Glycogen Metabolism

Glycogen

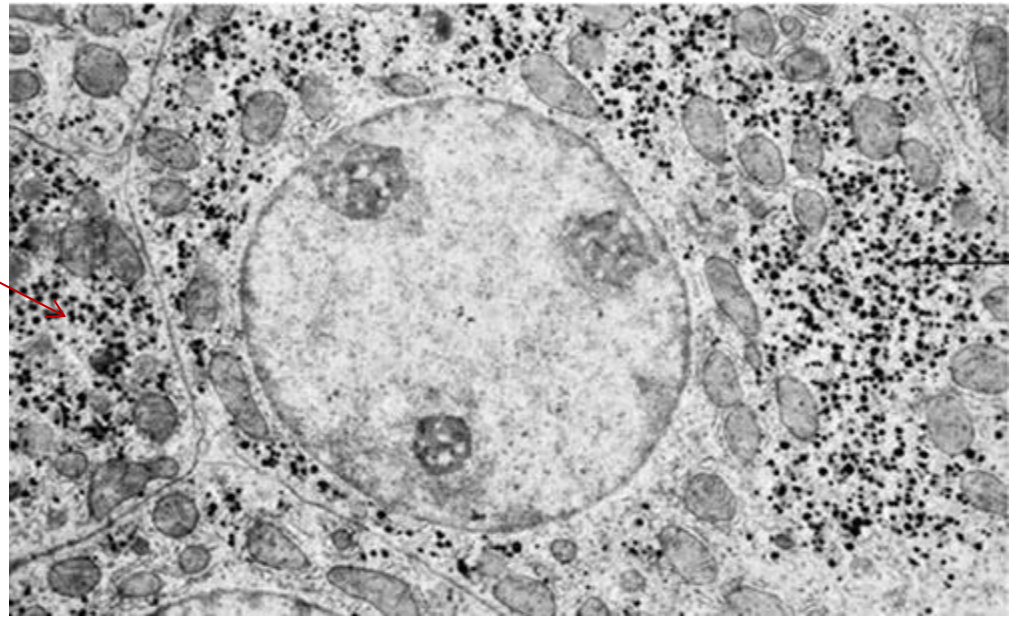
- Large, branched polysaccharide, available, storage form of glucose ([Glc]↓- degradation, [Glc]↑- synthesis)

Functions:

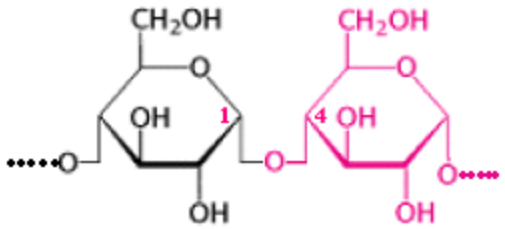
- Liver (5% = 90g) → blood glucose conc. maintenance
- Muscle (0,7% = 245g) → source of ATP

- Enzymes for glycogen biosynthesis and degradation are permanently and firmly bound in glycogen granules

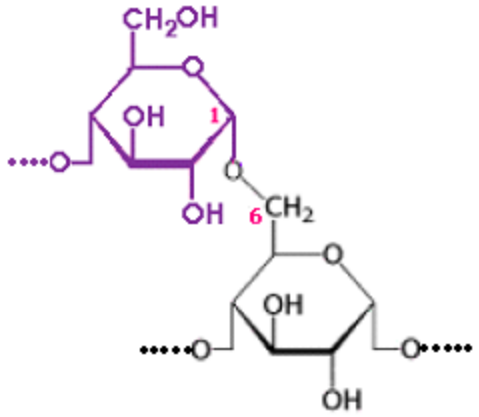
Glycogen granules in hepatocytes



Two basic types of glycosidic bonds in glycogen



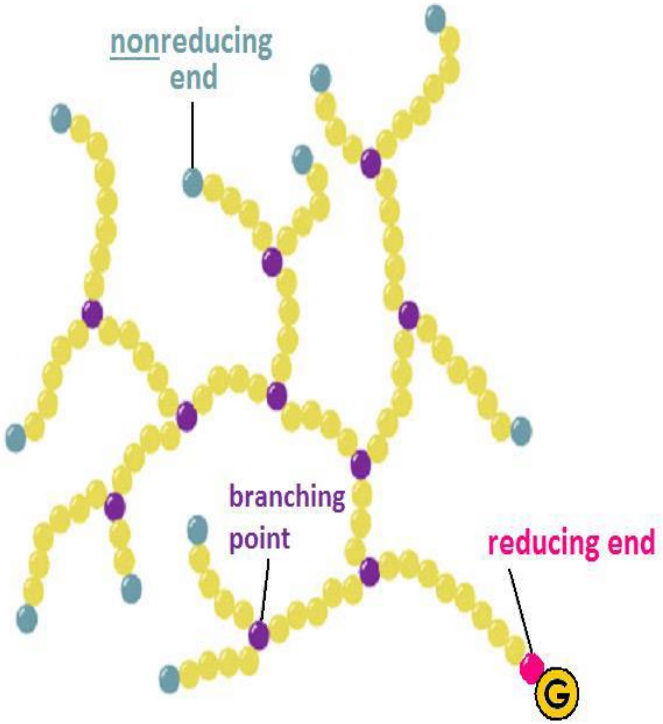
α -1,4 - glycosidic bond



α -1,6 - glycosidic bond

Glycogen structure

- Glucose units linked by α-1,4 glycosidic bonds (linear molecule), while in branching points α-1,6 bonds (~10:1)
- Non-reducing ends - DEGRADATION!!!
- ONLY 1 reducing end, but permanently bound to Glycogenin - self- glucosylating



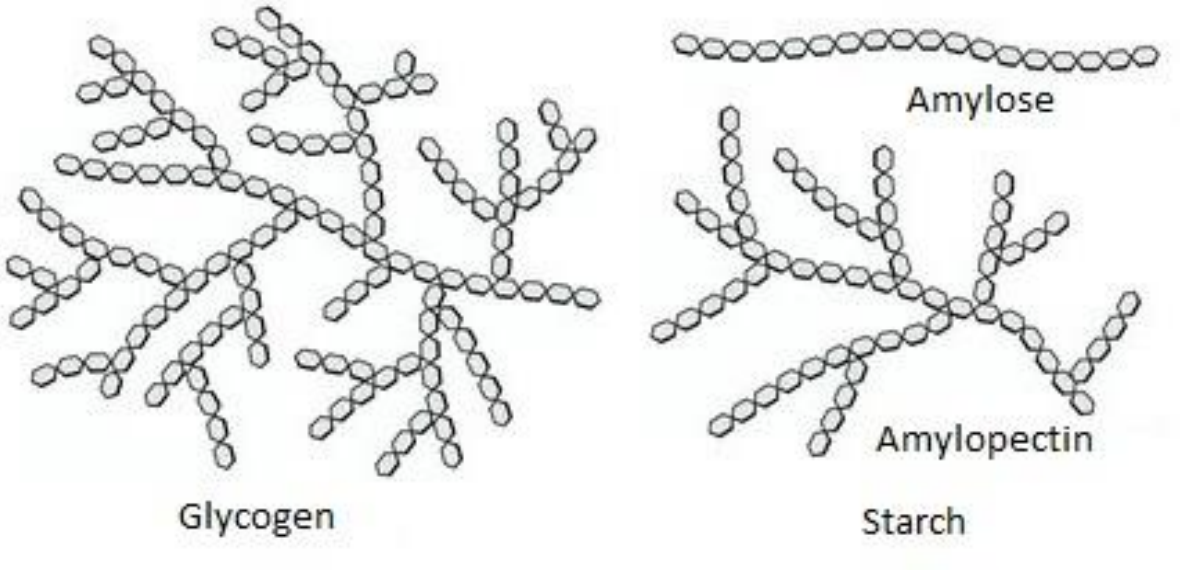
- Glycogen is more branched structure than amylopectin
- More soluble and more easy to degrade (nonreducing ends!!!)

- Starch is consisted of:

  Amylose - linear molecule, α-1,4 glycosidic bonds

  Amylopectin – α-1,4 and α-1,6 glycosidic bonds

- Cellulose – β-1,4 glycosidic bonds
- Humans lack **β- glucosidase** for cellulose degradation



Glycogenesis versus Glycogenolysis

- Different reaction pathways and Hormonal regulation
- Regulate glucose blood **concentration (liver)**
- Provide glucose **reserve for muscle work**

Glycogenesis

- It takes place in virtually all animal tissues, but especially prominent in the **liver and skeletal muscles**
- **3 enzymes**:

1. Glycogenin – self-glucosylating enzyme

- Synthesis of a primer- first 8 glucose molecules

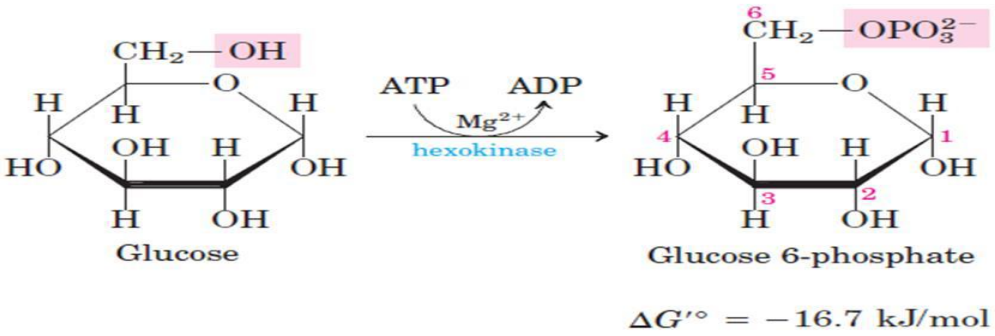
2. Glycogen synthase

- Further extension the primer by adding Glc molecules
- Formation of α-1,4 glycosidic bonds
- Substrate for the synthesis is UDP-glucose

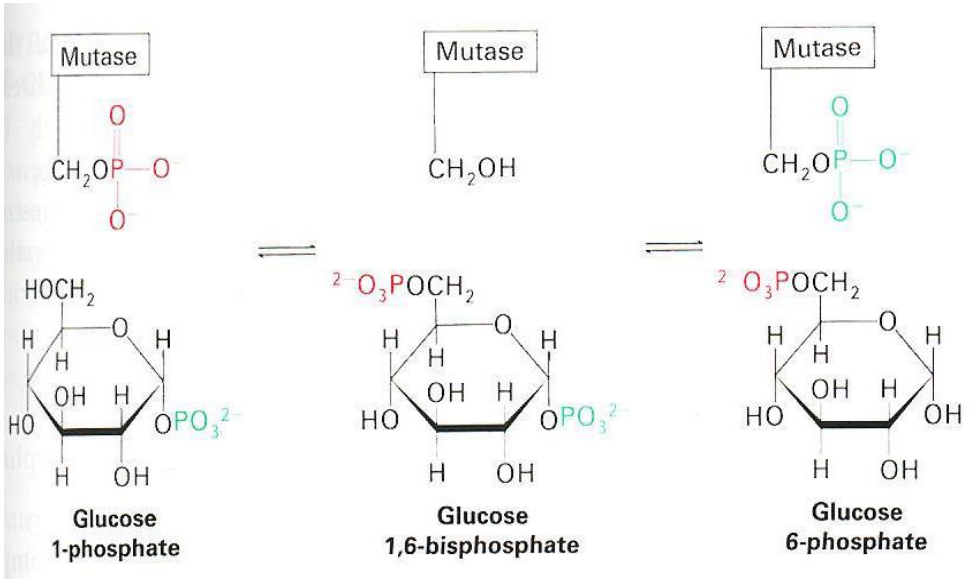
3. **Branching enzyme** [glycosyl(4→6)-transferase]

- Formation of α-1,6glycosidic bonds

1- After entering the cell, glucose is phosphorylated by the activity of hexokinase I and II (Glucokinase) forming glucose 6-phosphate



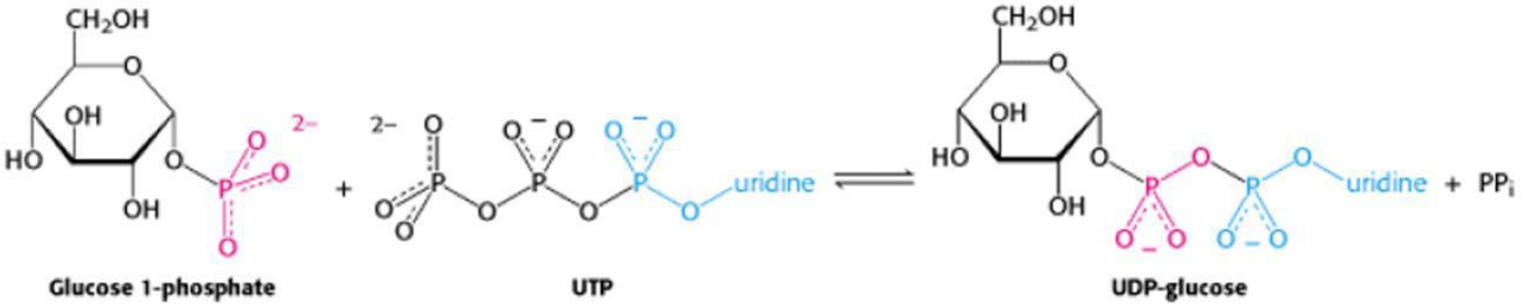
2- Glucose 6-phosphate isomerization (reversible reaction) by into glucose 1-P by the activity of phosphoglucomutase



- When higher amount of glucose 6-phosphate is present in the cell, the equilibrium of the reactions is shifted to the left, towards the formation of glucose 1-phosphate

3- **UDP glucose formation** (uridine diphosphate -glucose)

- UDP-glucose is formed by the activity of UDP-glucose pyrophosphorylase
- The synthesis of UDP-glucose is driven by the essentially irreversible hydrolysis of pyrophosphate catalyzed by pyrophosphatase (many biosynthetic reactions are driven by the hydrolysis of pyrophosphate)

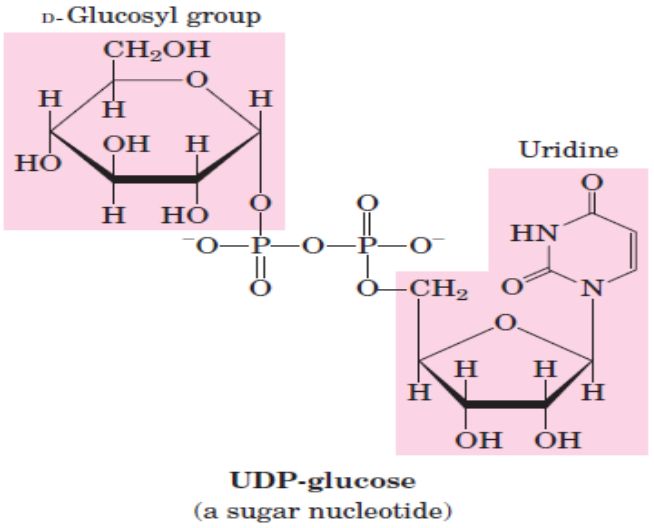


$$\text{Glucose 1-phosphate} + \text{UTP} \rightleftharpoons \text{UDP-glucose} + PP_i$$

$$PP_i + H_2O \longrightarrow 2\,P_i$$

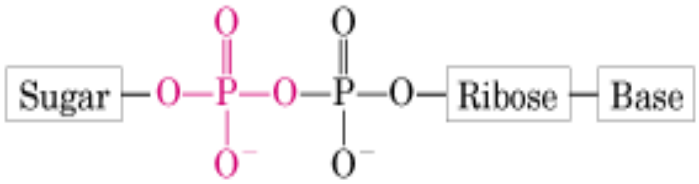
$$\text{Glucose 1-phosphate} + \text{UTP} + H_2O \longrightarrow \text{UDP-glucose} + 2\,P_i$$

- UDP-glucose is activated form of glucose
- Anomeric carbon of a sugar is activated by attachment to a nucleotide through a phosphate ester linkage



UDP-glucose
(a sugar nucleotide)

- Sugar nucleotides are the substrates for polymerization of monosaccharides into disaccharides, glycogen, starch, cellulose, and more complex extracellular polysaccharides



Sugar nucleotide
(NDP-sugar)

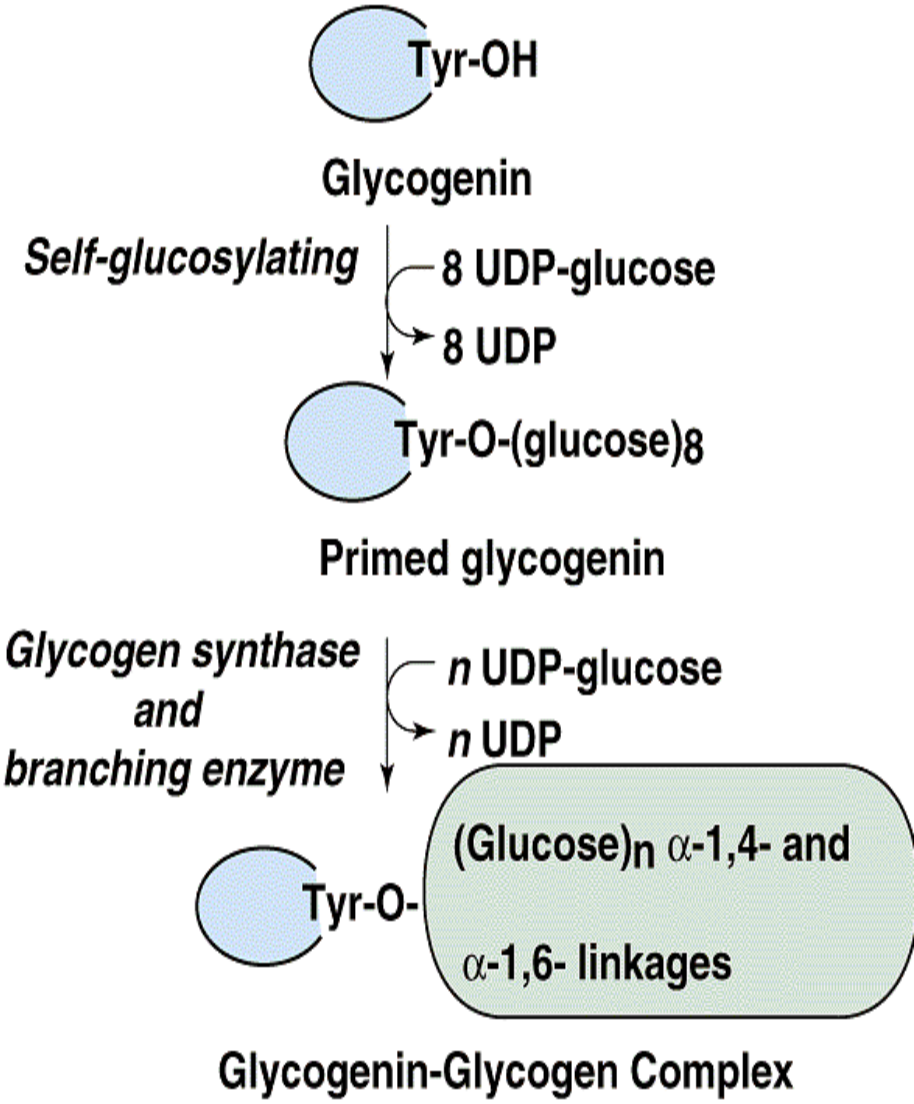
Sucrose: UDP-Glc + Fru-6-P

Lactose: UDP-Glc + UDP-Gal

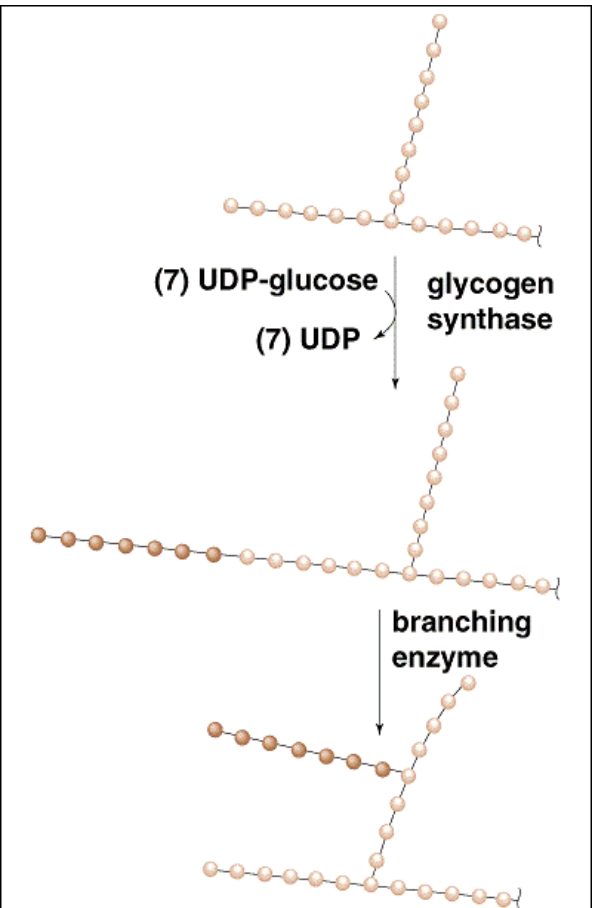
Glucuronides: UDP-Glc ⟶ UDP-GA (UDP- glucuronate)

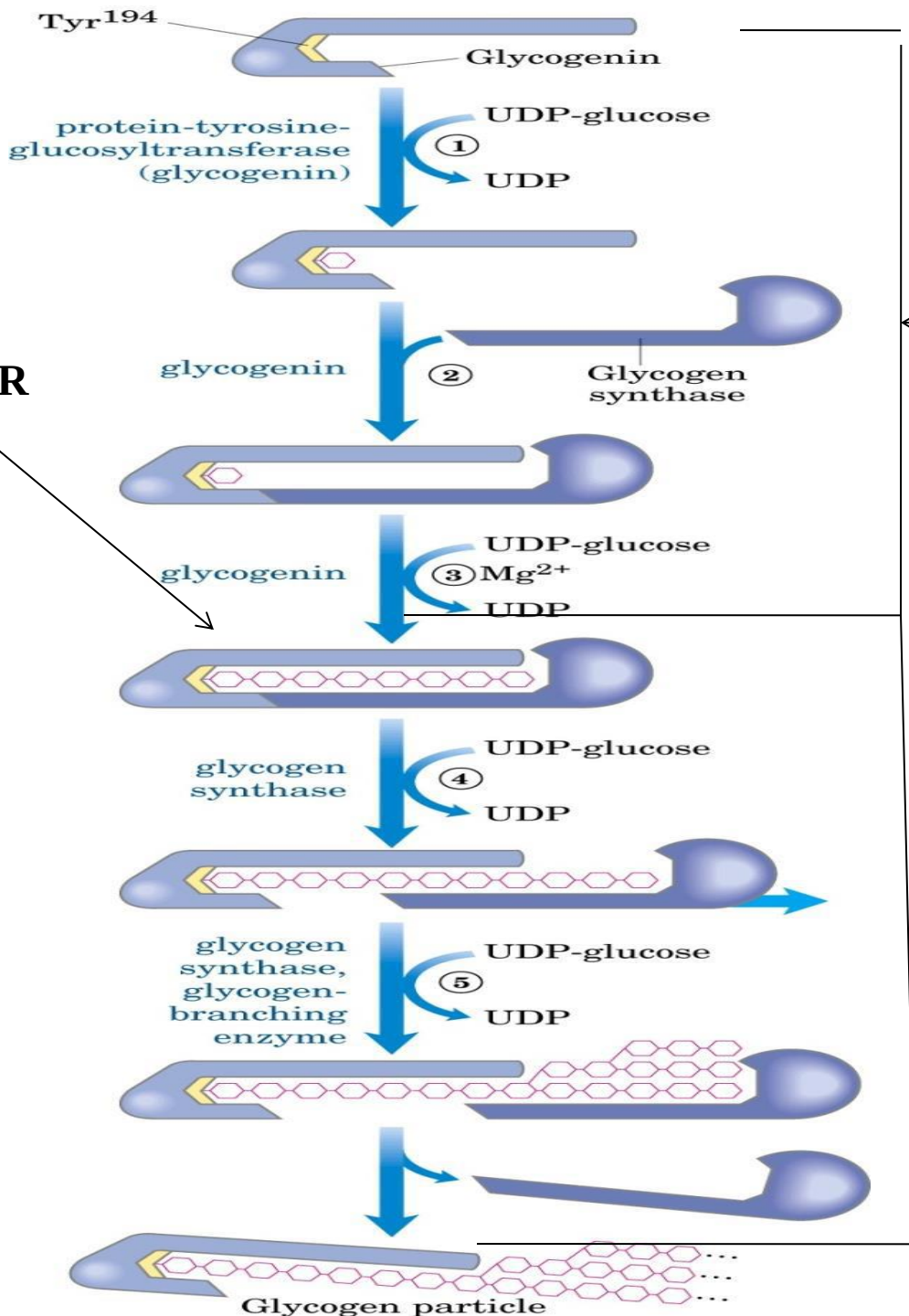
- Glycogen synthase cannot synthesize glycogen de novo
- Glycogenin starts glycogen synthesis
- Functions: bonding of 1st molecule UDP-glucose (with UDP release), and oligomerisation of the following 7 molecules of glucose

- Glycogen synthase can act (by adding Glu units) only upon existing oligosaccharide chain containing at least 8 glucose residues and reducing end of glycogen is permanently bond to glycogenin (self-glucosylating enzyme)

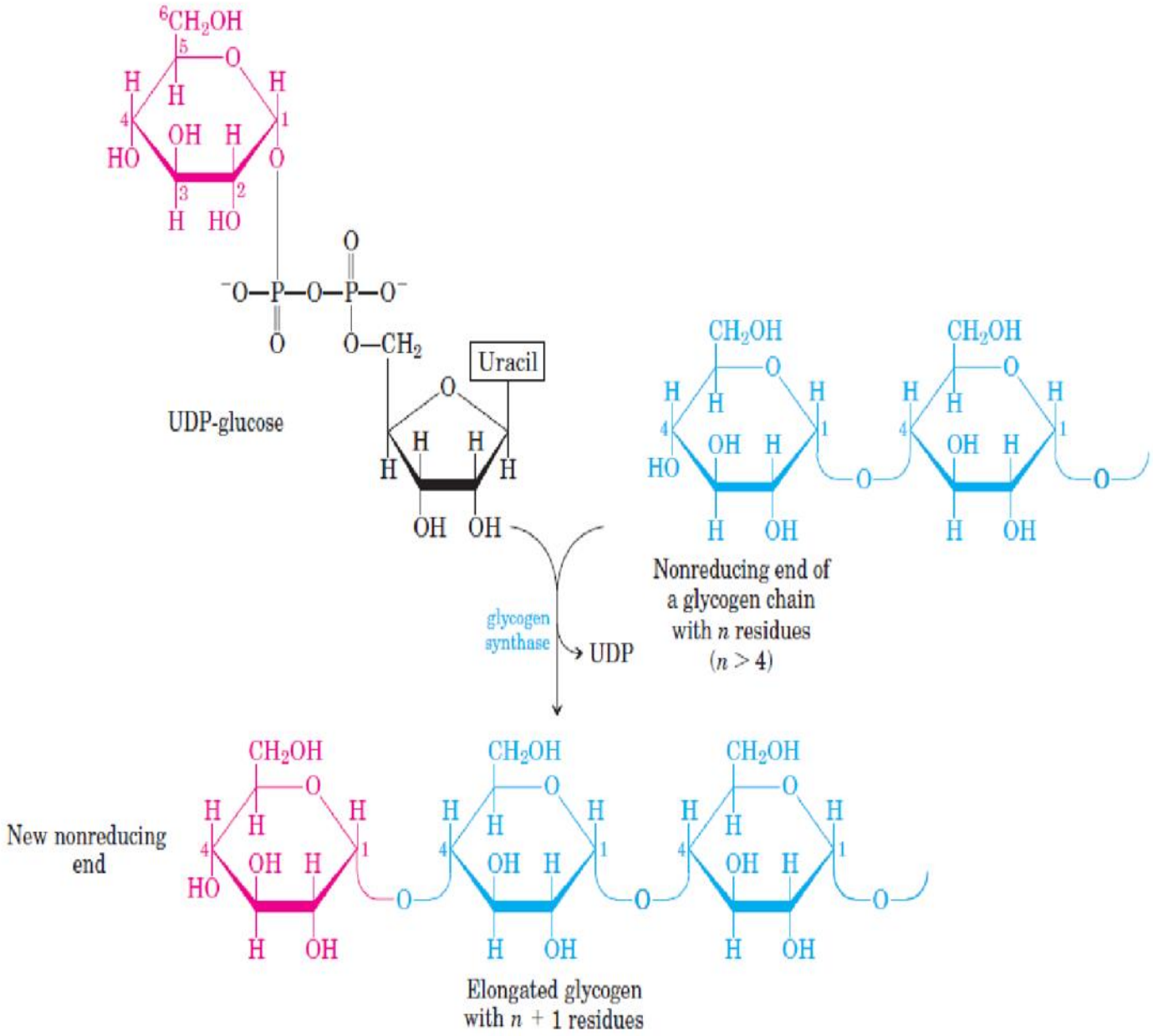


glycogen synthase transfers the glucose residue of UDP-glucose to the glycogen non-reducing end to make a new (α1,4) linkage



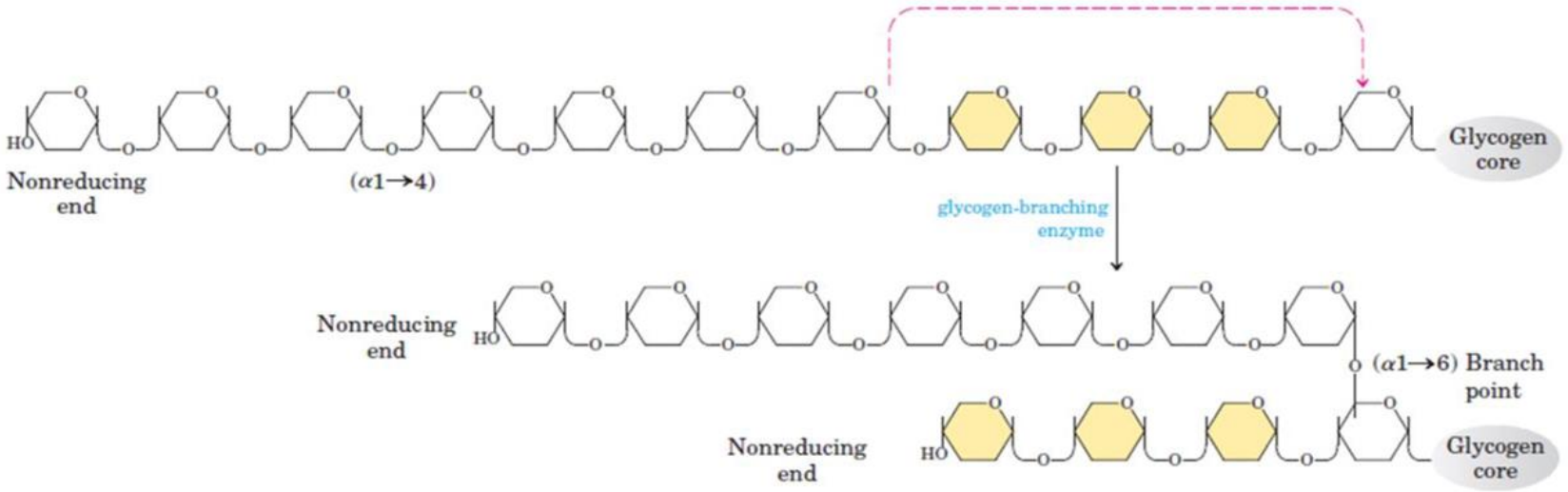


PRIMER


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

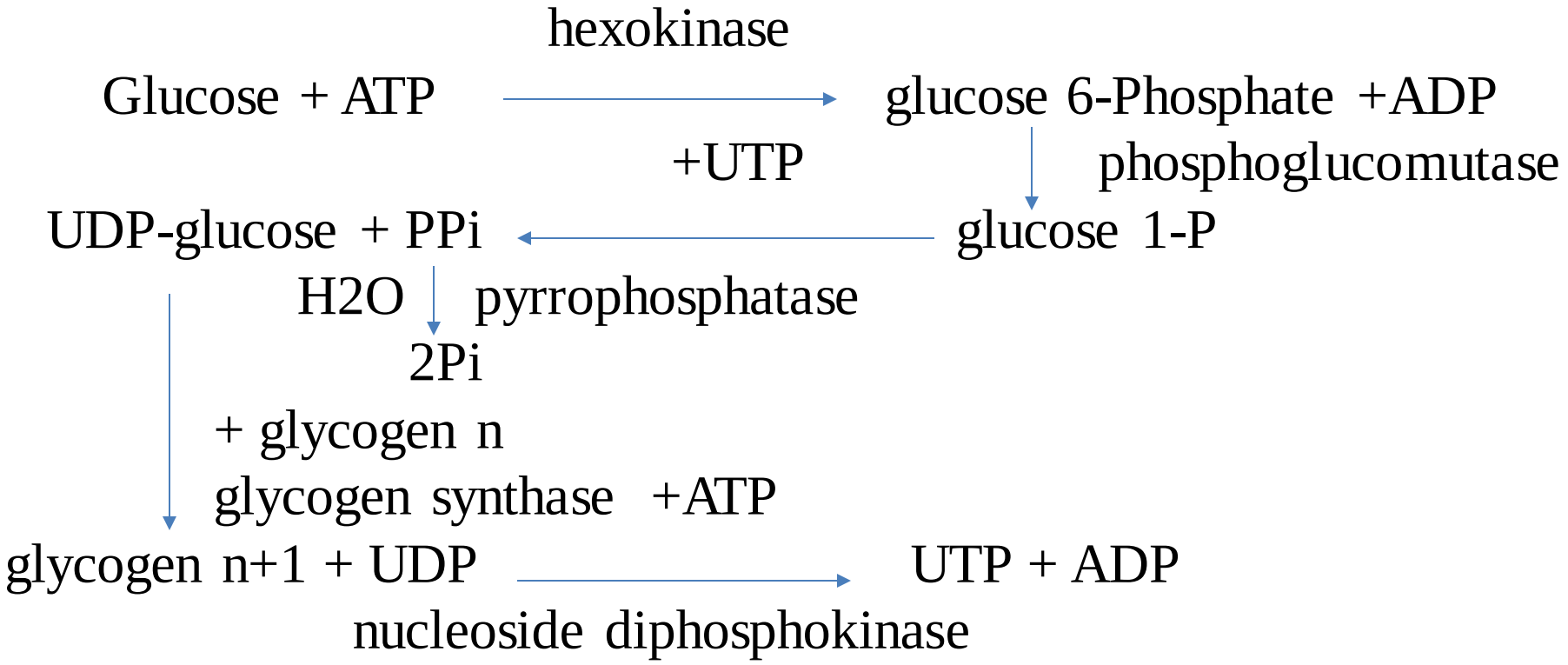
Glycogen branching - formation of α-1,6 bond

- Branching enzyme [glycosyl-(4→6) transferase] transfer of an oligosaccharide chain and formation of a new α-1,6 glycosidic bond, forming a new branch point.



- Some athletes consume large amounts of carbohydrates after training (carbohydrate loading)→ rapid glycogen synthesis and faster recovery
- The consumption of high-glycemic carbohydrates soon after exercise can maximize and sustain the rate of glycogen synthesis to help speed glycogen restoration.

Overall glycogenesis reactions



glucose 6-P + ATP + glycogen n + H2O → glycogen n+1 + ADP + 2 Pi

- If the starting substrate is Glu 6-P, 1 ATP is spent to store 1 Glu molecule (for UTP regeneration)
- If the starting substrate is glucose, 2 ATPs are needed (for Glu phosphorylation and UTP regeneration)

Glycogenolysis

- 3 enzymes involved:

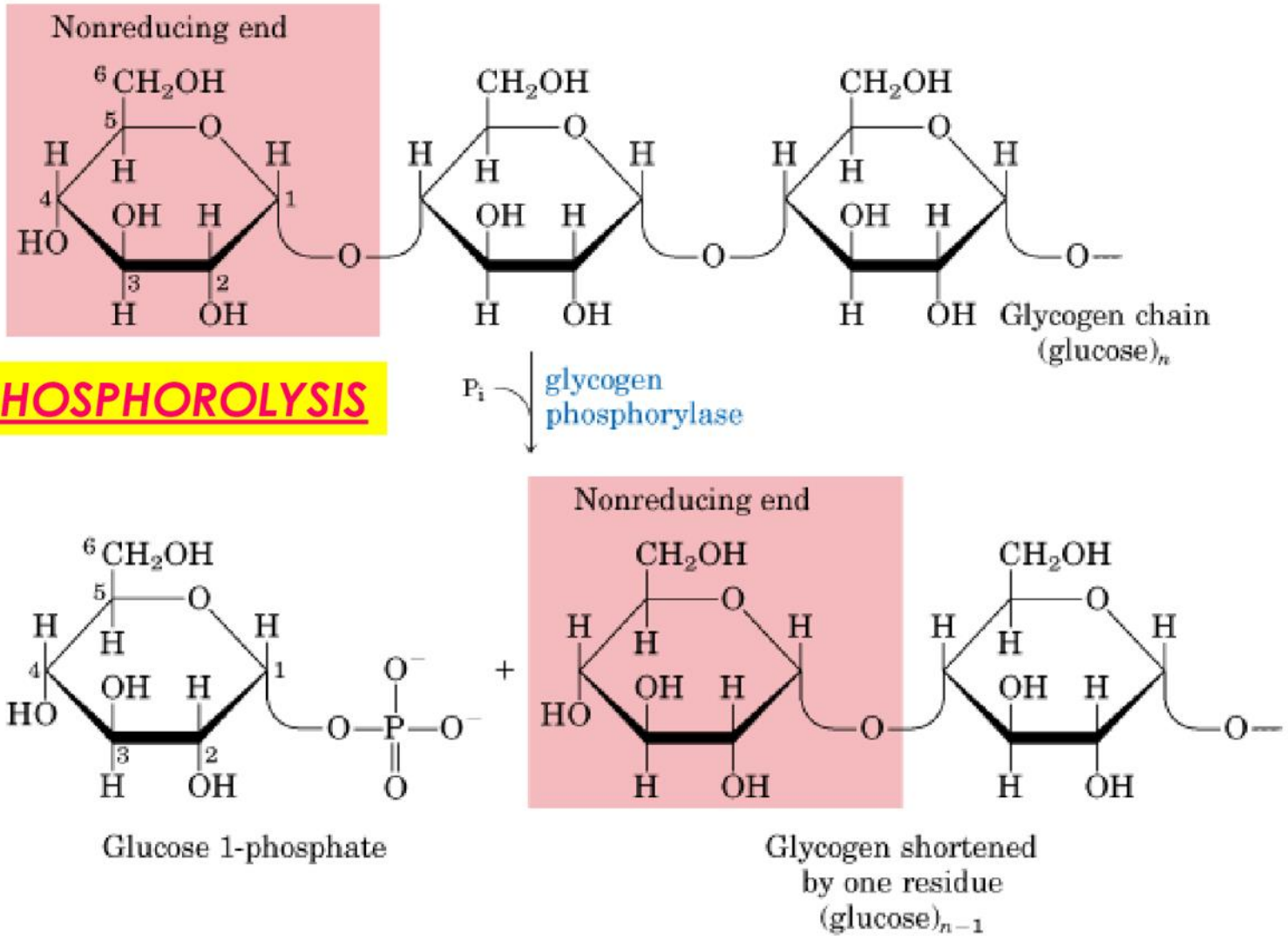
1. Glycogen-phosphorylase hydrolyses α-1,4 bonds forming glucose-1-phosphate

$$(glucose)n + Pi \rightarrow (glucose)n-1 + glucose\text{-}1\text{-}P$$

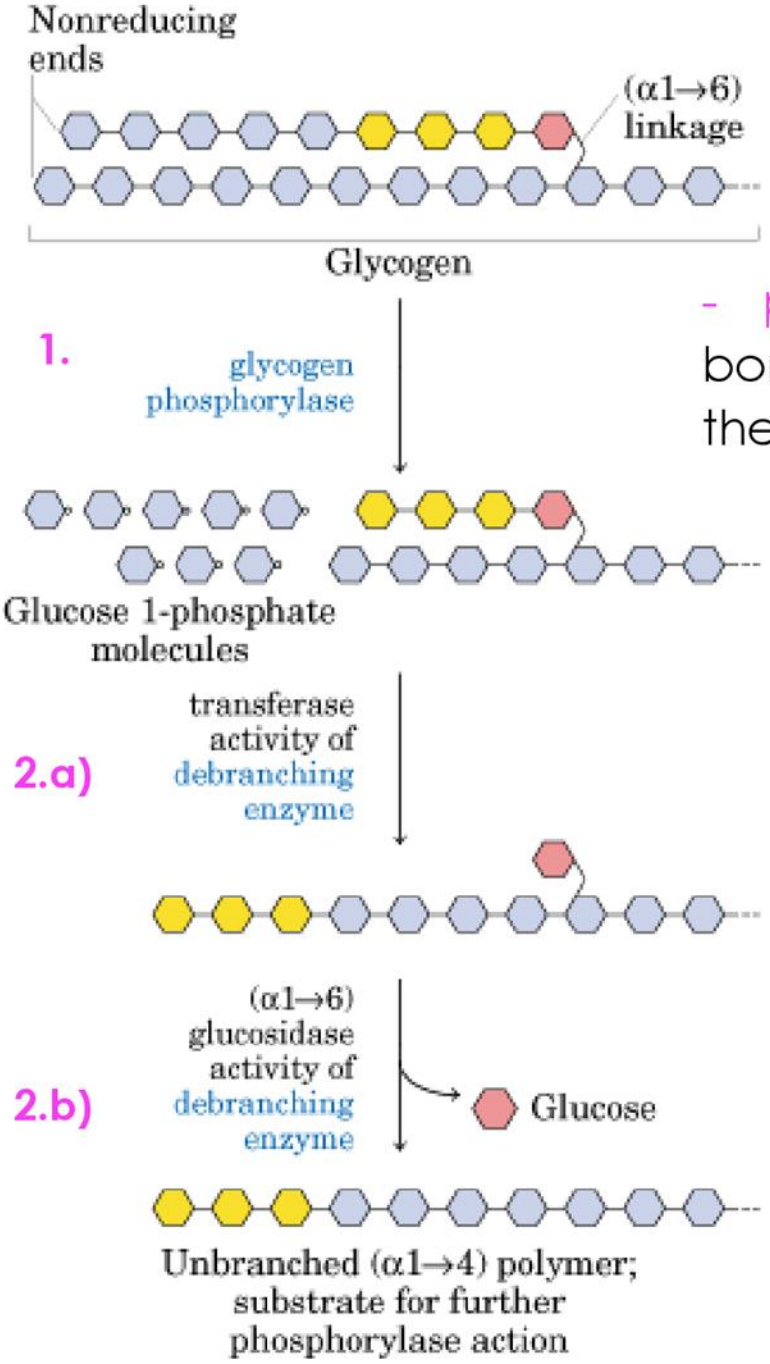
- Co-enzyme is PLP derived from pyridoxine (vitamin B6)

2. Debranching enzyme which has 2 activities
   a) Transferase - transfer of 3 glucose residues
   b) Glucosidase - hydrolysis of α-1,6 glycosidic bond
3. phosphoglucomutase transfers glucose-1-phosphate into glucose-6 phosphate

1) PHOSPHOROLYSIS



Glycogenolysis

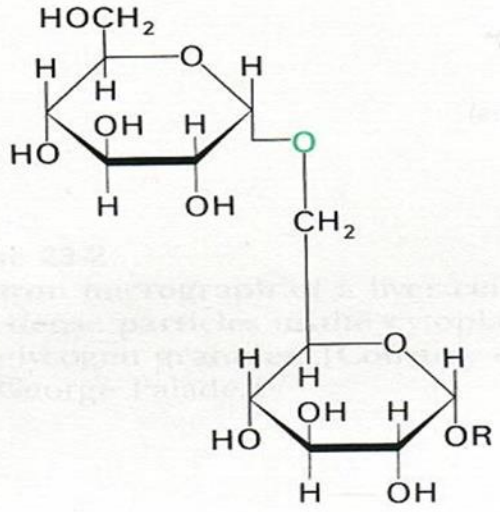


- phosphorolytic breaking of **α-(1,4)**-glycosidic bond, except for **4 glucose residues** away from the branching site
  - formation of **glucose 1-phosphate**

- transfere of **3 glucose residues** from one branch and formation of **α-(1,4)**-glycosidic bond on the other branch

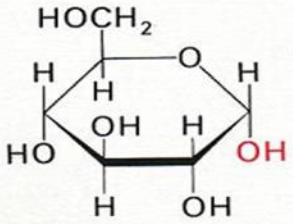
- hydrolysis of **α-(1,6)**-glycosidic bond with **glucose** formation

- products:
  glucose 1-phosphate and **glucose** in ratio **10 : 1**

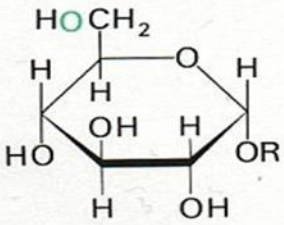


Glycogen
(*n* residues)

2.b) HYDROLYSIS



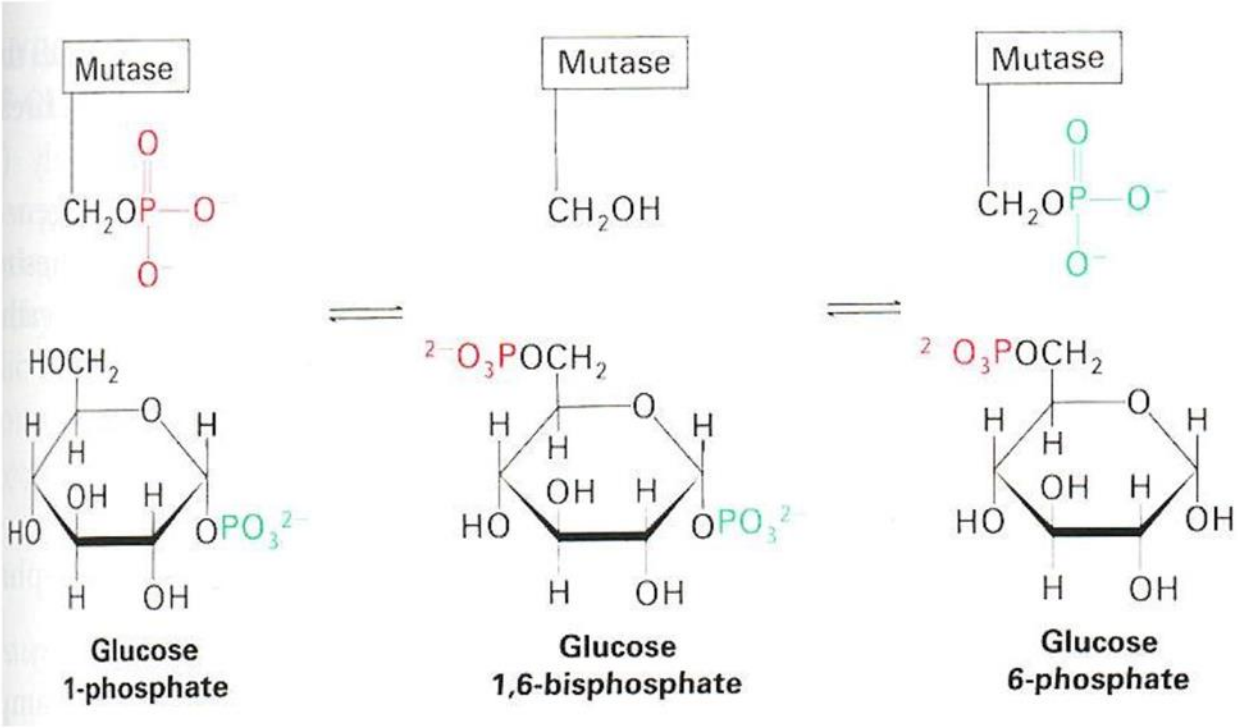
Glucose



Glycogen
(*n* − 1 residues)

3. ***phosphoglucomutase***

- isomerisation of **glucose 1-P** into **glucose 6-P**

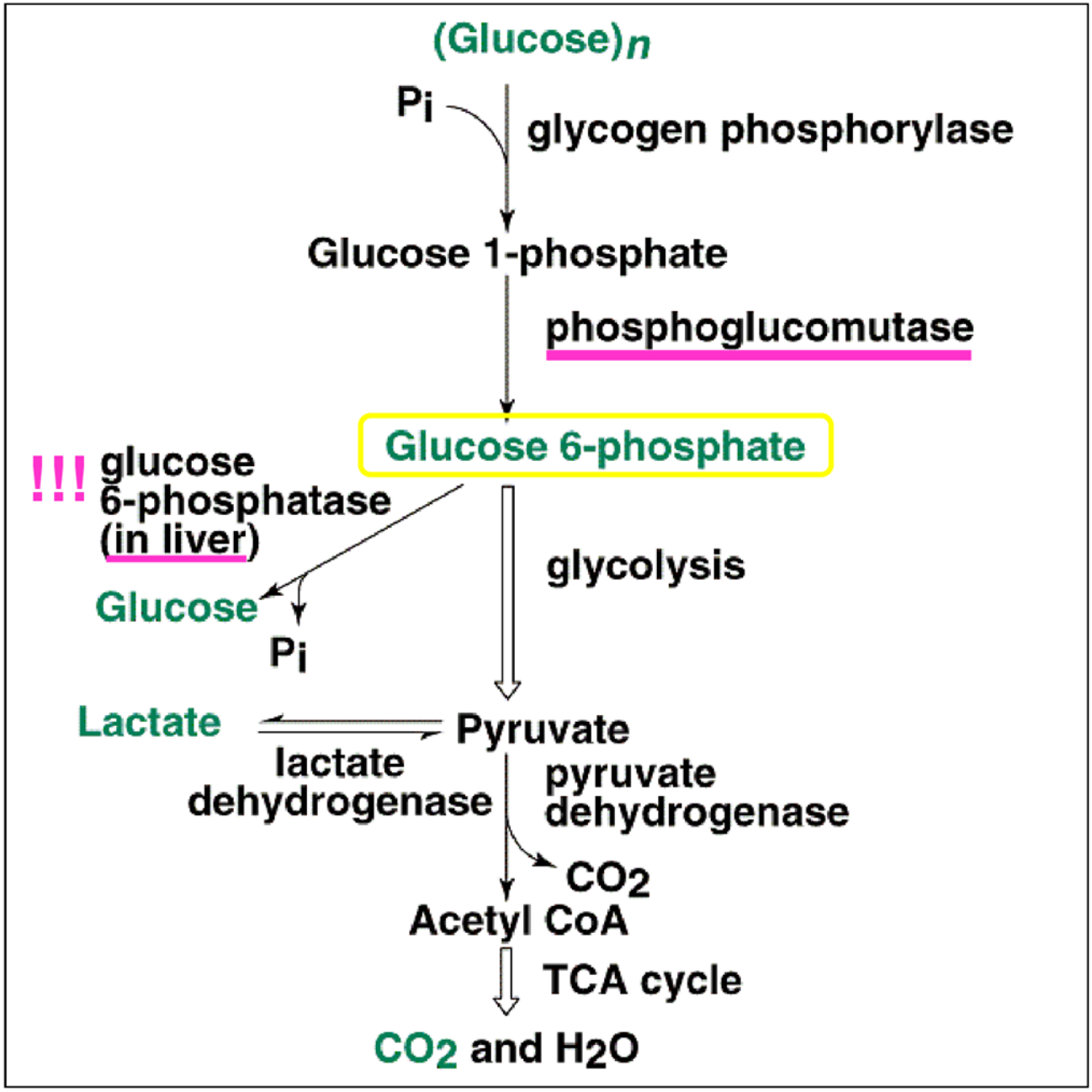


- ***phosphoglucomutase*** ***(phosphoenzyme!)*** catalyses the reaction in the direction of **glucose 6-P** formation, since the **glucose 1-P** concentration in the cell is much higher than of **glucose 6-P**

Glucose 6-phosphate
- different roles:

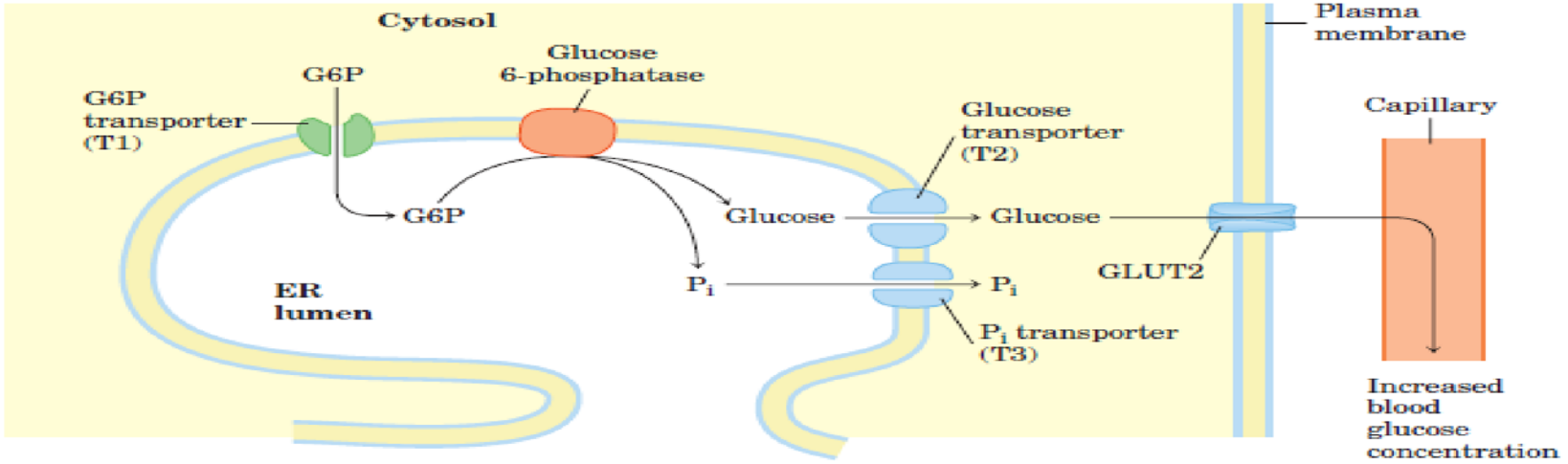
1. ***Muscle, brain***- **fuel** for aerobic and anaerobic metabolism (***pyruvate, lactate***)

2. ***Liver***, *kidneys* - tranformation of **G 6-P** into **glucose** for other tissues by **glucose 6-phosphatase** (other tissues do not have glucose 6-phosphatase!)



Glucose 6-phosphatase hydrolysis glucose 6-phosphate

- **liver, kidneys** - elevation of glucose blood concentration
- occurs in the lumen of **endoplasmatic reticulum (ER)** - separated from cytosol (glycolysis!)



- genetic defects in either **glucose 6-phosphatase** or **T1 transporter** lead to serious derangement of glycogen metabolism, resulting in **type Ia glycogen storage disease**

Glycogenolysis (summary)

- Rhosphorolytic cleavage of glycogen from the non-reducing end
- Released glucose is phosphorylated and thus ready to join the metabolism without ATP cost
- Glucose 1-phosphate cannot diffuse out of the cell
- Tissues which primarily use glucose as the energy source, do not contain glucose 6-phosphatase, but use G-6-P as fuel for glycolysis

Regulation of Glycogen Synthesis and Degradation

Importance of maintaining blood glucose levels.

- Glycogen storage form in liver and muscle.
- In liver:

  Glycogen synthesis during periods well fed state.

  Glycogen degradation during periods of fasting.

- In skeletal muscle:

  Glycogen degradation occurs during active exercise, activated by increase AMP and calcium calmodulin

  Synthesis begins as soon as the muscle is at rest.

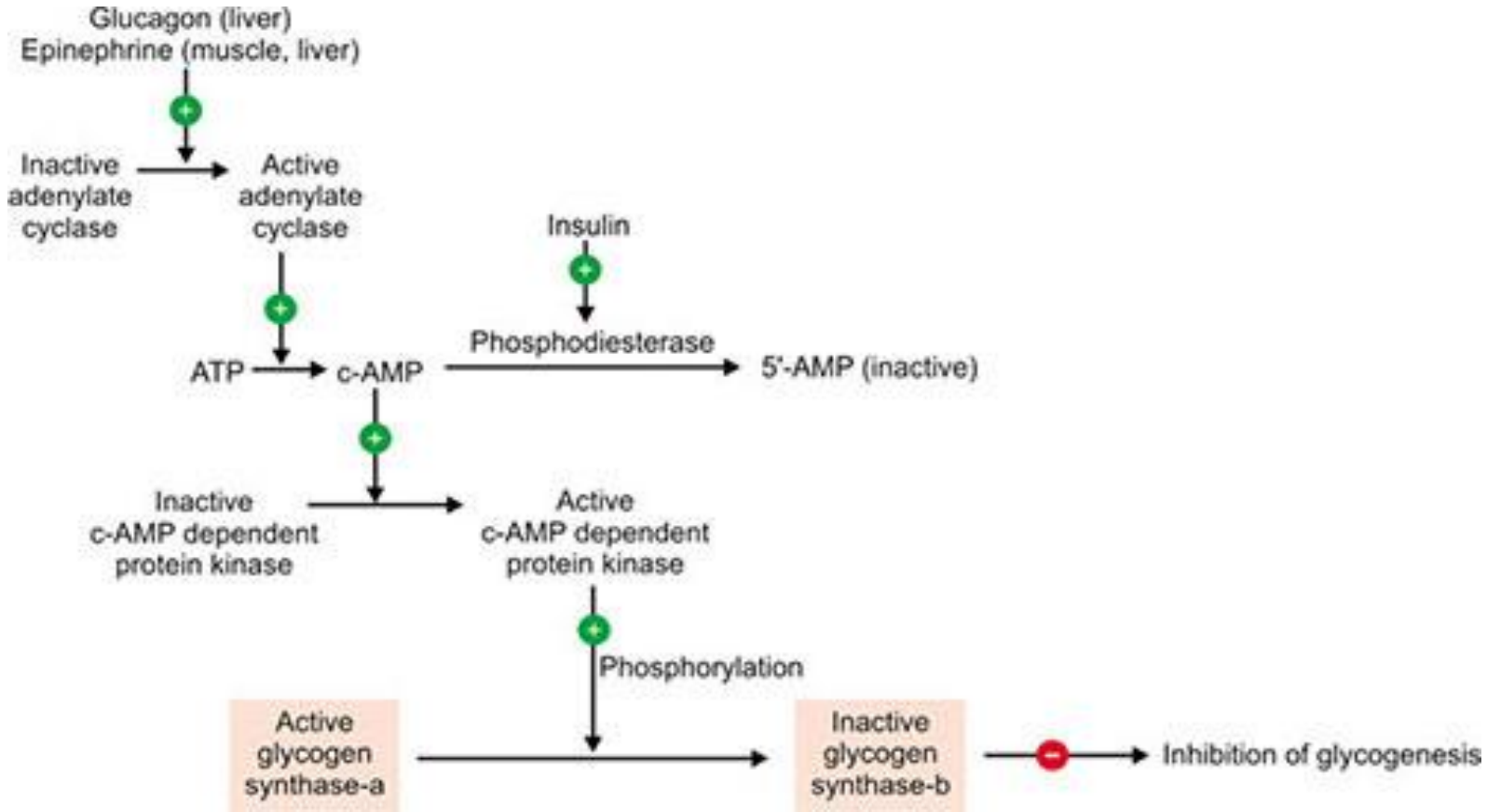
- Regulation of glycogen synthesis and degradation is accomplished on two levels:
- Glycogen synthase and phosphorylase are: allosterically controlled

- Glycogen synthesis and phosphorylase are: hormonally regulated.

- The regulation of glycogen synthesis and degradation is extremely complex, involving many enzymes: protein kinases and phosphatases

A. Covalent modification:

- Glycogen synthase is the key enzyme, present in two form:
  - Glycogen synthase a (active form) which is dephosphorylated.
  - Glycogen synthase b (inactive form) which is phosphorylated.



B. Induction and repression of the key enzyme:

- In well fed state: induce insulin synthesis for the key enzyme (induction) so, glycogenesis is stimulated.
- In fasting: decrease insulin leading to decrease synthesis of the key enzyme (repression) and hence glycogenesis is inhibited.

C. Allosteric regulation

Glycogen synthase is:

- allosterically activated by glucose-6-P.
- allosterically inhibited by glycogen molecule.

Regulation of Glycogenolysis:

Phosphorylase is the key enzyme

A. Covalent modification:

- It is present in two forms:
  - Phosphorylase "a" which is phosphorylated active form.
  - Phosphorylase "b" which is dephosphorylated inactive form

B- Induction and repression of phosphorylase enzyme.

- In well fed state : induce insulin which leads to decrease synthesis of key enzyme (repression) so glycogenolysis is inhibited.
- Fasting decrease insulin which increase synthesis of key enzyme (induction) so glycogenolysis is stimulated.

C. Allosteric regulation:

Muscle phosphorylase is:

- Allosterically activated by AMP which is increase during muscular exercise.
- Allosterically inhibited by ATP and G-6-P

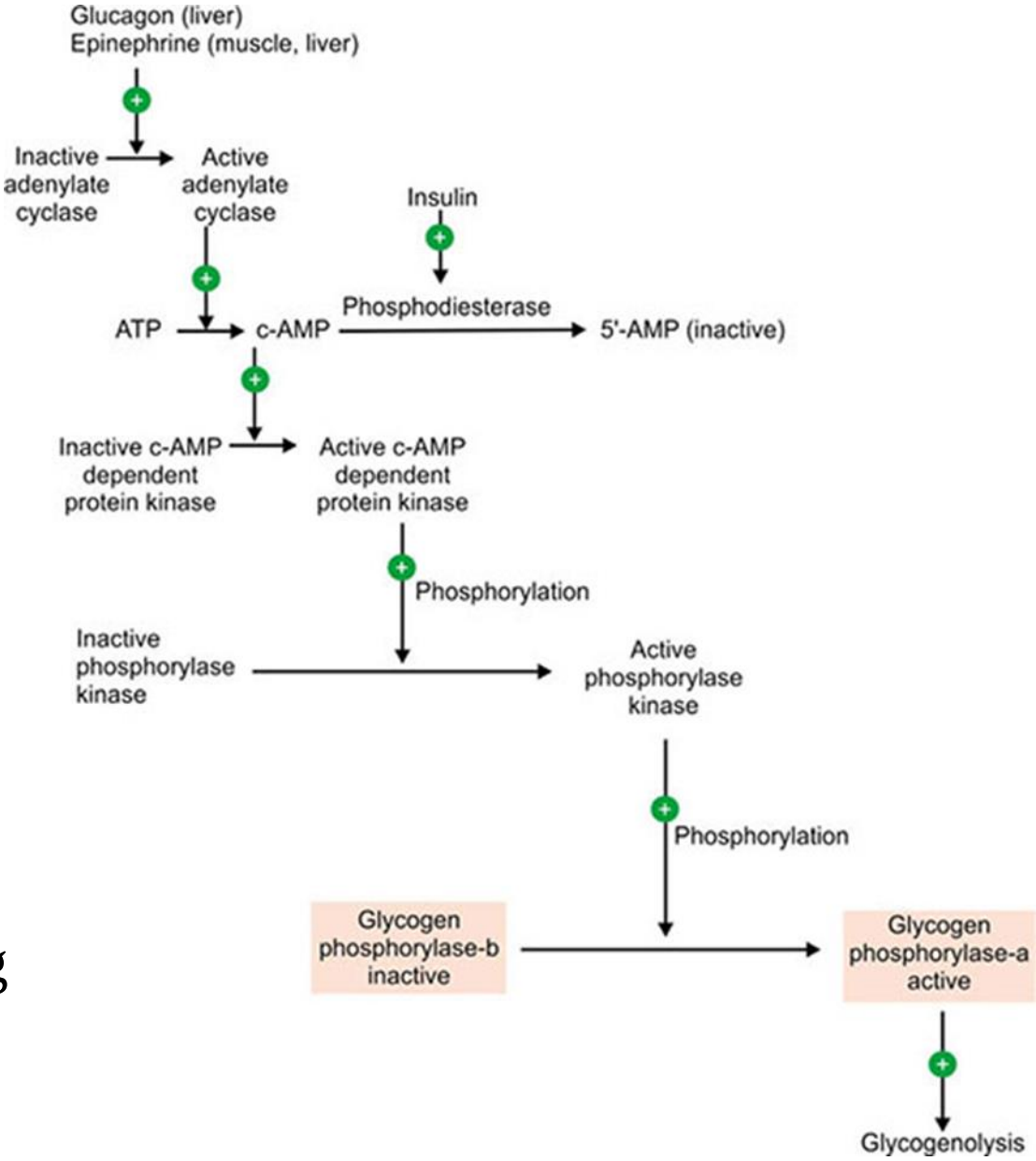


TABLE 1 Glycogen Storage Diseases of Humans

Type (name)	*Enzyme affected*	*Primary organ affected*	*Symptoms*
Type 0	Glycogen synthase	Liver	Low blood glucose, high ketone bodies, early death
Type Ia (von Gierke's)	Glucose 6-phosphatase	Liver	Enlarged liver, kidney failure
Type Ib	Microsomal glucose 6-phosphate translocase	Liver	As in Ia; also high susceptibility to bacterial infections
Type Ic	Microsomal P_i transporter	Liver	As in Ia
Type II (Pompe's)	Lysosomal glucosidase	Skeletal and cardiac muscle	Infantile form: death by age 2; juvenile form: muscle defects (myopathy); adult form: as in muscular dystrophy
Type IIIa (Cori's or Forbes's)	Debranching enzyme	Liver, skeletal and cardiac muscle	Enlarged liver in infants; myopathy
Type IIIb	Liver debranching enzyme (muscle enzyme normal)	Liver	Enlarged liver in infants
Type IV (Andersen's)	Branching enzyme	Liver, skeletal muscle	Enlarged liver and spleen, myoglobin in urine
Type V (McArdle's)	Muscle phosphorylase	Skeletal muscle	Exercise-induced cramps and pain; myoglobin in urine
Type VI (Hers's)	Liver phosphorylase	Liver	Enlarged liver
Type VII (Tarui's)	Muscle PFK-1	Muscle, erythrocytes	As in V; also hemolytic anemia
Type VIb, VIII, or IX	Phosphorylase kinase	Liver, leukocytes, muscle	Enlarged liver
Type XI (Fanconi-Bickel)	Glucose transporter (GLUT2)	Liver	Failure to thrive, enlarged liver, rickets, kidney dysfunction