METABOLIC BIOCHEMISTRY

GLYCOGEN

Glycogen

Glycogen is found primarily in the:

- Liver; it may represent up to 10% of it's weight
- Skeletal muscle; represent up to 1%-2% of it's weight.
- Glycogen in muscle provides a quick source of energy for either aerobic or anaerobic metabolism. Muscle glycogen can be exhausted in less than an hour during vigorous activity.
- Liver glycogen serves as a reservoir of glucose for other tissues when dietary glucose is not available (between meals or during a fast); this is especially important for the neurons of the brain, which cannot use fatty acids as fuel. Liver glycogen can be depleted in 12 to 24 hours.

Why stored as glycogen?

- Glucose :soluble in water

*be sent out of the body via kidneys.

*disturb the osmotic pressure (hypertonic)=lysis

-**G6P**: be degraded via the glycolysis

-**Glycogen** a polymerized form of glucose; insoluble do not disturb the osmotic pressure; non reducing ends accessible for glycogen metabolism

Glycogen breakdown

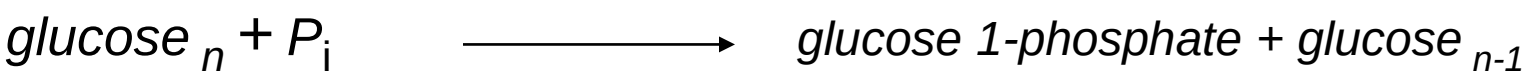
“Glycogenolysis”

Dr. Suheir Ereqat

Glycogen

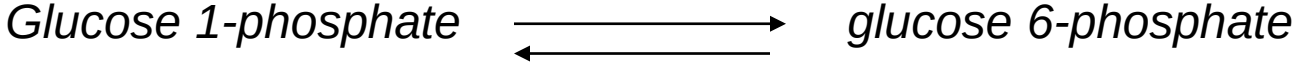
glycogen enter the glycolytic pathway through the action of three enzymes:

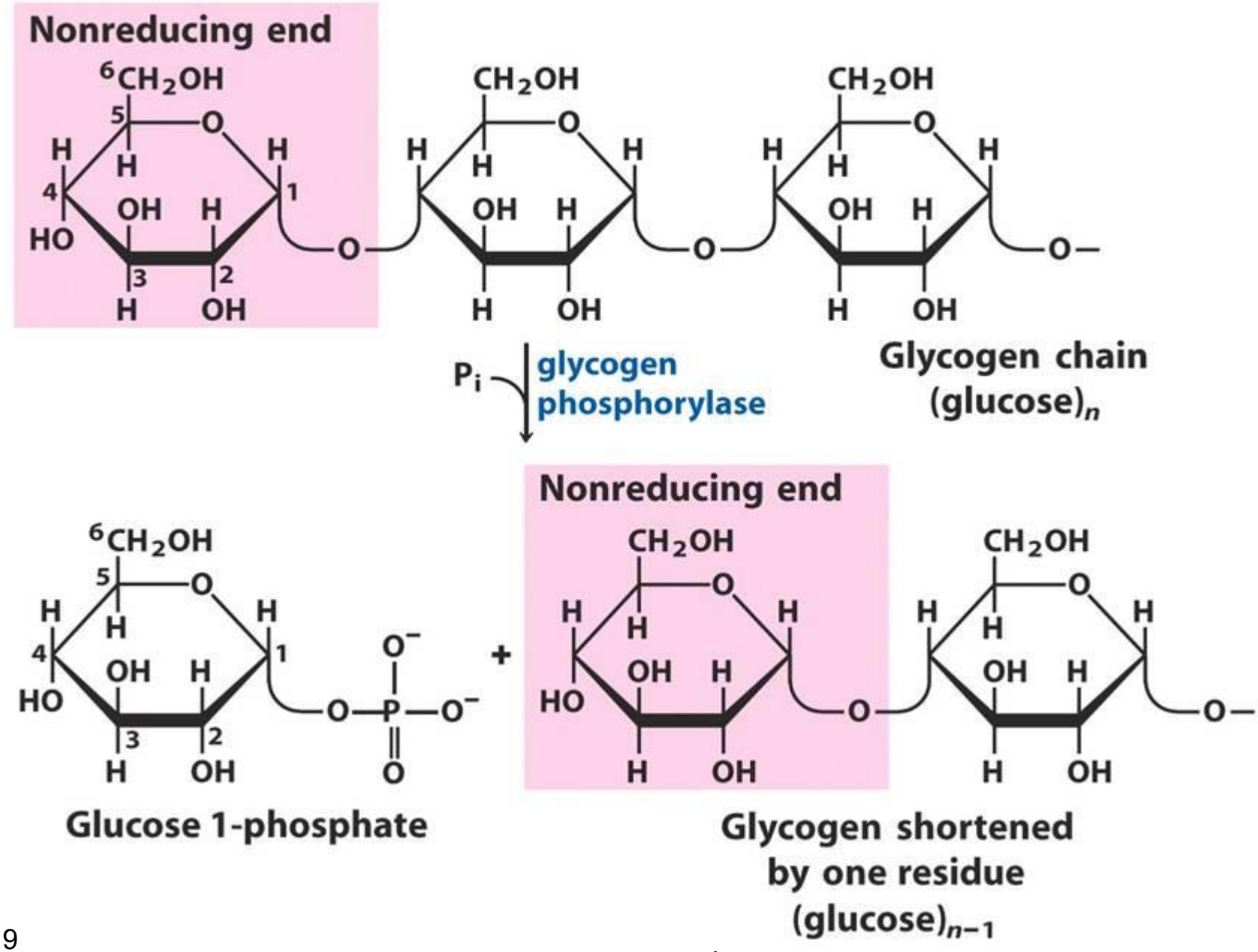
- ***glycogen phosphorylase***;



- ***glycogen debranching enzyme***, formally known as oligo (1ά 6) to (1ά 4) glucantransferase, catalyzes two successive reactions that transfer branches.

- ***phosphoglucomutase*** catalyzes the reversible reaction



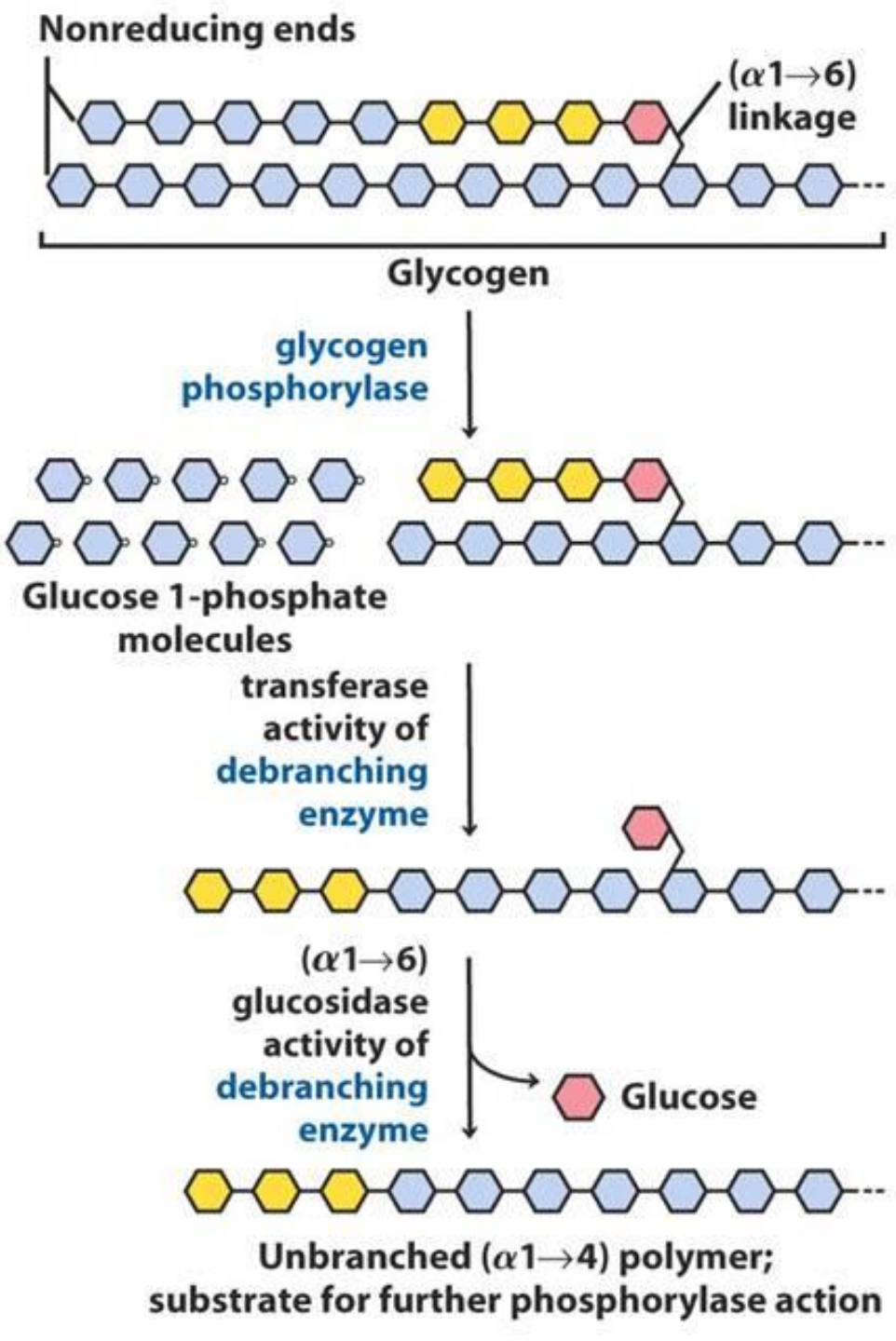

Nonreducing end
$^6CH_2OH$
5
O
H
H
4
OH
H
1
HO
3
2
H
OH
O
CH_2OH
Glycogen chain
$(glucose)_n$
P_i
glycogen
phosphorylase
Nonreducing end
Glucose 1-phosphate
+
O^-
O^-
P
Glycogen shortened
by one residue
$(glucose)_{n-1}$

Glycogen phosphorylase

- Uses P_i
- Pyridoxal phosphate cofactor

  PLP used in transamination
- Chops off a glucose 1-phosphate from nonreducing end
  - Stops four glucoses from an (α1-6) branch point
- Resumes work after branch removed

Glycogen breakdown near an (1ά 6) branch point



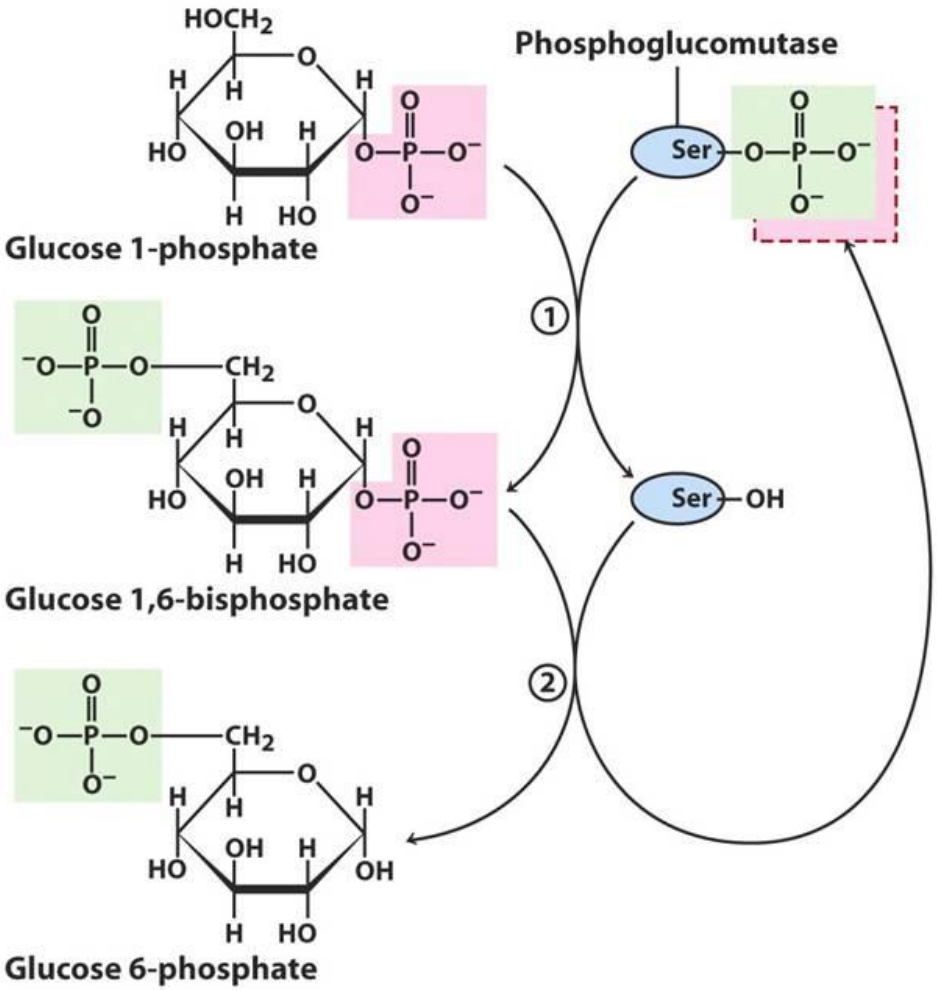
Debranching enzyme

- Transfers a branch to nonreducing end, leaving one glucose branch (tranferase activity)
- Removes single glucose (NOT G 1-P)

Following sequential removal of terminal glucose residues by glycogen phosphorylase, glucose residues near a branch are removed in a two-step process that requires a bifunctional "debranching enzyme."

First, the transferase activity of the enzyme shifts a block of three glucose residues from the branch to a nearby nonreducing end, to which they are reattached in (1ά4) linkage.

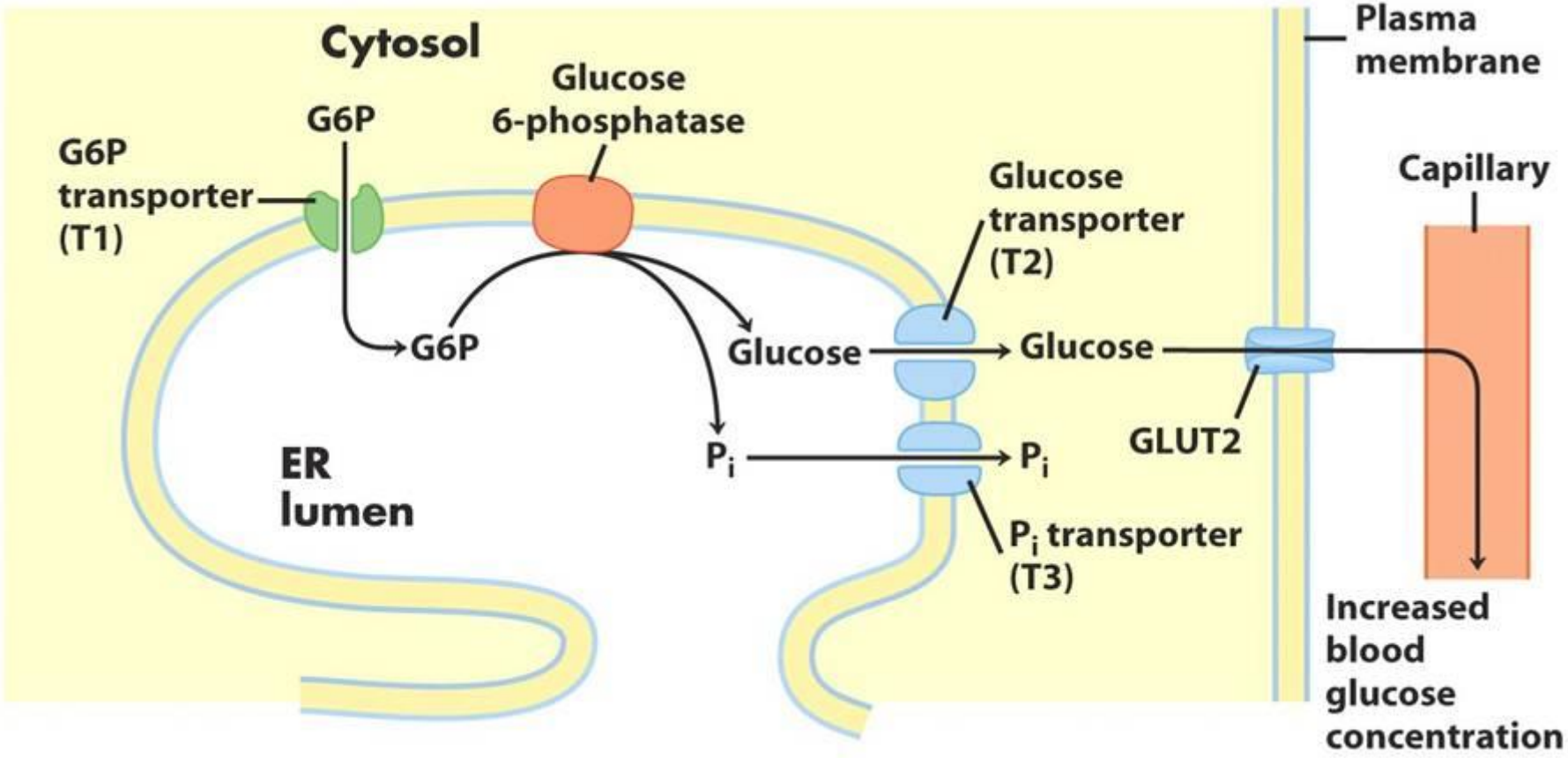
The single glucose residue remaining at the branch point, in (1ά6) linkage, is then released as free glucose by the enzyme's (1ά6) glucosidase activity



Because muscle and adipose tissue lack glucose 6-phosphatase, they cannot convert the glucose 6-phosphate formed by glycogen breakdown to glucose, and these tissues therefore do not contribute glucose to the blood.

Liver glucose 6-phosphate

- Converted to glucose for blood sugar augmentation
- Must enter endoplasmic reticulum (transporters)
  - glucose 6-phosphatase on inside wall
  - Leaves cell (another transporter)


Cytosol
Glucose
6-phosphatase
G6P
G6P
transporter
(T1)
Glucose
transporter
(T2)
Plasma
membrane
Capillary
G6P
Glucose
Glucose
GLUT2
ER
lumen
Pi
Pi
Pi transporter
(T3)
Increased
blood
glucose
concentration

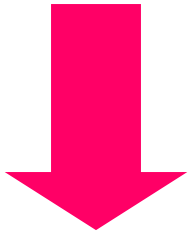
Glycogen Synthesis

“Glycogenesis”

Dr. Suheir Ereqat

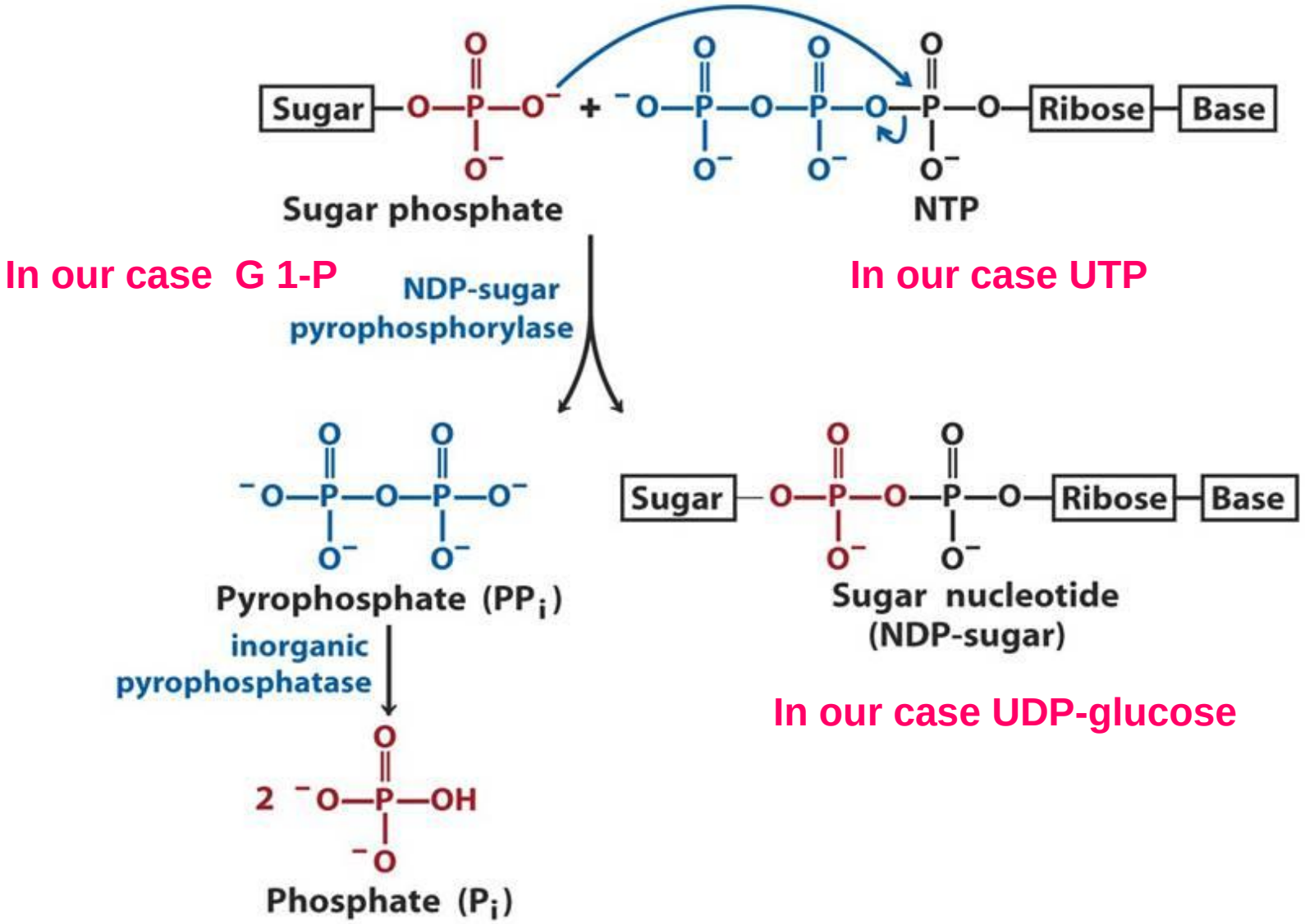
Glucose, glucose 6-phosphate, glucose 1-phosphate

- G must be phosphorylated (hexokinase) to G 6-P
- then isomerized (phosphoglucomutase) to G 1-P
- G 1-P is ready to go



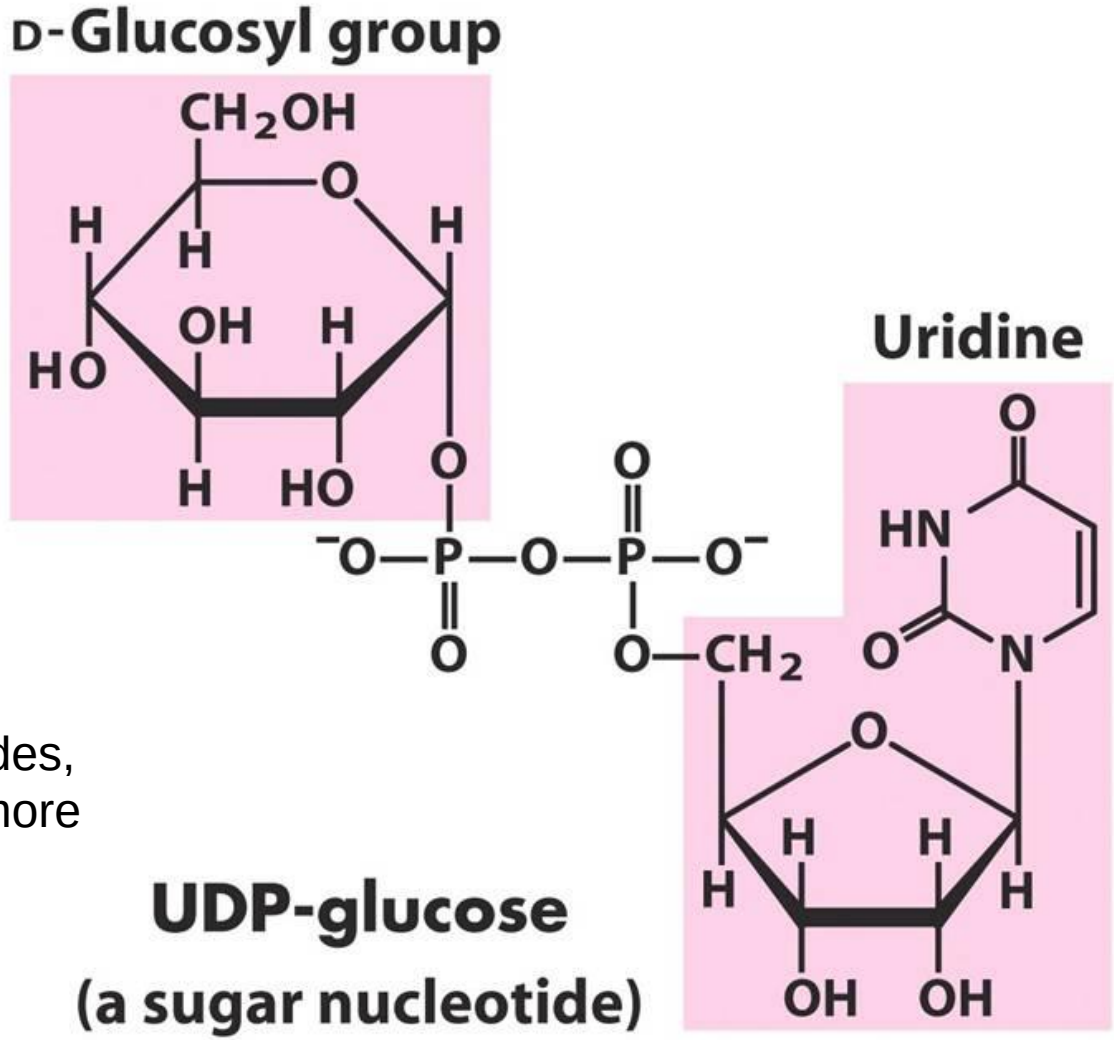
UDP-glucose pyrophosphorylase

Glucose 1-phosphate + UTP → UDP-glucose + PP_i

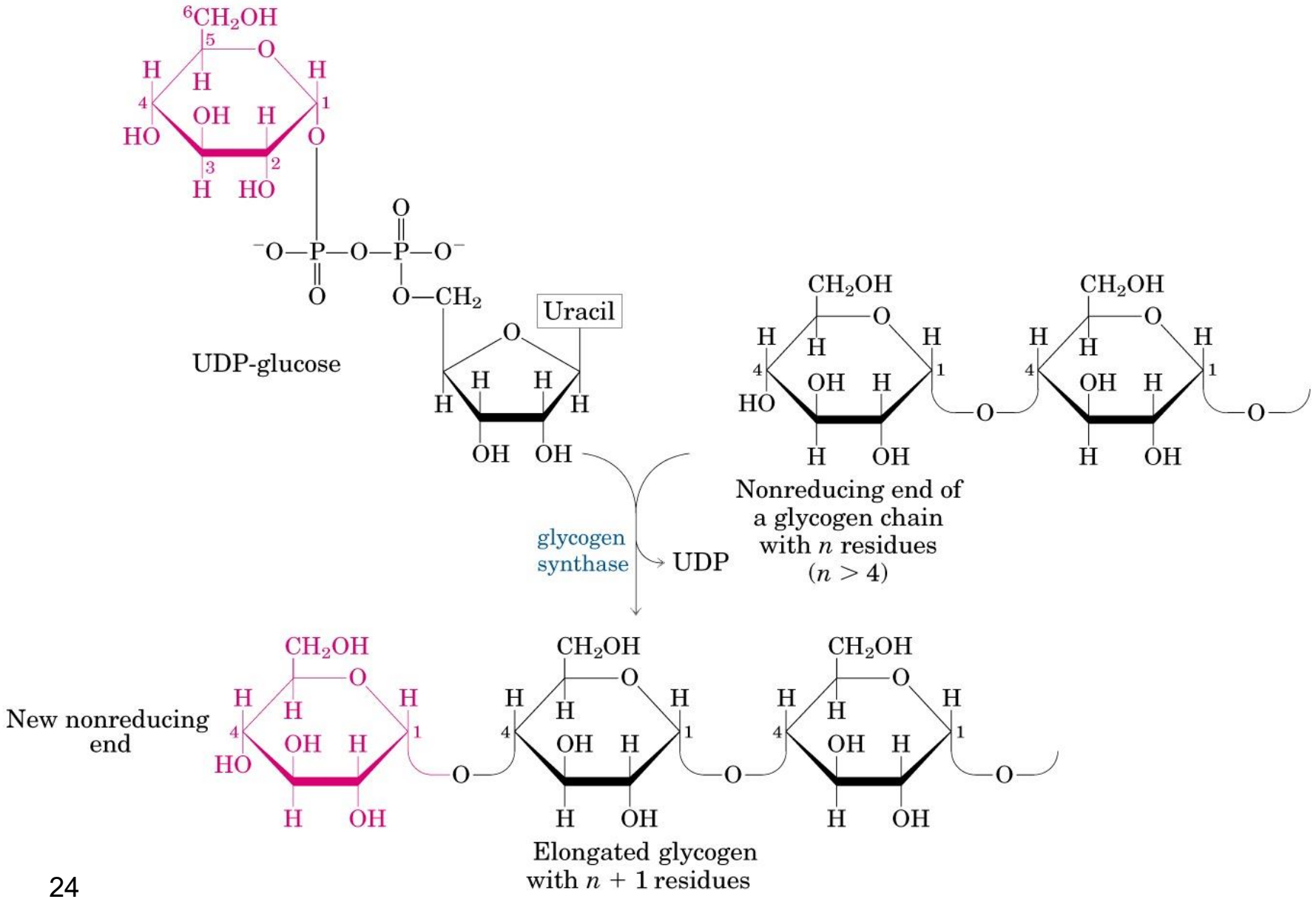

Sugar
Ribose
Base
Sugar phosphate
NTP
In our case G 1-P
In our case UTP
NDP-sugar pyrophosphorylase
Pyrophosphate (PP_i)
Sugar nucleotide (NDP-sugar)
In our case UDP-glucose
inorganic pyrophosphatase
Phosphate (P_i)
Net reaction: Sugar phosphate + NTP ⟶ NDP-sugar + $2P_i$

Sugar nucleotides, compounds in which the anomeric carbon of a sugar is activated by attachment to a nucleotide through a phosphate ester linkage.

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

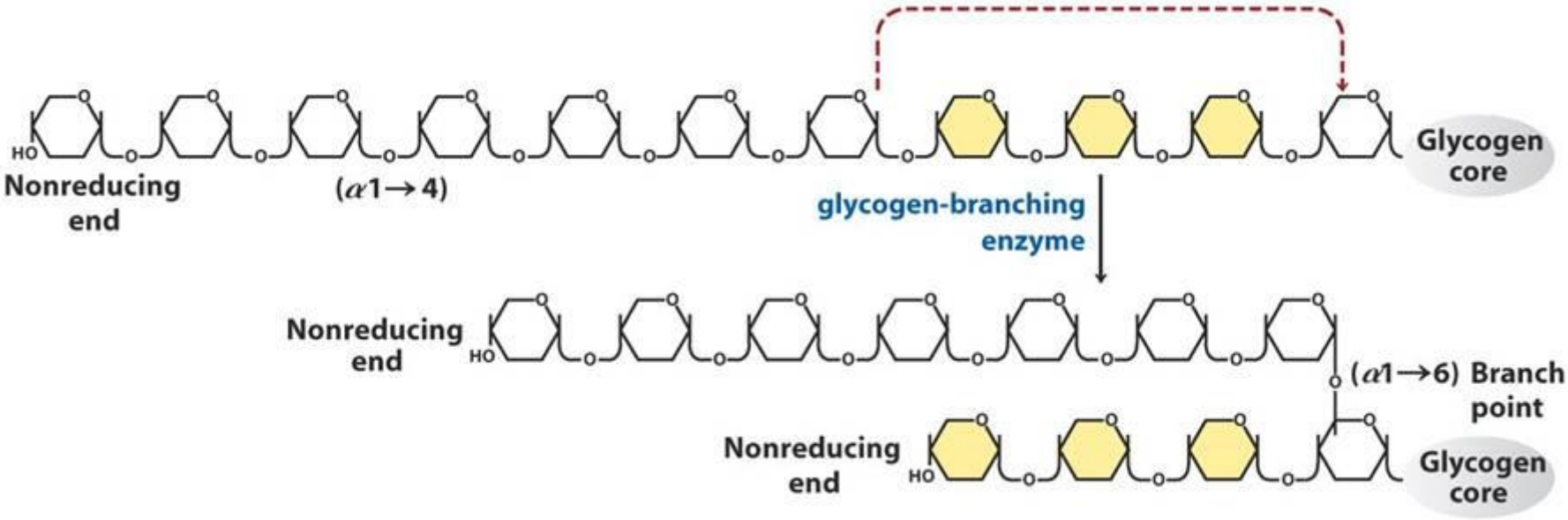


Glycogen Synthesis



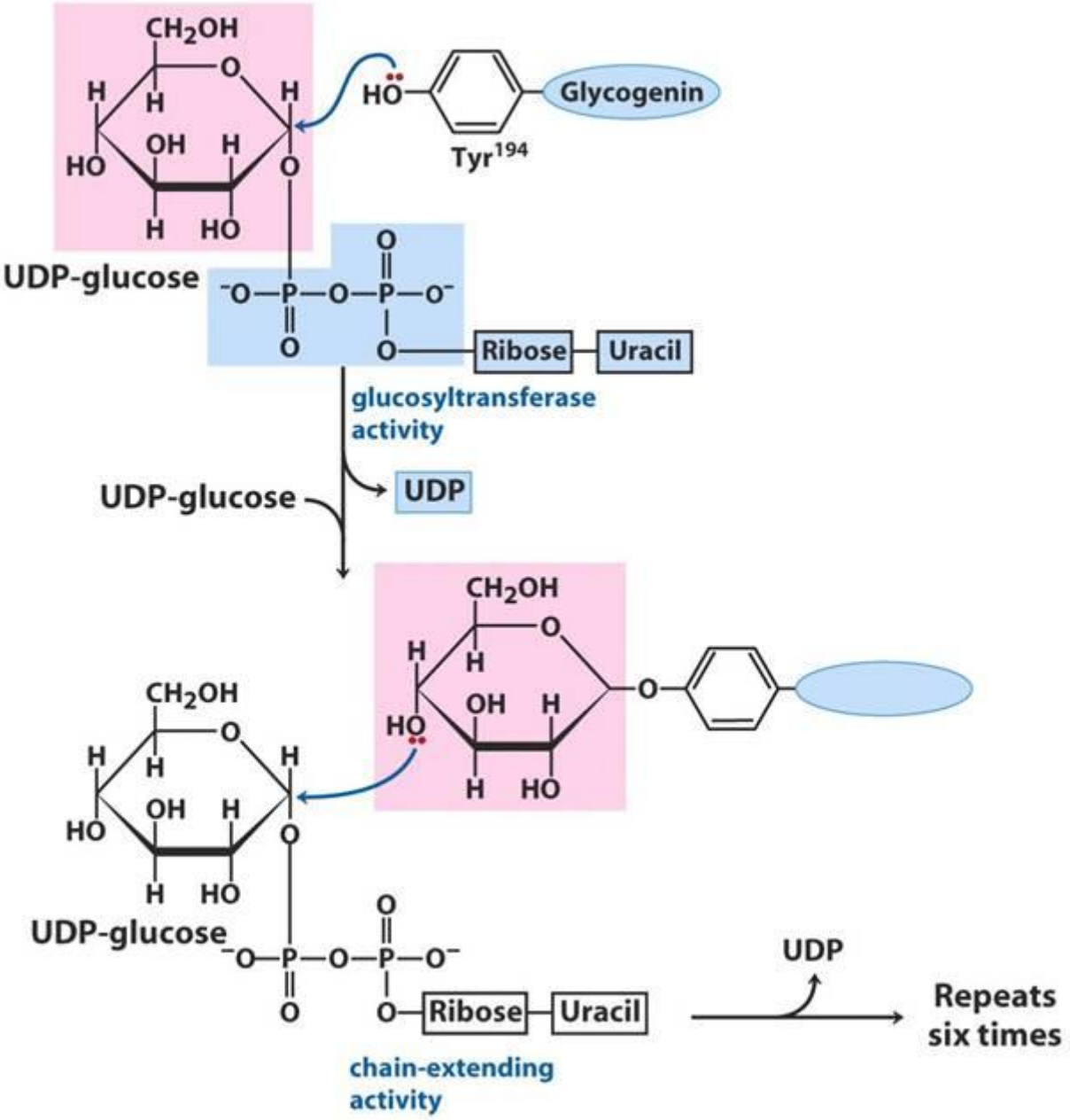
Glycogen synthase

- Adds glucose (via UDP-glucose) to nonreducing end of growing glycogen chain
- Releases UDP
- Chain must be longer than 4 units

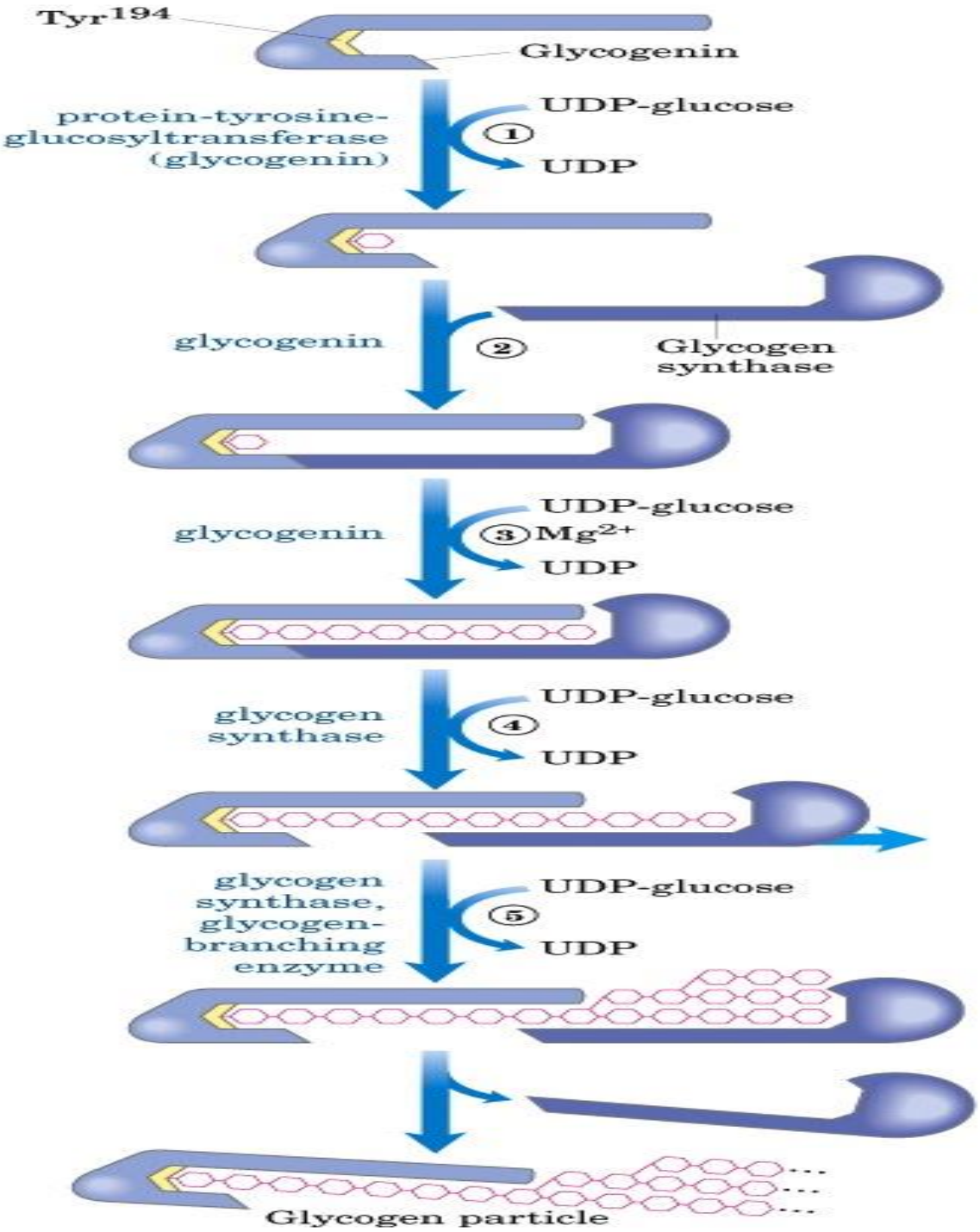

HO
Nonreducing end
(α1→4)
Glycogen core
glycogen-branching enzyme
Nonreducing end
HO
(α1→6) Branch point
Nonreducing end
HO
Glycogen core

Glycogen-branching enzyme

- Moves a 6 or 7 glucose chain to a more interior position on a chain
  - Unbranched end must be at least 11 long
  - New place must be at least 4 units away from the branch point


CH2OH
O
H
H
HO
OH
H
HO
Glycogenin
Tyr194
UDP-glucose
Ribose
Uracil
glucosyltransferase activity
UDP-glucose
UDP
UDP-glucose
chain-extending activity
UDP
Repeats six times

Glycogenin Primes the Initial Sugar Residues in Glycogen



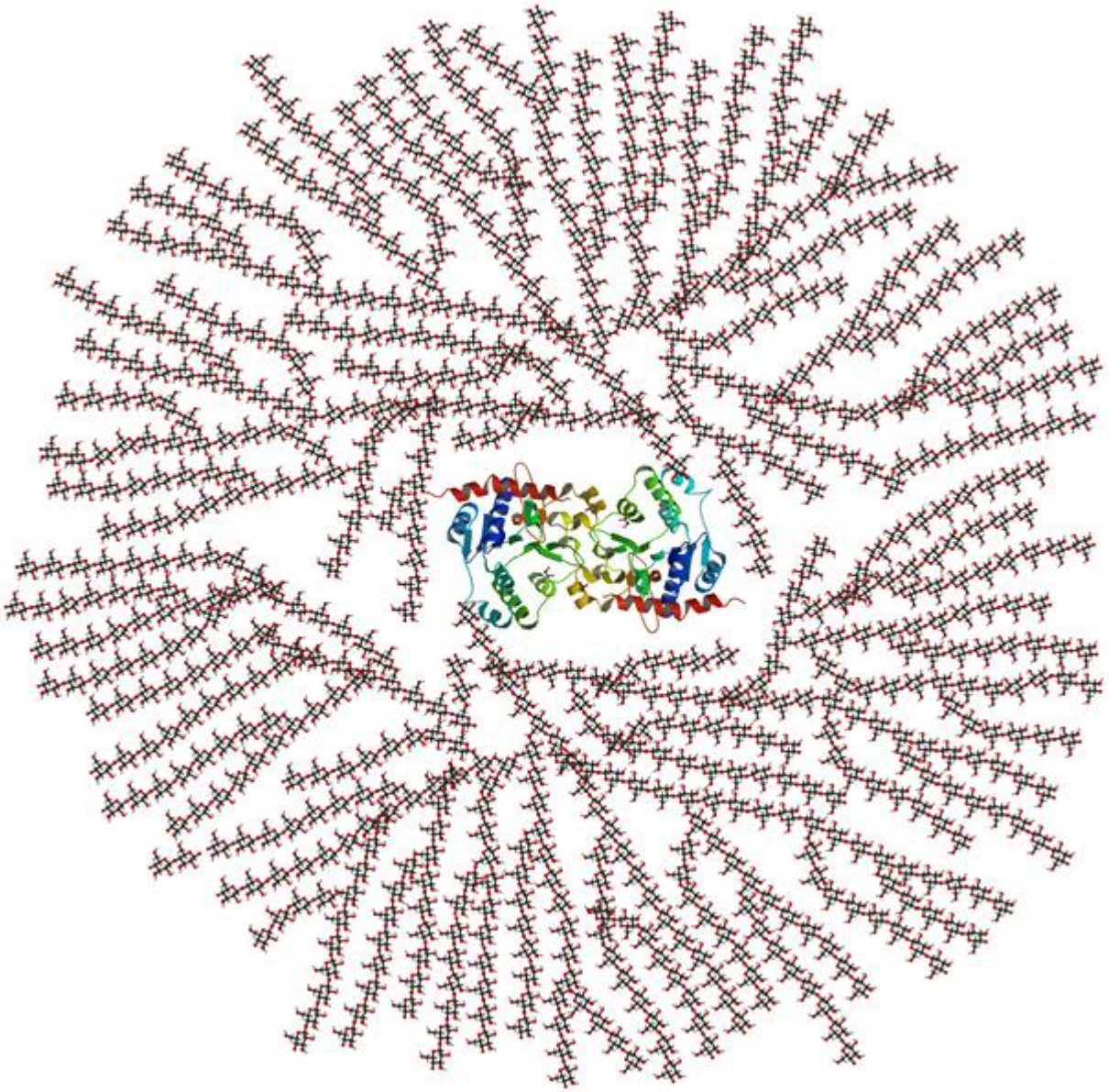
Glycogenin Primes the Initial Sugar Residues in Glycogen

The first step in the synthesis of a new glycogen molecule is the transfer of a glucose residue from UDPglucose to the hydroxyl group of Tyr194 of glycogenin, catalyzed by glucosyltransferase.

The nascent chain is extended by the sequential addition of seven more glucose residues, each derived from UDP-glucose; the reactions are catalyzed by the chain-extending activity of glycogenin.

At this point, glycogen synthase takes over, further extending the glycogen chain.

Glycogenin remains buried within the particle, covalently attached to the single reducing end of the glycogen molecule



Schematic 2-D cross-sectional view of glycogen. A core protein of glycogenin is surrounded by branches of glucose units. The entire globular granule may contain approximately 30,000 glucose units .

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Summary-Glycogen Synthesis

Glycogen synthase cannot make the (1ά 6) bonds found at the branch points of glycogen; these are formed by the *glycogen-branching enzyme*.

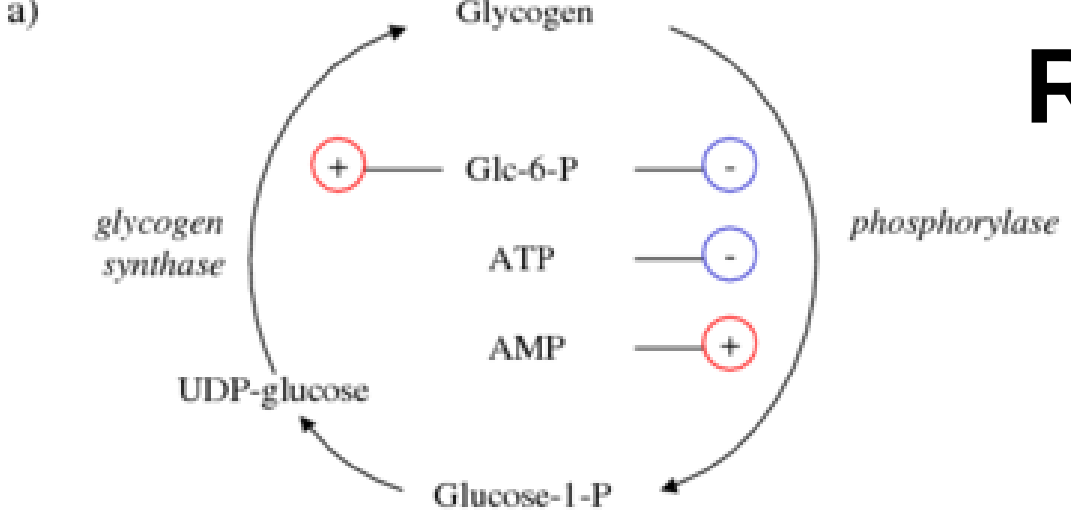
The *glycogen-branching enzyme* catalyzes transfer of a terminal fragment of 6 or 7 glucose residues from the nonreducing end of a glycogen branch having at least 11 residues to the C-6 hydroxyl group of a glucose residue at a more interior position of the same or another glycogen chain, thus creating a new branch.

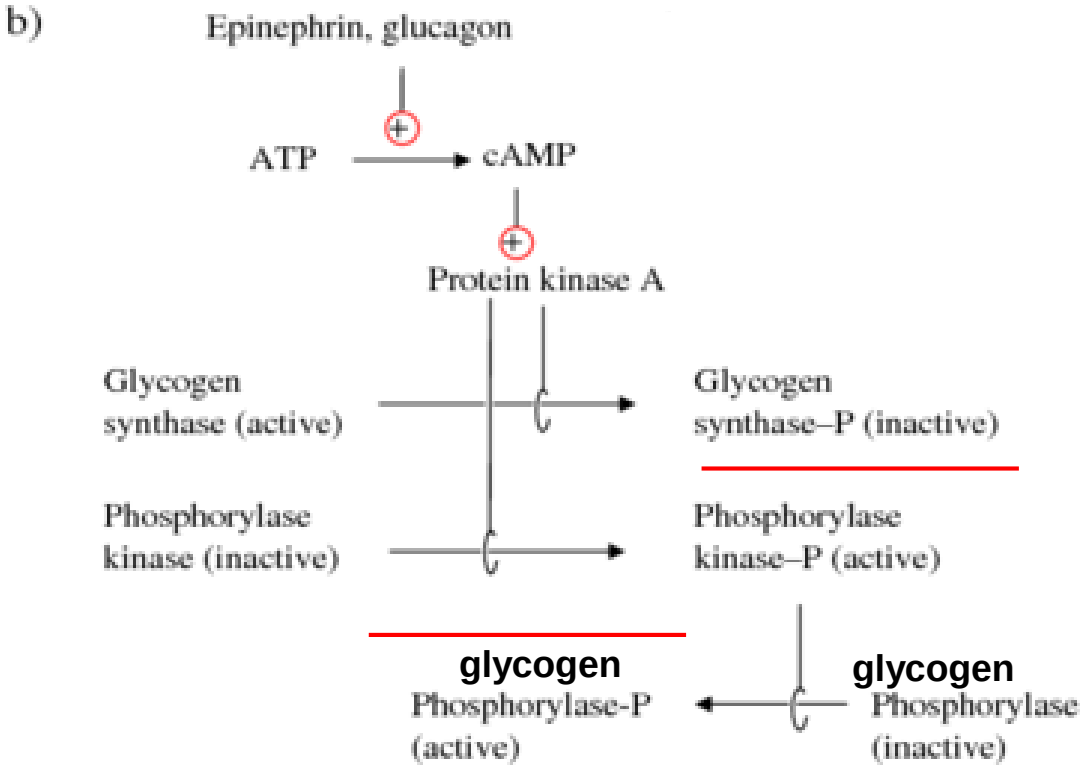
Further glucose residues may be added to the new branch by glycogen synthase.

The biological effect of branching is to make the glycogen molecule more soluble and to increase the number of nonreducing ends.

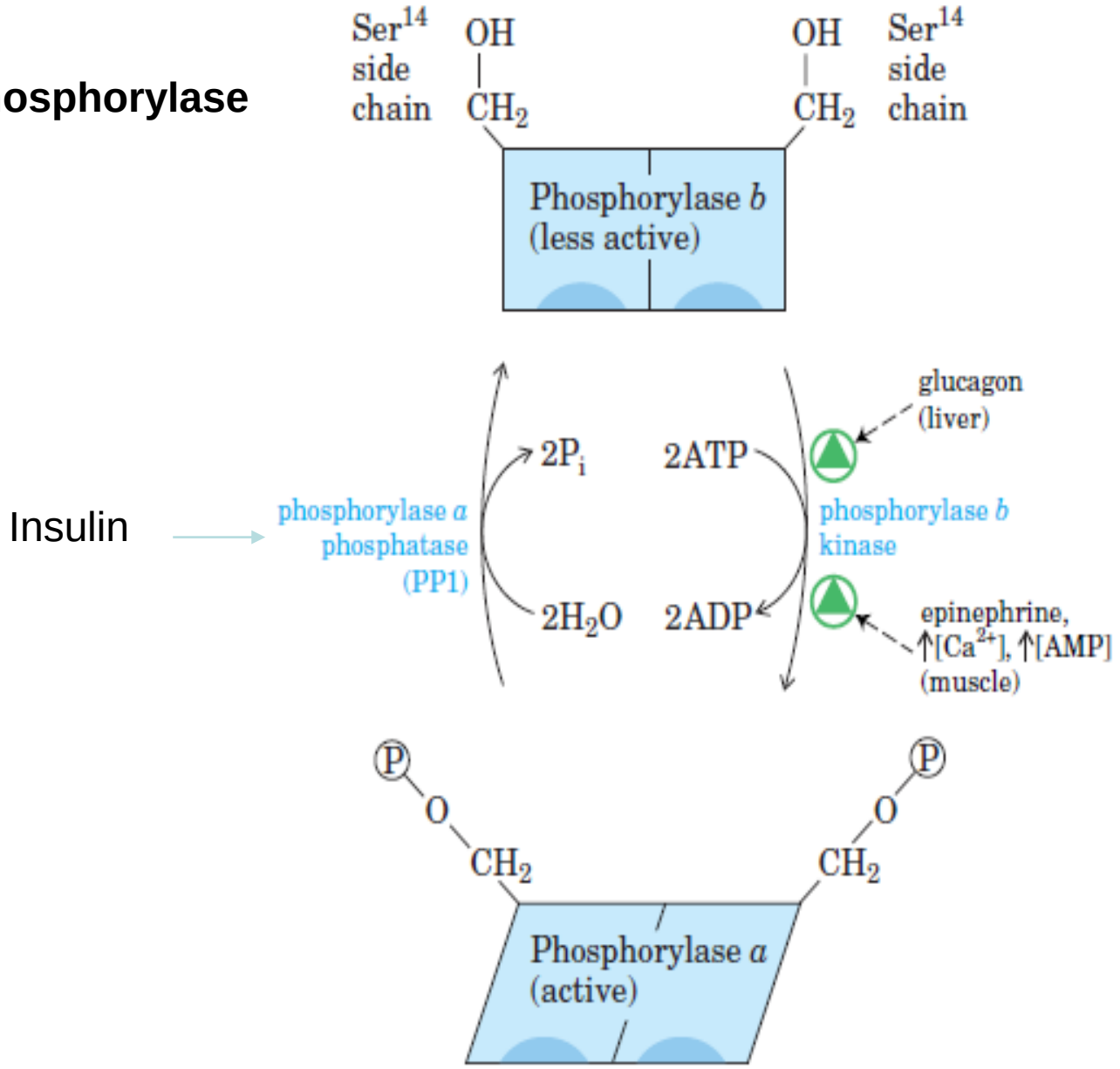
This increases the number of sites accessible to glycogen phosphorylase and glycogen synthase, both of which act only at nonreducing ends.

Regulation


a)
Glycogen
Glc-6-P
ATP
AMP
glycogen synthase
phosphorylase
UDP-glucose
Glucose-1-P


b)
Epinephrin, glucagon
ATP
cAMP
Protein kinase A
Glycogen synthase (active)
Glycogen synthase–P (inactive)
Phosphorylase kinase (inactive)
Phosphorylase kinase–P (active)
glycogen Phosphorylase-P (active)
glycogen Phosphorylase (inactive)

Glycogen phosphorylase



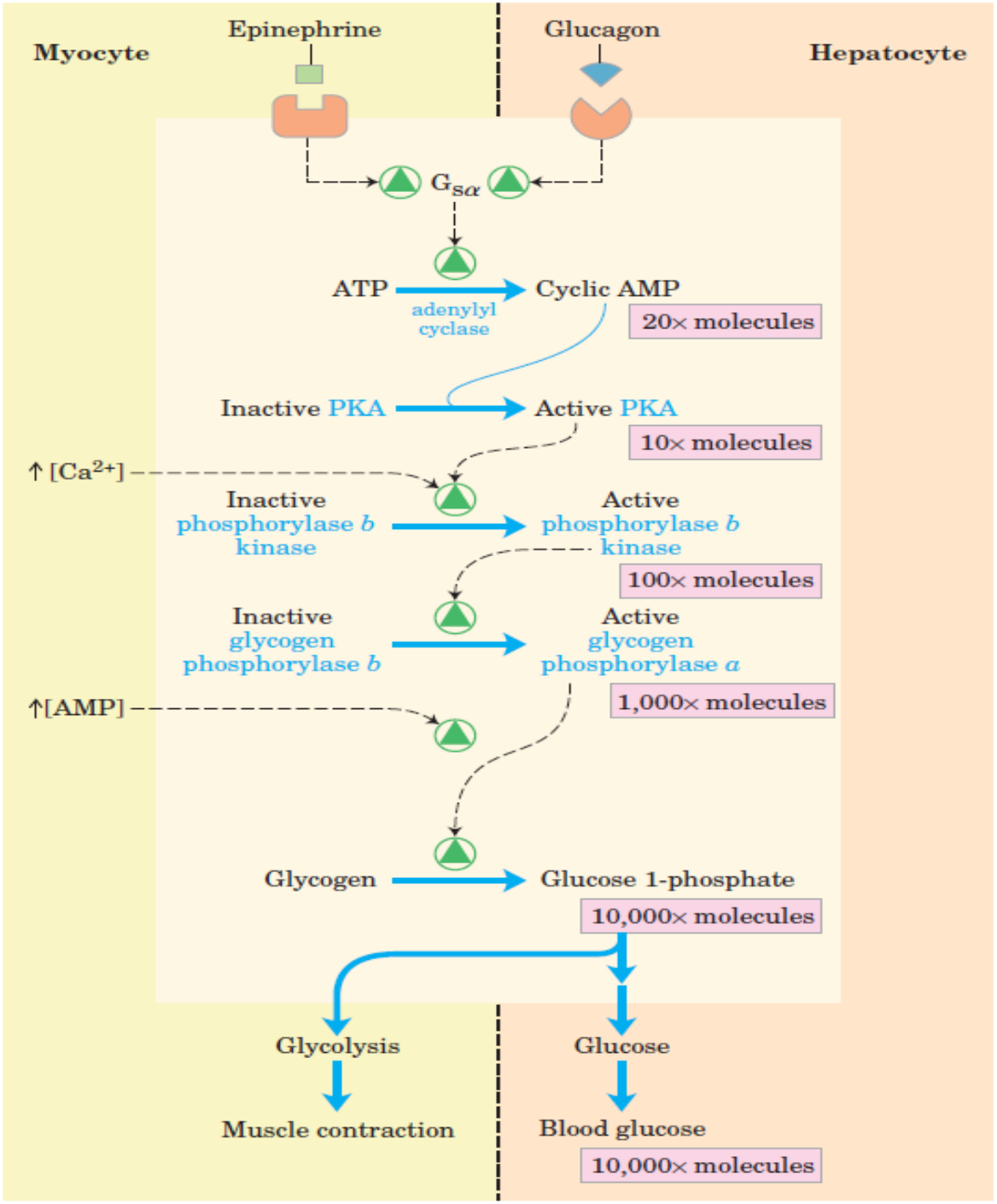
Regulation

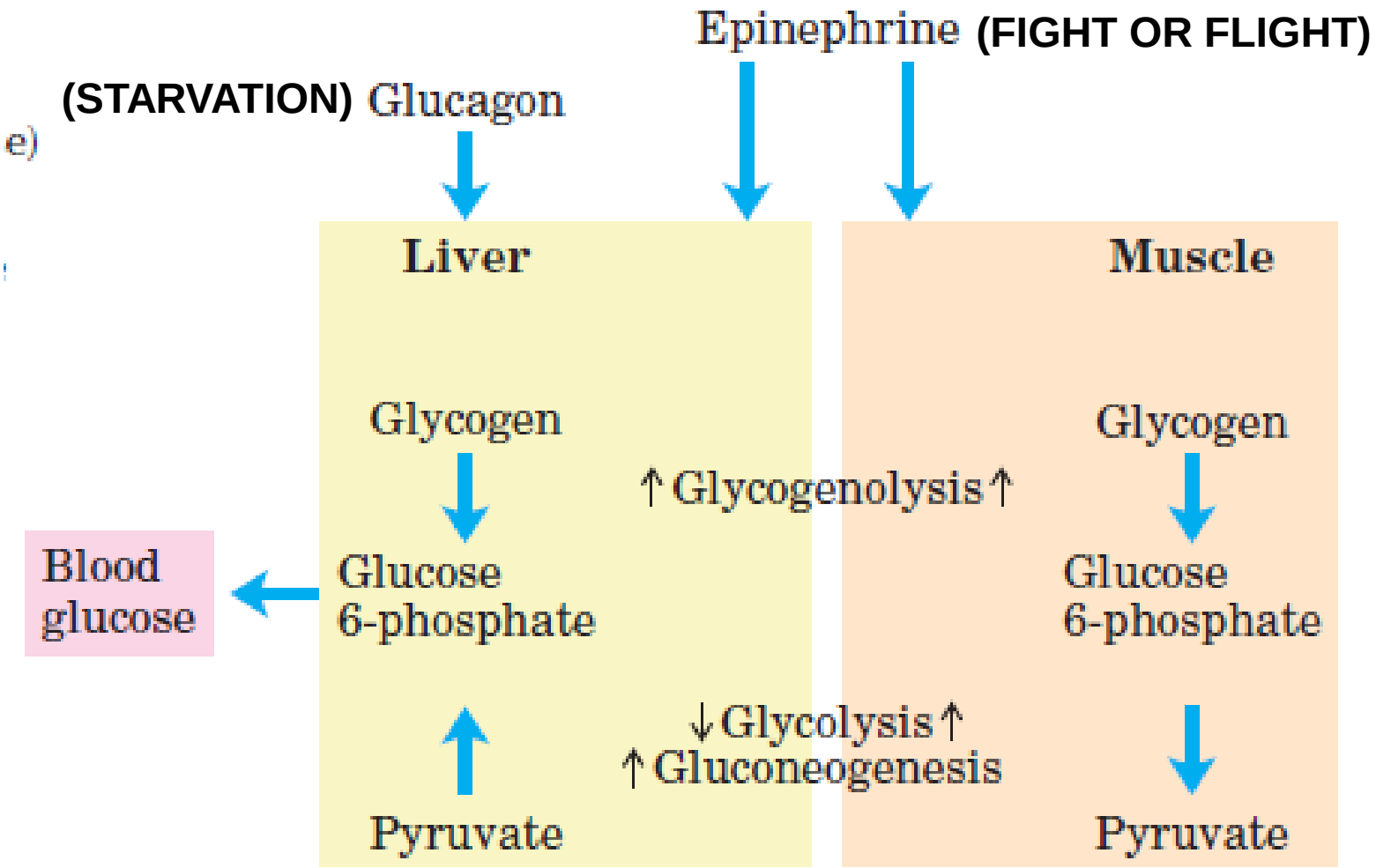
The allosteric regulatory **effects by ATP, AMP and glucose-6-phosphate (Figure a) make sense:**

Depletion of ATP would be an excellent reason to regenerate it by tapping into the glucose store. On the other hand, glucose-6-phosphate will be plentiful exactly when glucose itself is abundant, so it should promote glycogen synthesis rather than breakdown

Hormonal control (Figure b) : **Protein kinase A decreases glycogen synthesis via direct phosphorylation of glycogen synthase. Glycogen breakdown is stimulated by phosphorylation of a dedicated phosphorylase kinase ,which then in turn phosphorylates glycogen phosphorylase. Note that glycogen synthase and phosphorylase respond in opposite ways to phosphorylation: The first one is inactivated, the second activated .**

Signal cascade by which Glycogen Phosphorylase is activated

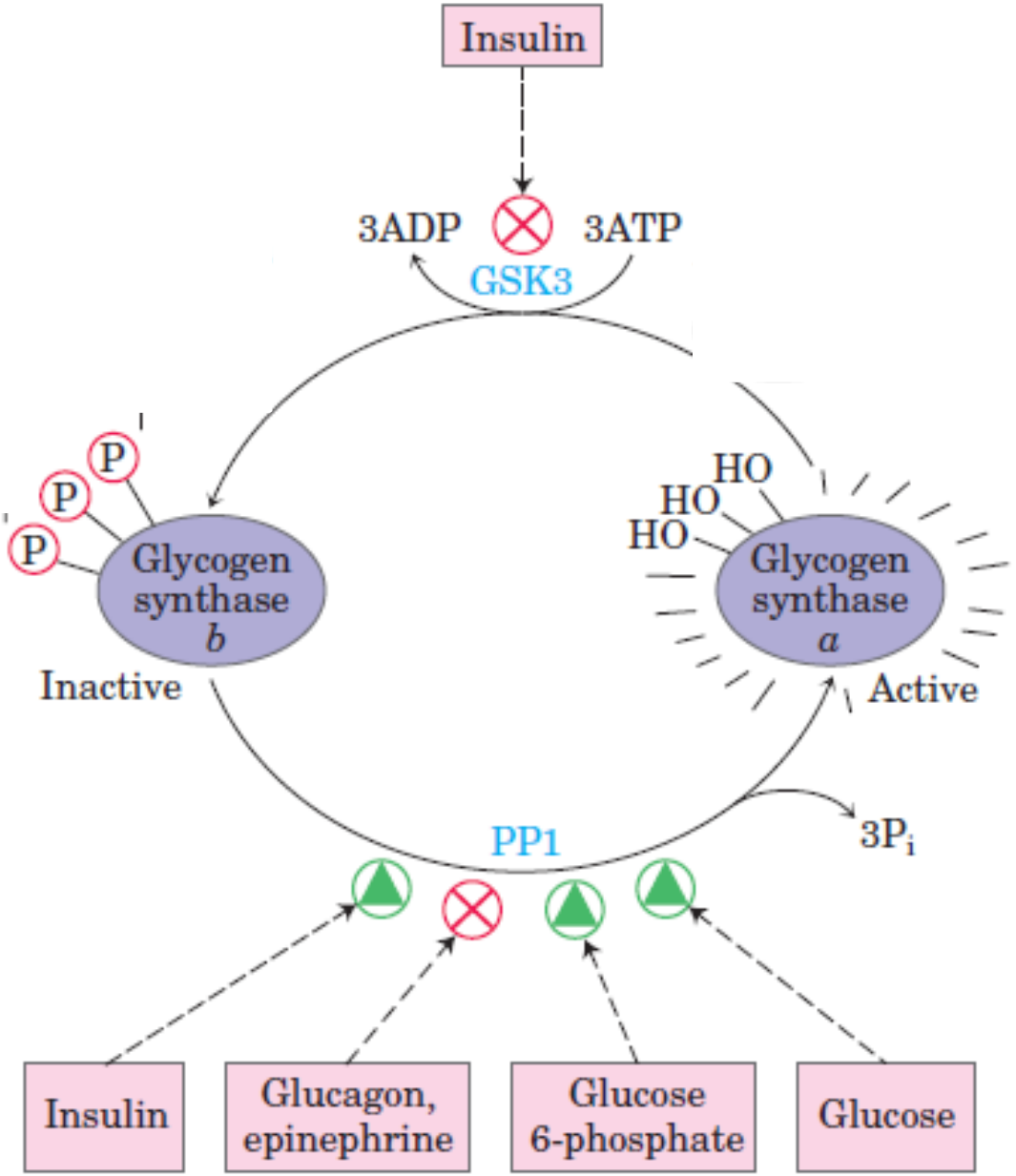



Epinephrine (FIGHT OR FLIGHT)
(STARVATION) Glucagon
e)
Liver
Muscle
Glycogen
Glycogen
↑ Glycogenolysis ↑
Blood glucose
Glucose 6-phosphate
Glucose 6-phosphate
↓ Glycolysis ↑
↑ Gluconeogenesis
Pyruvate
Pyruvate

Comparison of Glycogen Phosphorylase in Liver and Muscle

Glycogen Phosphorylase	Liver	Skeletal Muscle
Activated by	Epinephrine Glucagon	Epinephrine AMP Ca++
Inhibited by	Insulin Glucose	Insulin ATP

Insulin triggers activation of Glycogen synthase

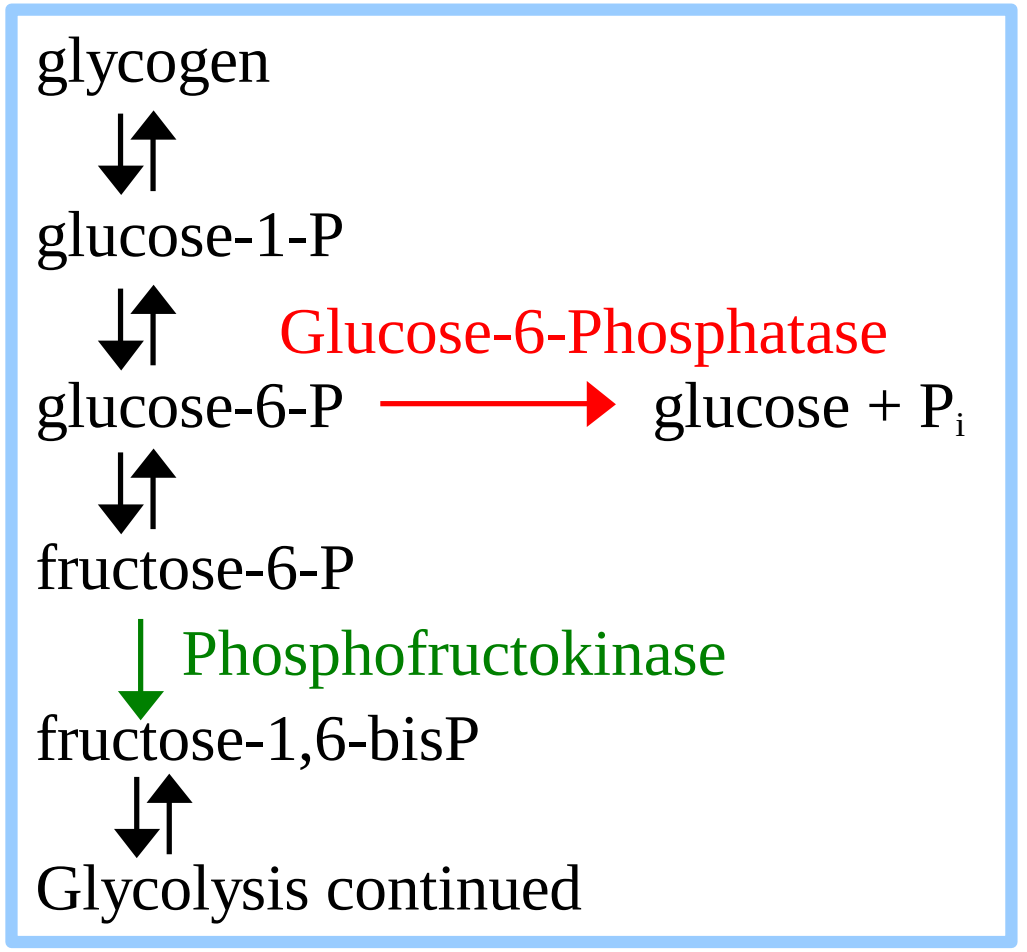


Glycogen Storage Diseases

Dr. Suheir Ereqat

Glycogen Storage Diseases are genetic enzyme deficiencies associated with **excessive glycogen accumulation** within cells.

Some enzymes whose deficiency leads to glycogen accumulation are part of the inter-connected pathways shown here.



Type	Deficient Enzyme	Clinical Features	organ
I: von Gierke's	Glu-6-pase (also gluconeogenic)	**Severe** hypoglycemia, hepatomegaly, kidney failure	liver
II: Pompe's	Lysosomal a -1,4 glucosidase (acid maltase)	Cardiomegaly, muscle weakness, death by 2 year due to heart failure and respiratory weakness.	skeletal muscles, heart
III: Cori,s	Debranching enzyme	**Mild** hypoglycemia, Liver enlargement, myopathy	Liver, Muscles
IV: Anderson's	Branching Enzyme	Cirrhosis, death by 2 year	Liver, muscles
V: McArdle's	Muscle glycogen phosporylase	Muscle cramp and weakness on exercise	muscles myoglobin in urine
VI :Her's	Hepatic glycogen phosporylase	**Mild** hypoglycemia, hepatomegaly - cirrhosis	liver
VII: Tarui's	PFK1- muscles	Inability to exercise Hemolytic anemia	RBC; myoglobin in urine