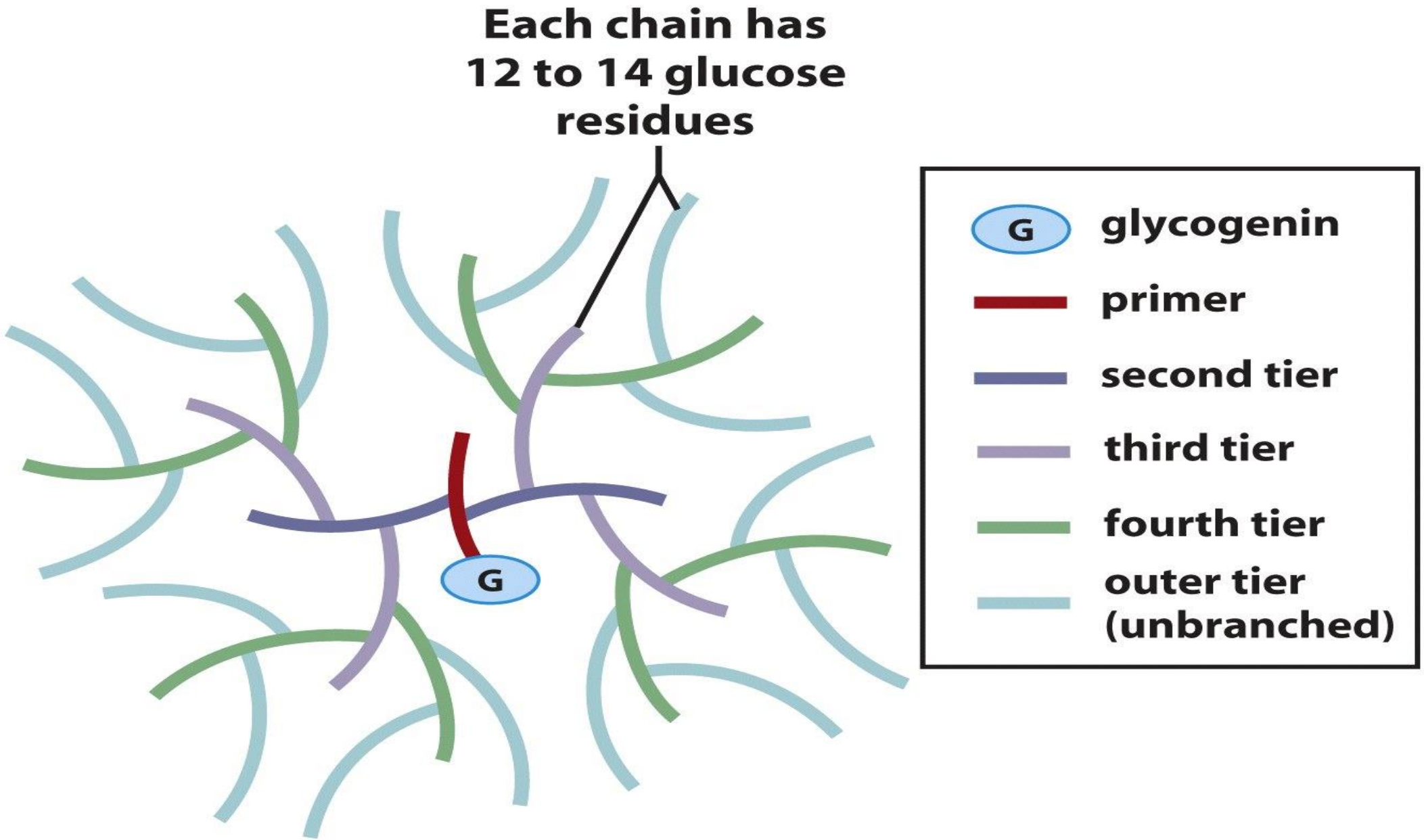
- When a growing chain is at least 11 glucose residues long, glycogen branching is done by branching enzyme (glucosyl α-4-6 transferase).
- Branching enzyme transfers at least six glucose residues of α 1-4 chain, to a neighboring chain by α 1 → 6 linkage.
- Branches grow by further additions of 1 → 4-glucosyl units.



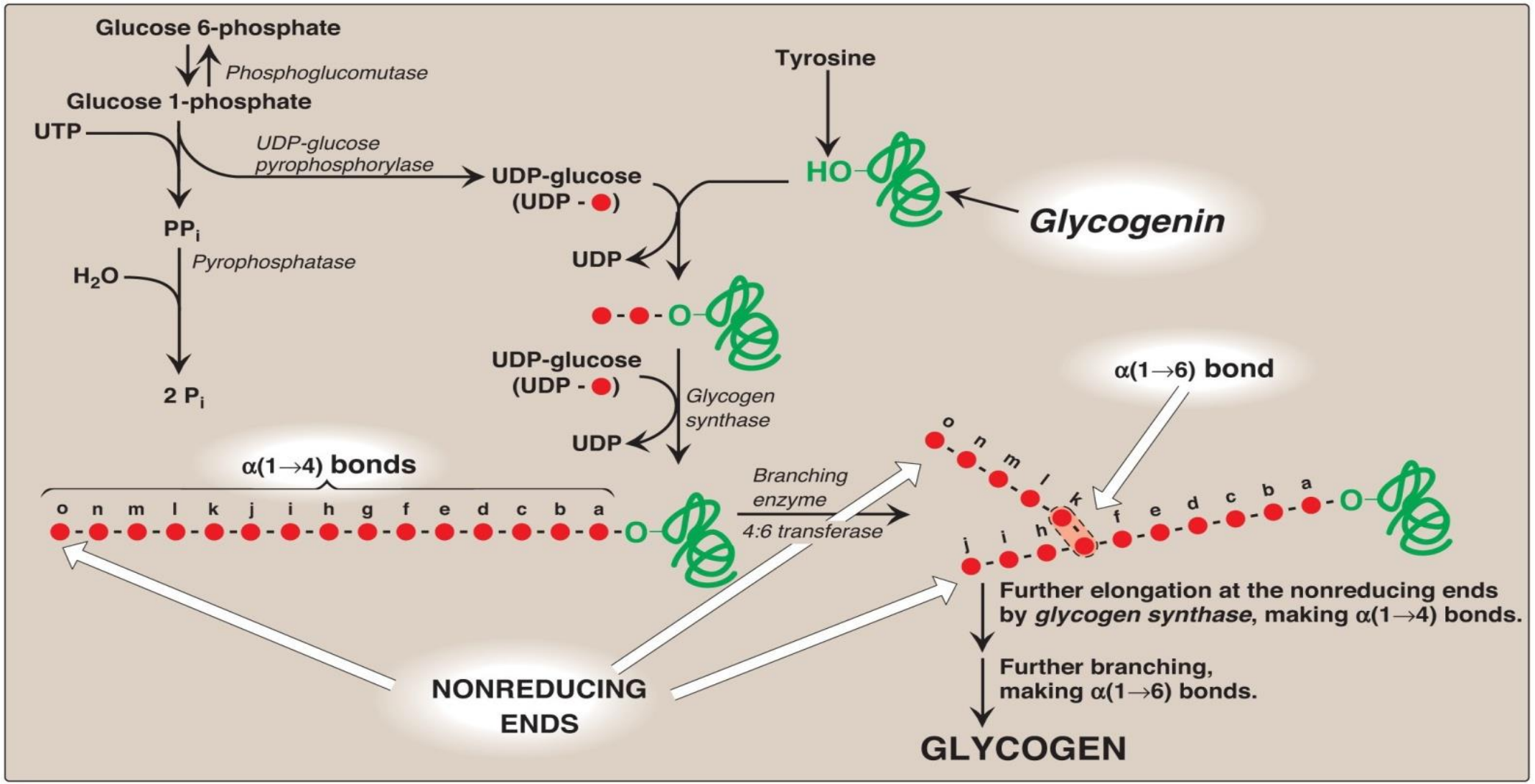
4. Branching by glycogen-branching enzyme



- Glycogen-branching enzyme transfer of a terminal fragment of 6 or 7 glucose residues from the non-reducing end of a glycogen branch having at least 11 residues to the C-6 hydroxyl group of a glucose residue at a more interior position of the same or another glycogen chain.


Each chain has
12 to 14 glucose
residues
G
G
glycogenin
primer
second tier
third tier
fourth tier
outer tier
(unbranched)

Synthesis of glycogen (Glycogenesis)



Glycogenolysis

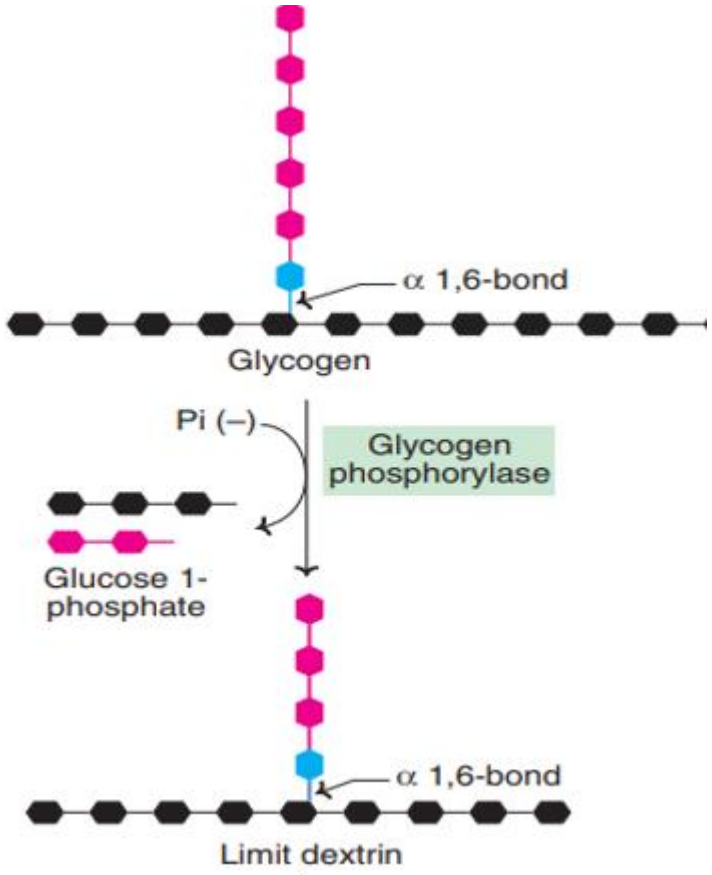
Mobilizing glycogen

Glycogenolysis

- **Glycogenolysis is not the reverse of glycogenesis**
- End product of glycogenolysis: glucose 6-phosphate or glucose.
- Glycogen is degraded by breaking D-1,4- and D-1,6-glycosidic bonds.
- Independent set of enzymes are required:
  - Glycogen phosphorylase
  - Debranching enzyme
  - Phosphoglucomutase.

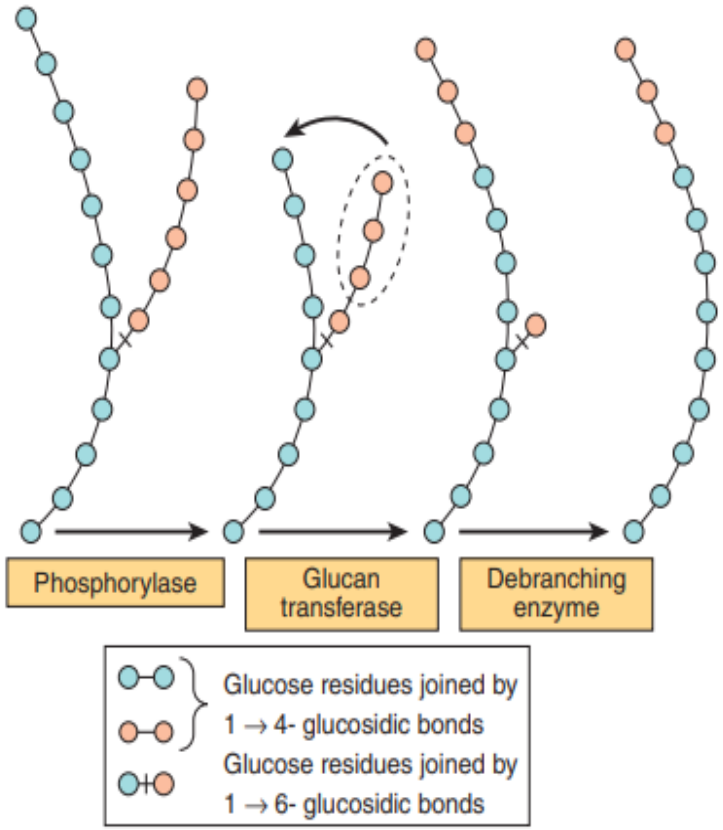
Phosphorolysis—Shortening of chains

- Glycogen phosphorylase sequentially cleaves the α(1→4) glycosidic bonds at the nonreducing ends of the glycogen chains
- This simple phosphorolysis continues until four glucosyl units remain on each chain before a branch point.
- Limit dextrin formed, cannot be further degraded by phosphorylase.
- Glycogen phosphorylase requires pyridoxal phosphate as a coenzyme



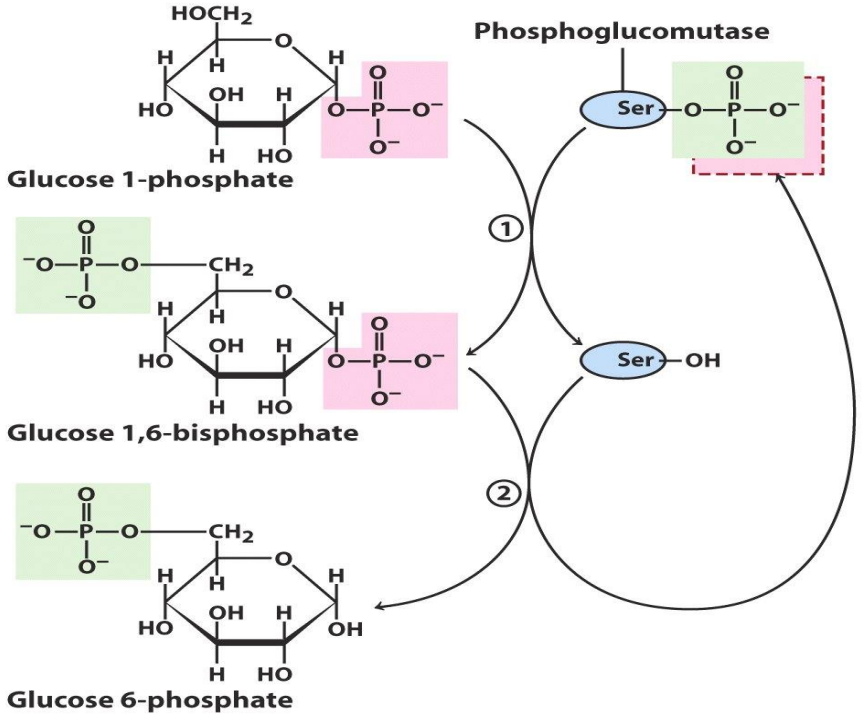
Removal of branches

- Branches of glycogen are removed by two enzyme activities of the **debranching enzyme**.
- One is a **glucan transferase** that transfers a trisaccharide unit from one branch to the other, exposing the 1 → 6 branch point.
- Other is a **1,6-glycosidase** that catalyzes the hydrolysis of the 1 → 6 glycoside bond to liberate free glucose.



Formation of glucose 6-phosphate and glucose

- Action of glycogen phosphorylase and debranching enzyme, produce glucose 1-phosphate and free glucose in a ratio of 8 : 1.
- Glucose 1-phosphate is converted to glucose 6-phosphate by the enzyme phosphoglucomutase.



Fate of glucose 6-phosphate

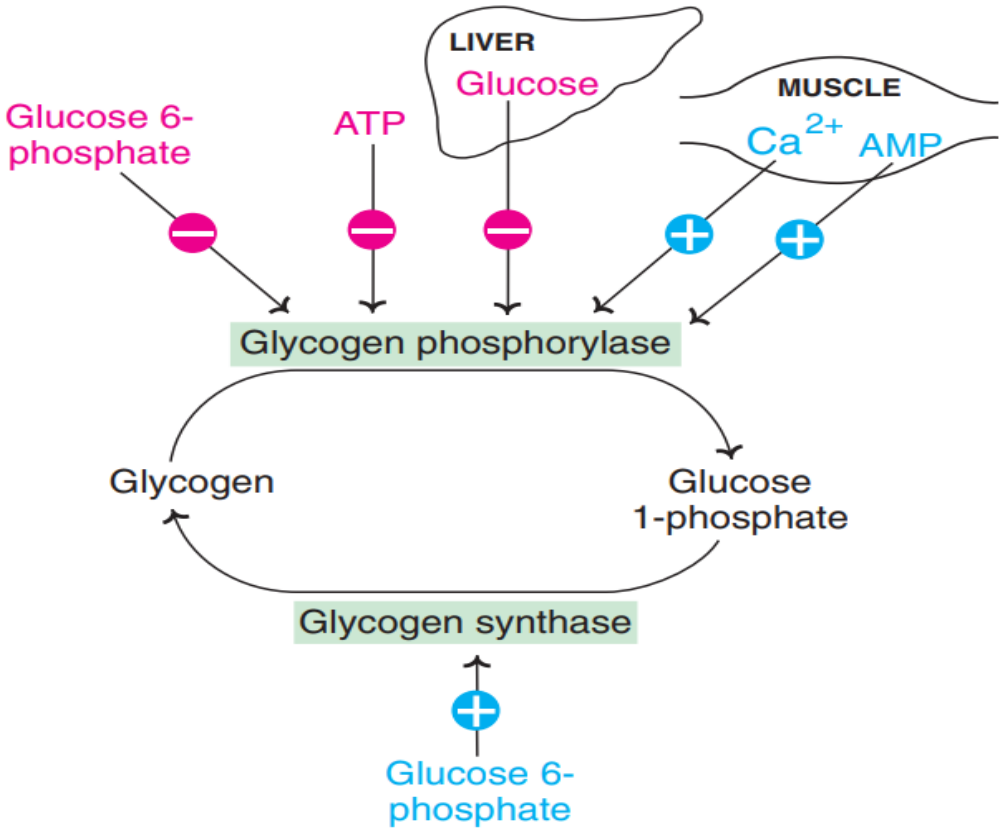
- Liver, Kidney, and Intestine contain the enzyme glucose 6-phosphatase that cleaves glucose 6-phosphate to glucose.
- This enzyme is absent in muscle and brain, hence free glucose cannot be produced in these tissues.

Regulation of glycogenesis and glycogenolysis

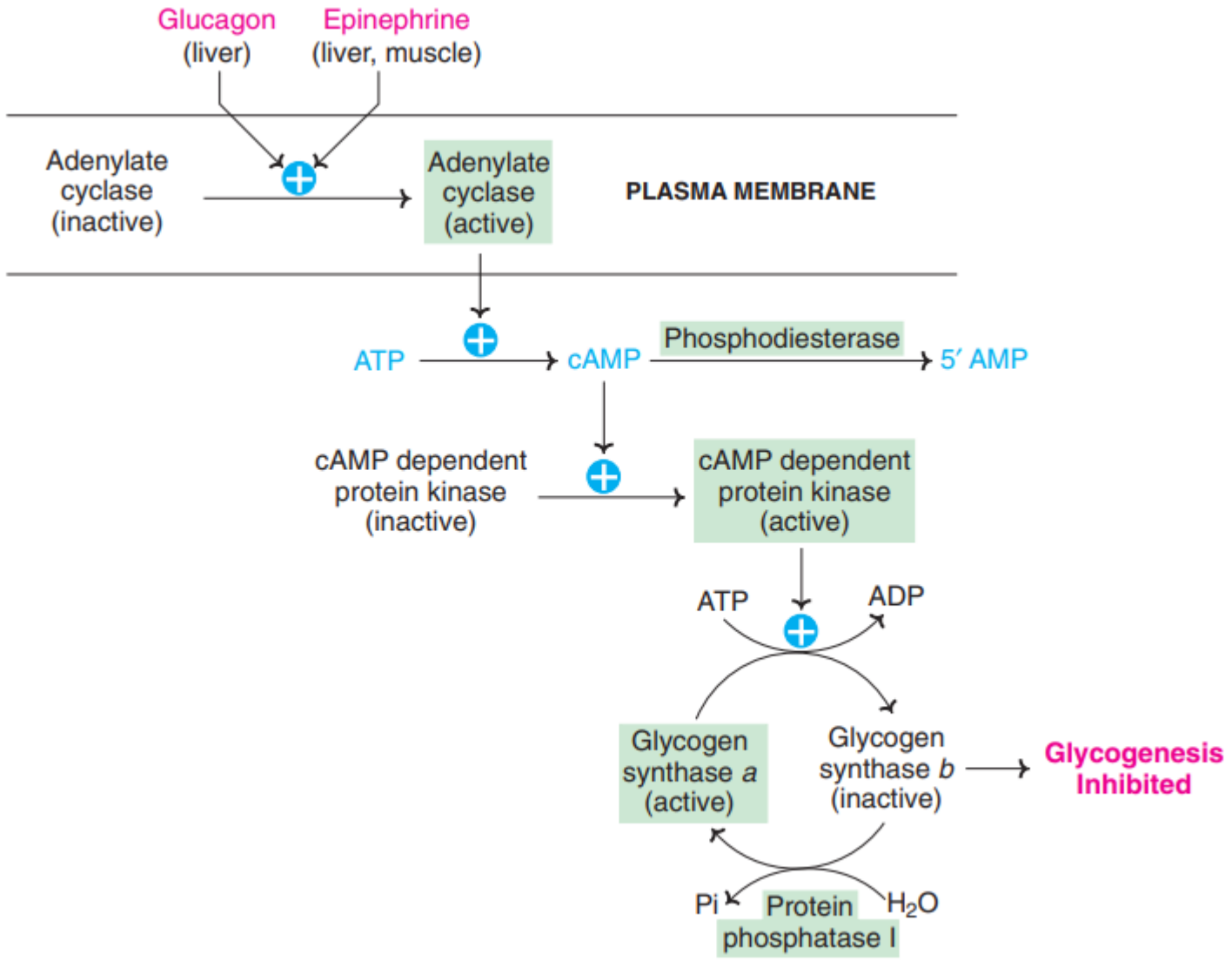
- Both glycogenolysis and glycogen synthesis occur in the cytosol
- Both pathways have G-6-P and G-1-P as intermediates
- So, need some mechanism to ensure only one pathway is active at any one time.
- **Signals that activate glycogen synthase inhibit glycogen phosphorylase.**
  - ✓Allosteric regulation
  - ✓Hormonal regulation
  - ✓Influence of calcium

Allosteric regulation of glycogen metabolism

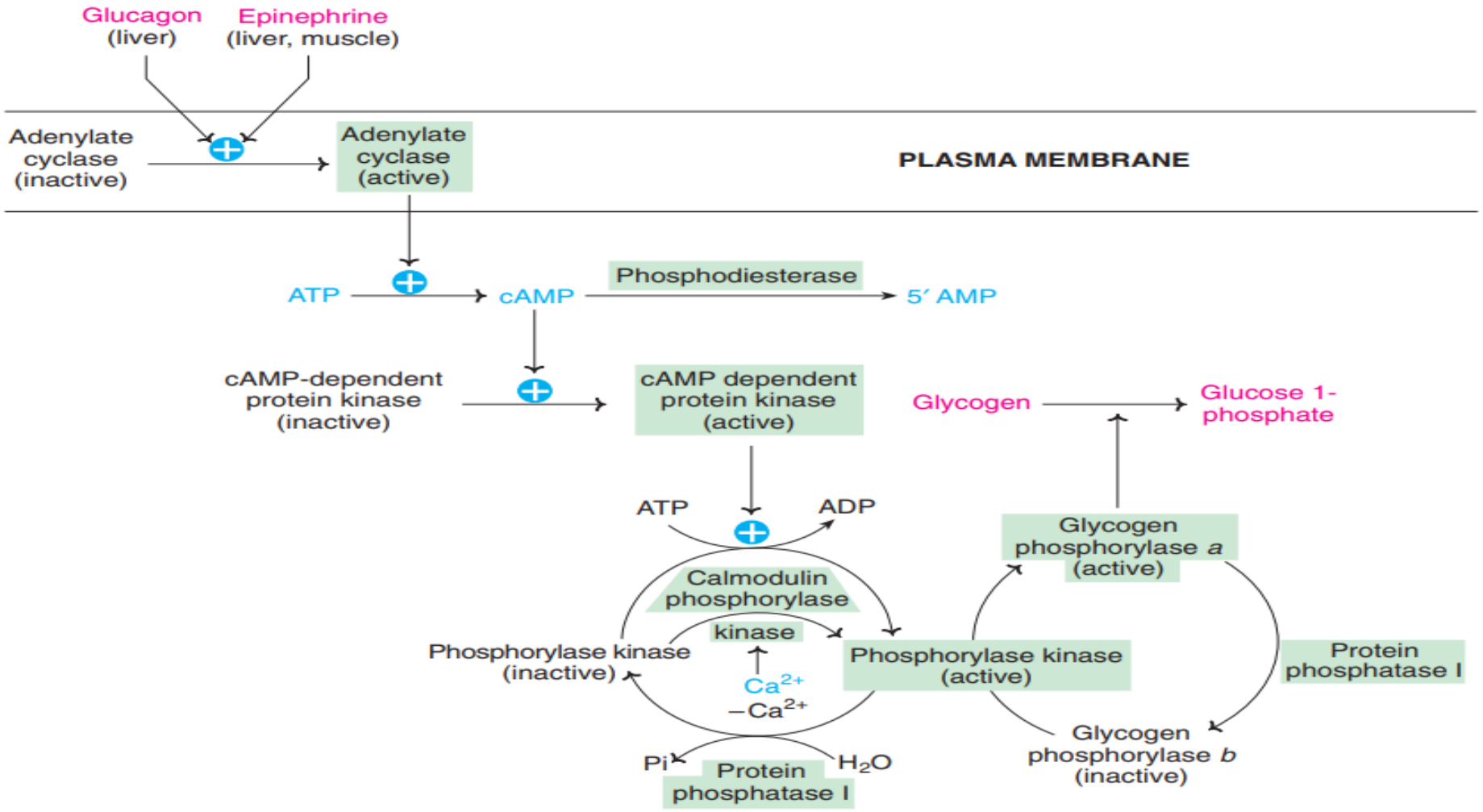
- Certain metabolites that allosterically regulate the activities of glycogen synthase phosphorylase.



Hormonal regulation of glycogenesis



Hormonal regulation of glycogenolysis



Effect of Ca^{2+} ions on glycogenolysis

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

Glycogen Storage Diseases

(Glycogenoses)

Glycogen storage diseases

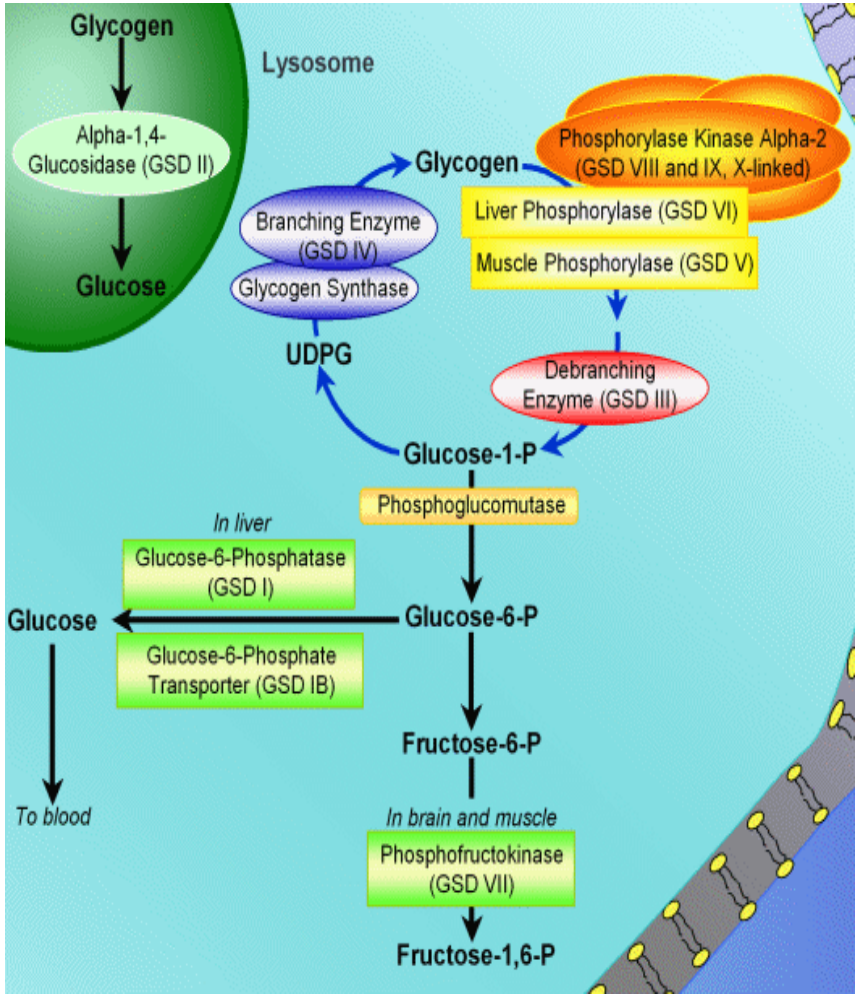
- These disorders are characterized by the deposition of normal or abnormal types of glycogen in one or more tissues.
- Metabolic defects concerned with glycogen synthesis and degradation
- Found principally in liver and muscle

TABLE 18–2 Glycogen Storage Diseases

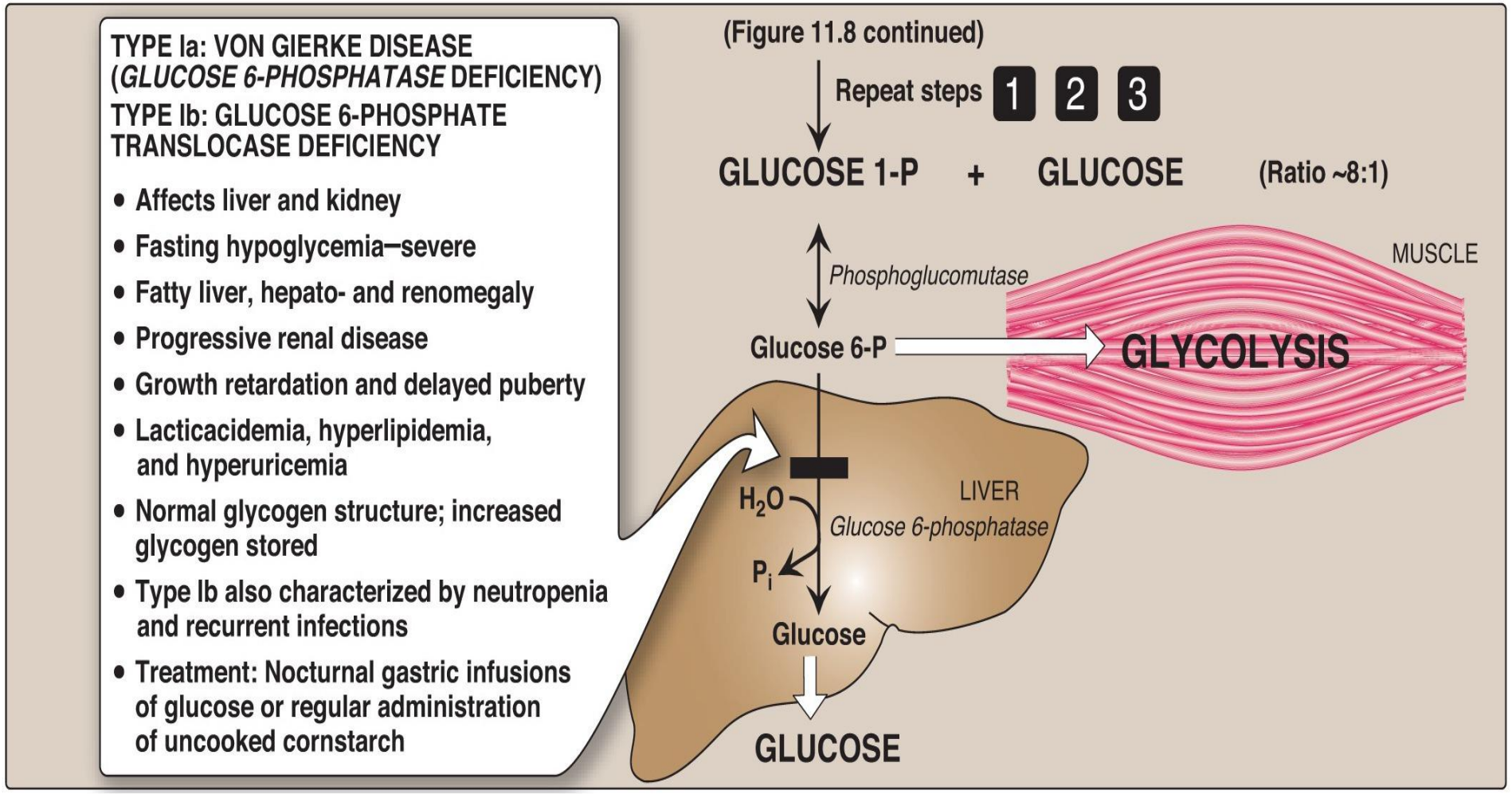
Type	Name	Enzyme Deficiency	Clinical Features
0	—	Glycogen synthase	Hypoglycemia; hyperketonemia; early death
Ia	Von Gierke disease	Glucose-6-phosphatase	Glycogen accumulation in liver and renal tubule cells; hypoglycemia; lactic acidemia; ketosis; hyperlipemia
Ib	—	Endoplasmic reticulum glucose-6-phosphate transporter	As type Ia; neutropenia and impaired neutrophil function leading to recurrent infections
II	Pompe disease	Lysosomal $\alpha_1 \rightarrow 4$ and $\alpha_1 \rightarrow 6$ glucosidase (acid maltase)	Accumulation of glycogen in lysosomes: juvenile onset variant, muscle hypotonia, death from heart failure by age 2; adult onset variant, muscle dystrophy
IIIa	Limit dextrinosis, Forbe or Cori disease	Liver and muscle debranching enzyme	Fasting hypoglycemia; hepatomegaly in infancy; accumulation of characteristic branched polysaccharide (limit dextrin); muscle weakness
IIIb	Limit dextrinosis	Liver debranching enzyme	As type IIIa, but no muscle weakness
IV	Amylopectinosis, Andersen disease	Branching enzyme	Hepatosplenomegaly; accumulation of polysaccharide with few branch points; death from heart or liver failure before age 5
V	Myophosphorylase deficiency, McArdle syndrome	Muscle phosphorylase	Poor exercise tolerance; muscle glycogen abnormally high (2.5%-4%); blood lactate very low after exercise
VI	Hers disease	Liver phosphorylase	Hepatomegaly; accumulation of glycogen in liver; mild hypoglycemia; generally good prognosis
VII	Tarui disease	Muscle and erythrocyte phosphofructokinase 1	Poor exercise tolerance; muscle glycogen abnormally high (2.5%-4%); blood lactate very low after exercise; also hemolytic anemia
VIII		Liver phosphorylase kinase	Hepatomegaly; accumulation of glycogen in liver; mild hypoglycemia; generally good prognosis
IX		Liver and muscle phosphorylase kinase	Hepatomegaly; accumulation of glycogen in liver and muscle; mild hypoglycemia; generally good prognosis
X		cAMP-dependent protein kinase A	Hepatomegaly; accumulation of glycogen in liver

Features of glycogen storage diseases

Type	Name	Enzyme defect	Organ(s) involved	Characteristic features
I	von Gierke's disease (type I glycogenosis)	Glucose 6-phosphatase	Liver, kidney and intestine	Glycogen accumulates in hepatocytes and renal cells, enlarged liver and kidney, fasting hypoglycemia, lactic acidemia; hyperlipidemia; ketosis; gouty arthritis.
II	Pompe's disease	Lysosomal α-1,4 glucosidase (acid maltase)	All organs	Glycogen accumulates in lysosomes in almost all the tissues; heart is mostly involved; enlarged liver and heart, nervous system is also affected; death occurs at an early age due to heart failure.
III	Cori's disease (limit dextrinosis, Forbe's disease)	Amylo α-1,6-glucosidase (debranching enzyme)	Liver, muscle, heart, leucocytes	Branched chain glycogen accumulates; liver enlarged; clinical manifestations are similar but milder compared to von Gierke's disease.
IV	Anderson's disease (amylopectinosis)	Glucosyl 4-6 transferase (branching enzyme)	Most tissues	A rare disease, glycogen with only few branches accumulate; cirrhosis of liver, impairment in liver function.
V	McArdle's disease (type V glycogenosis)	Muscle glycogen phosphorylase	Skeletal muscle	Muscle glycogen stores very high, not available during exercise; subjects cannot perform strenous exercise; suffer from muscle cramps; blood lactate and pyruvate do not increase after exercise; muscles may get damaged due to inadequate energy supply.
VI	Her's disease	Liver glycogen phosphorylase	Liver	Liver enlarged; liver glycogen cannot form glucose; mild hypoglycemia and ketosis seen.
VII	Tarui's disease	Phosphofructokinase	Skeletal muscle, erythrocytes	Muscle cramps due to exercise; blood lactate not elevated; hemolysis occurs.



Type 1:Von Gierke's disease



THANK YOU