Metabolism of Carbohydrates:

GLYCOGEN METABOILISM

Dr. Shoaib Ahmad Malik

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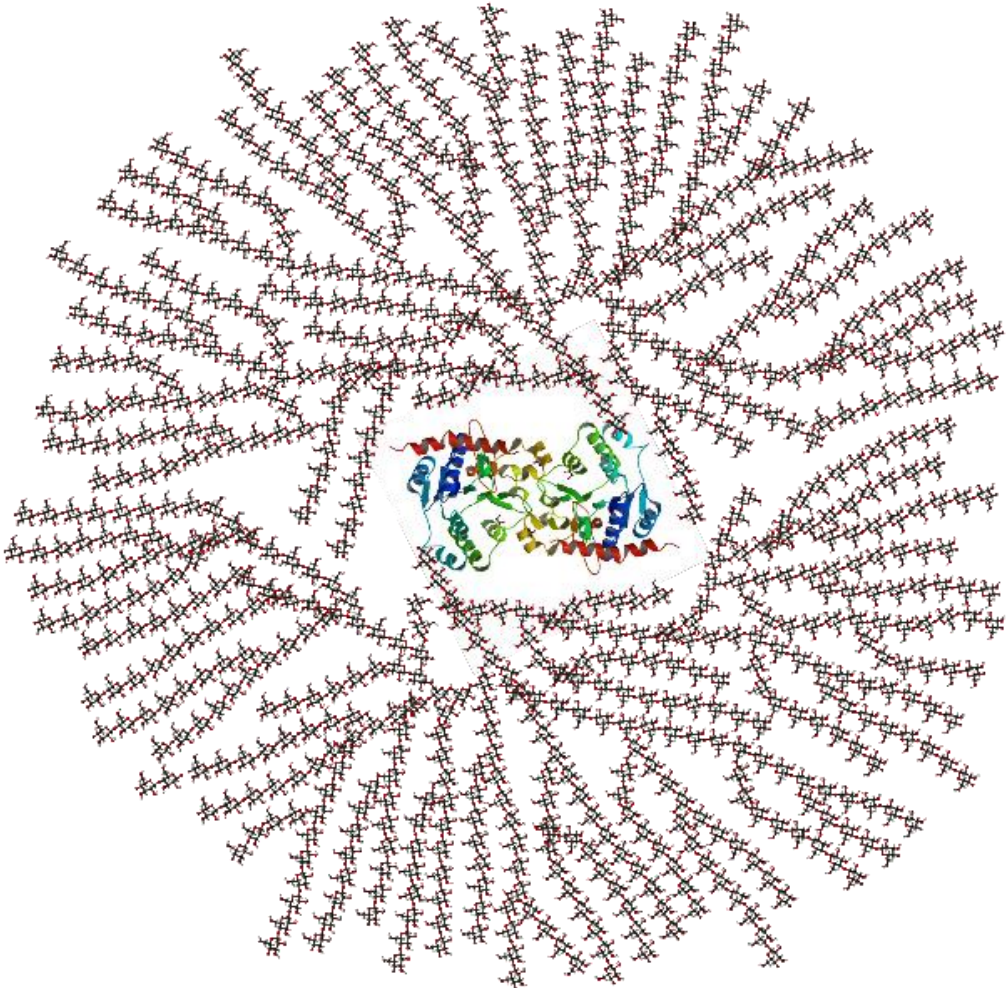
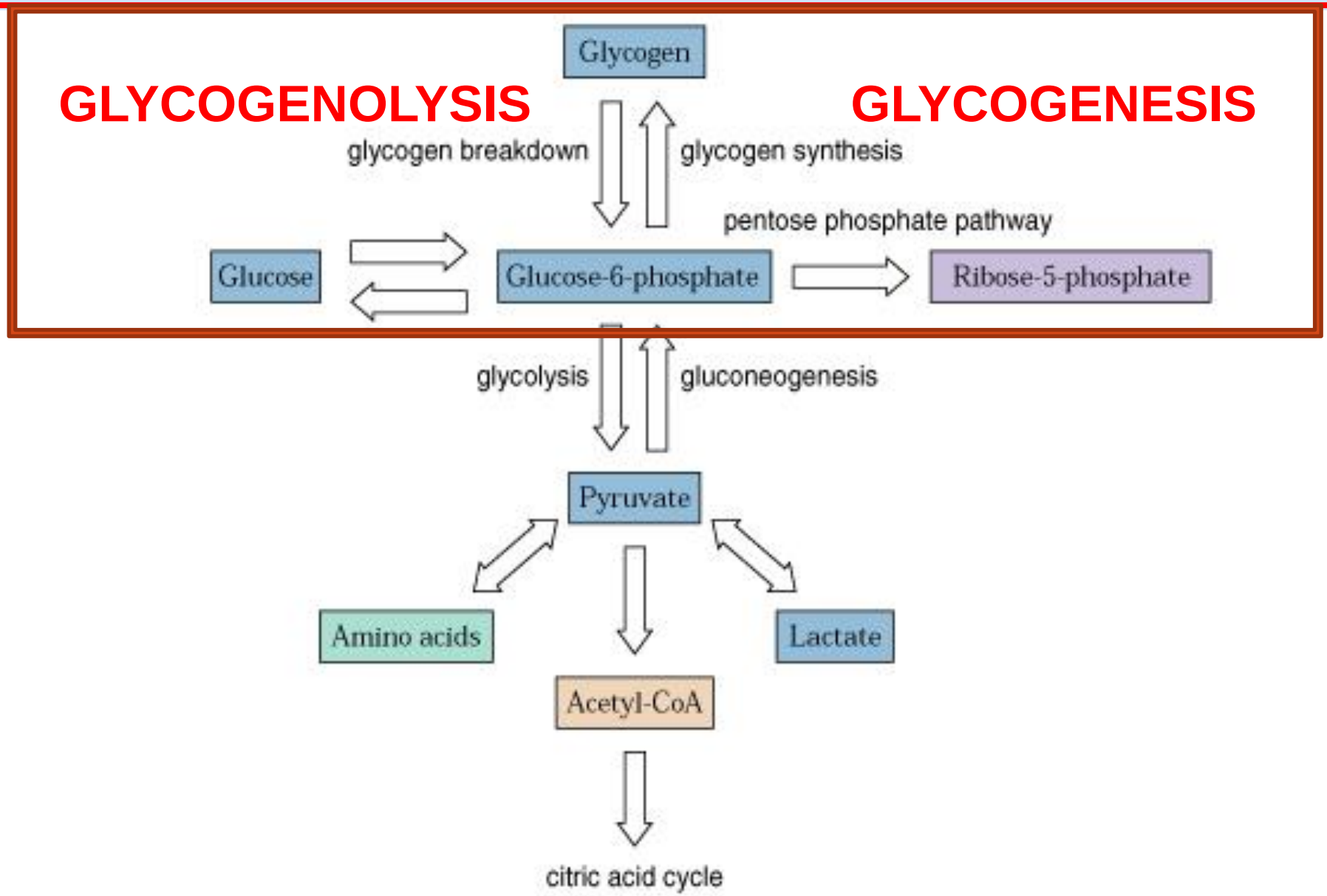


Objectives:

- Describe the structure of glycogen and its roles in the liver and muscle, with functional importance of branching.
- Know the Substrates for glycogen synthesis
- Outline the steps in the synthesis of glycogen, including the key enzymes (glycogen Synthase), and the requirement for a primer and the roles of UDP-glucose.
- Outline the steps in glycogen breakdown, including the roles of glycogen phosphorylase enzyme, glycogen debranching enzyme, Glucose-6-phasphrase enzyme
- Learn the regulation of glycogen metabolism:
  - Interactions with allosteric effectors and reversible covalent modifications;
  - Compare the effects of different hormones in liver and muscle;
  - Explain the roles of cAMP and PKA in these processes.

Overview of Glucose Metabolism



- ✓ Glycogen is the major storage carbohydrate in animals.
- ✓ Occurs mainly in liver and muscle, with modest amounts in the brain.
- ✓ Glycogen is a branched-chain homo-polysaccharide made exclusively from α-glucose
- ✓ The primary glycosidic bond is an α(1→4) linkage.
- ✓ After an av. of 8-10 glucosyl residues, there is a branch containing an α(1→6) linkage.
- ✓ A single glycogen molecule can contain up to 30,000 to 60,000 glucose residue.
- ✓ These molecules exist in discrete cytoplasmic granules that contain most of the enzymes necessary for glycogen synthesis & degradation

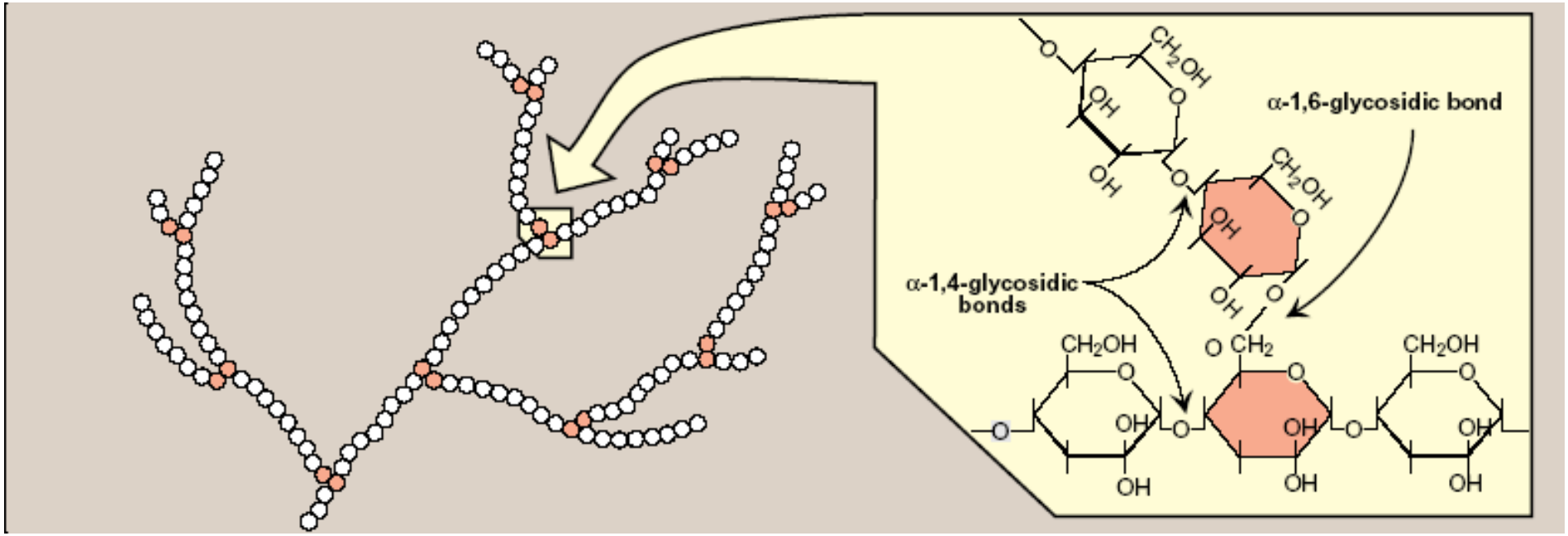
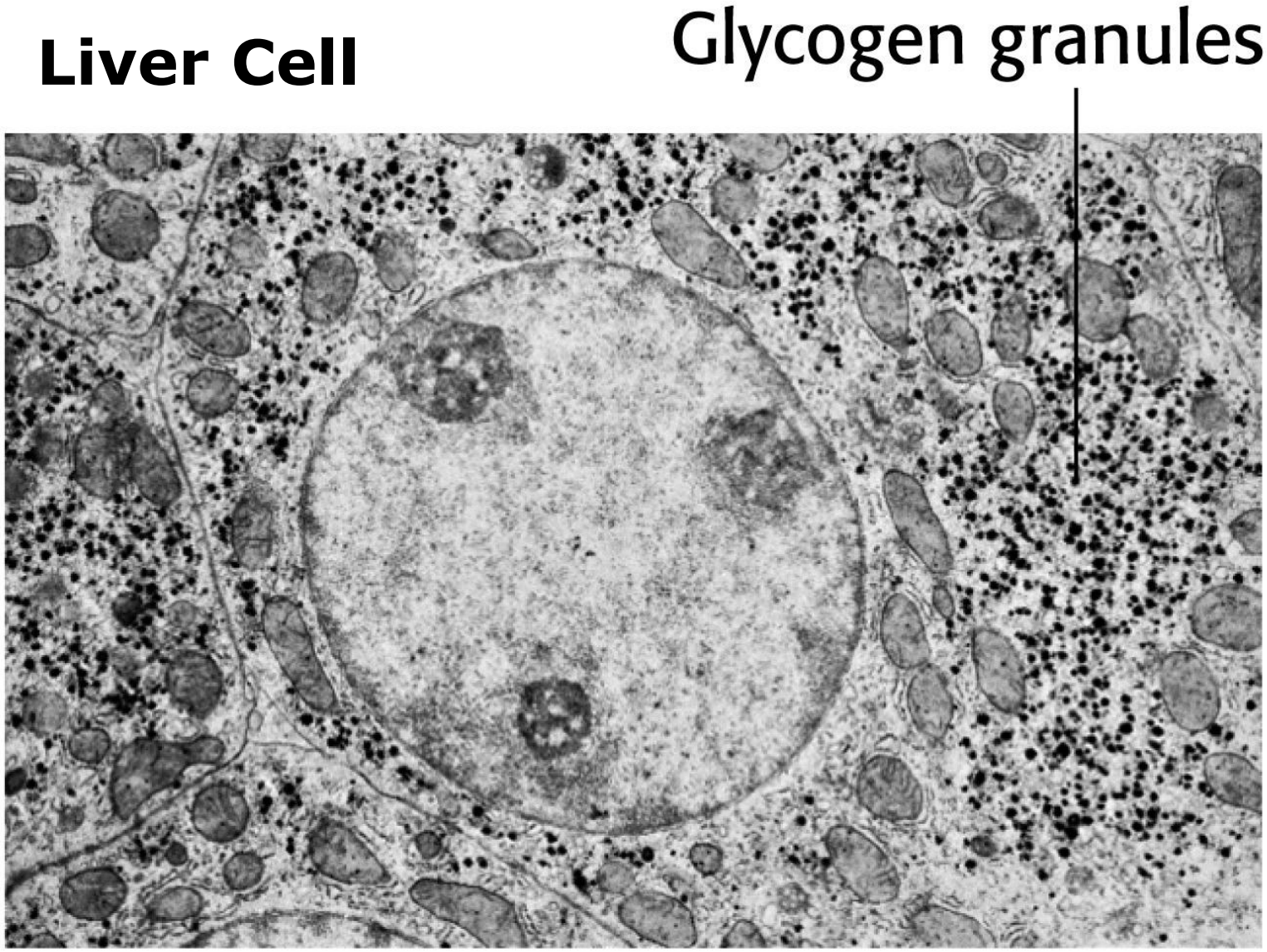


Figure 11.3. Branched structure of glycogen, showing a-1,4 and a-1,6 linkages.

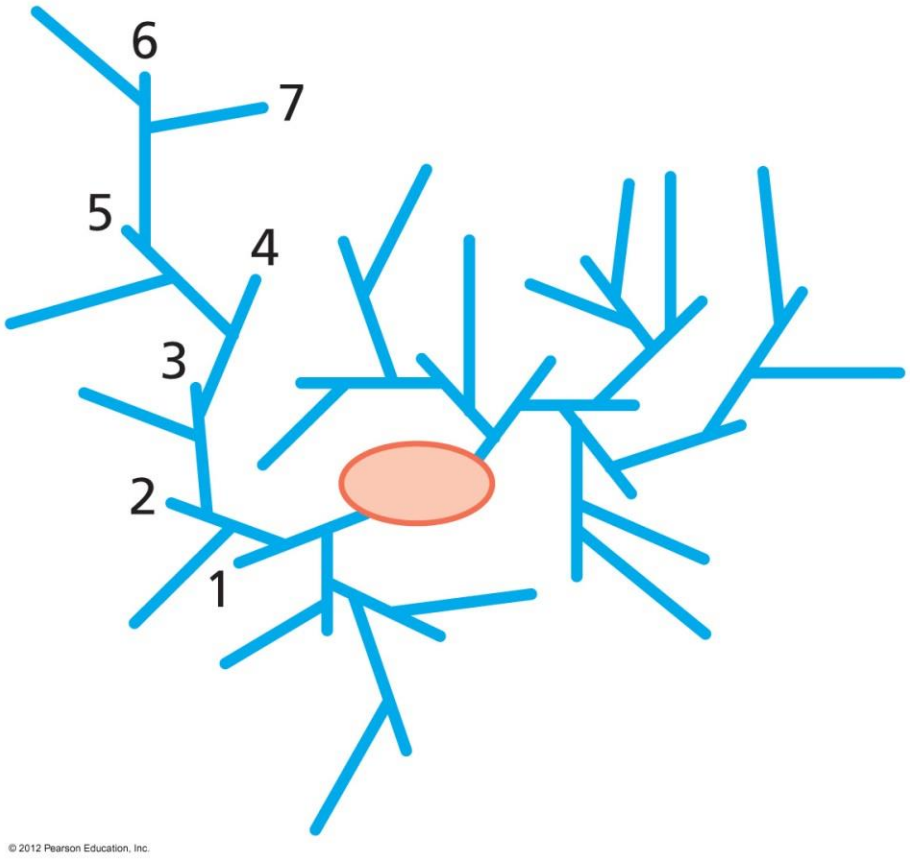
Liver Cell

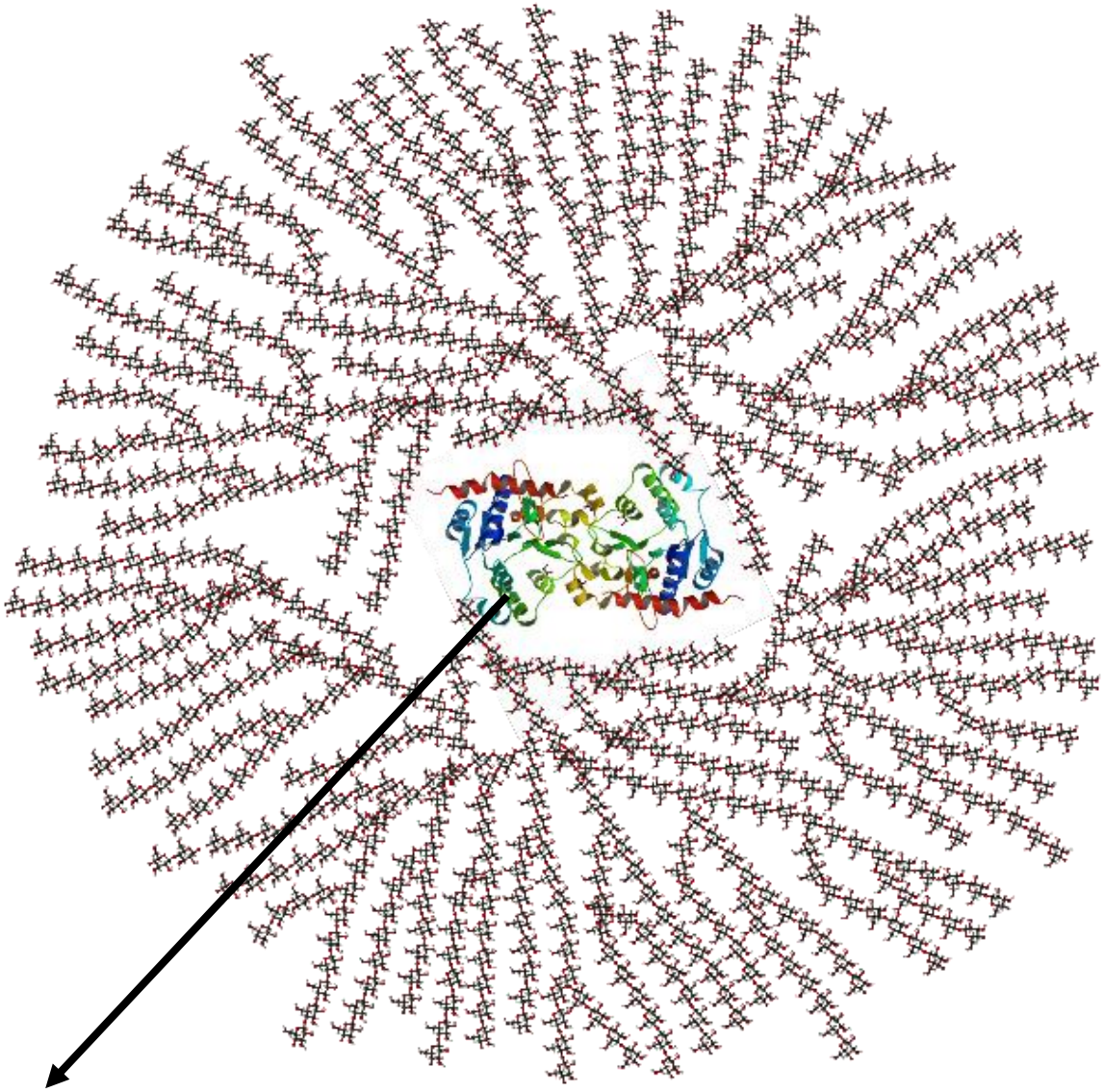


Glucose is stored as glycogen predominantly in liver & muscle cells.

Glycogen

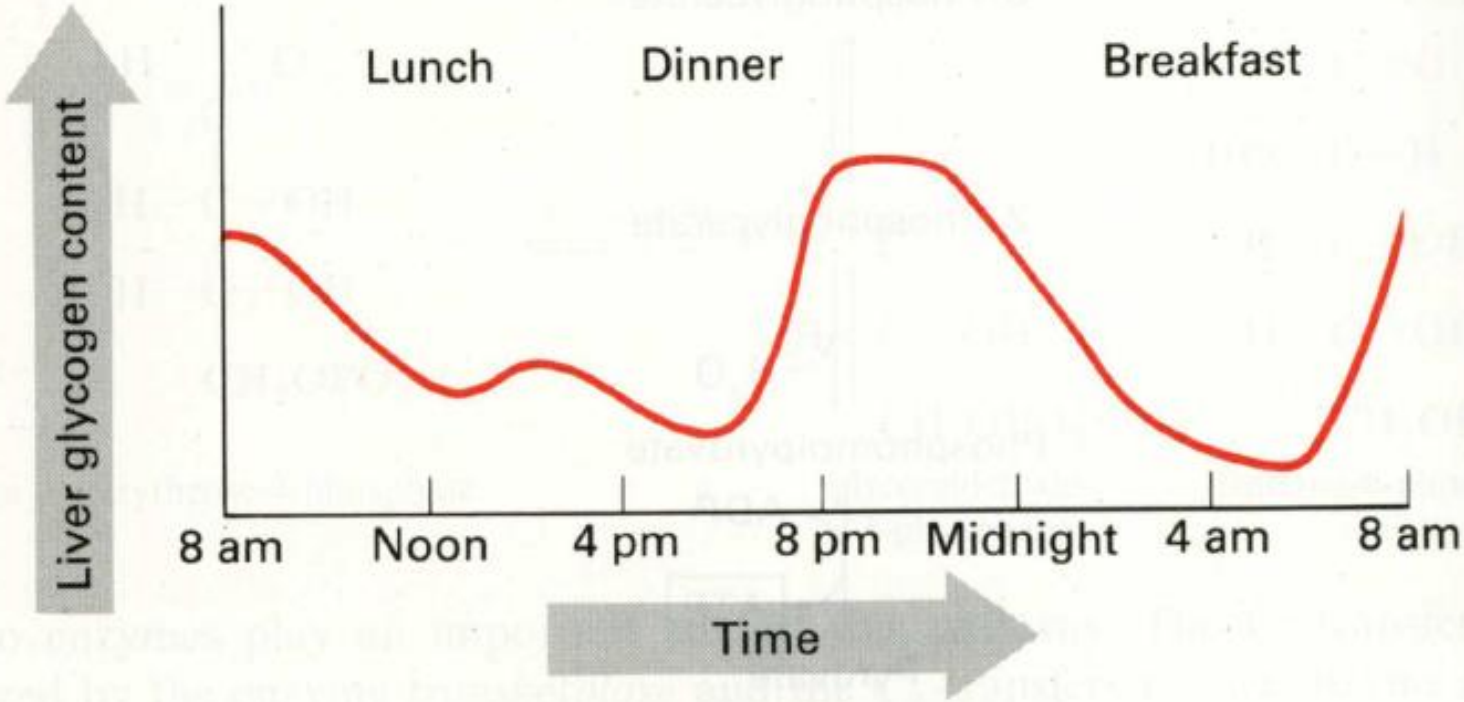
- Storage molecule
- Primer (glycogenin) necessary for synthesis
- Multiple ends allow for quick synthesis and degradation





Glycogenin is a protein/enzyme that lies in the center and acts as a primer in glycogen synthesis

FIGURE 29–10 Variation of liver glycogen levels between meals.



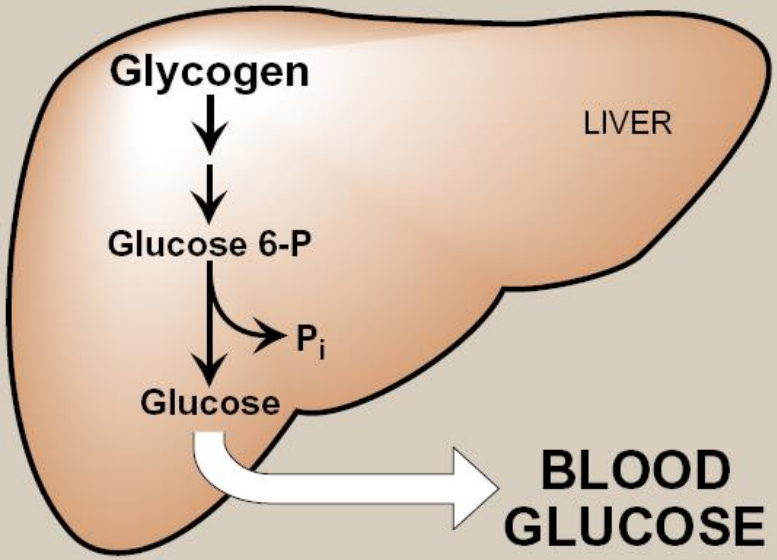
Functions of Glycogen

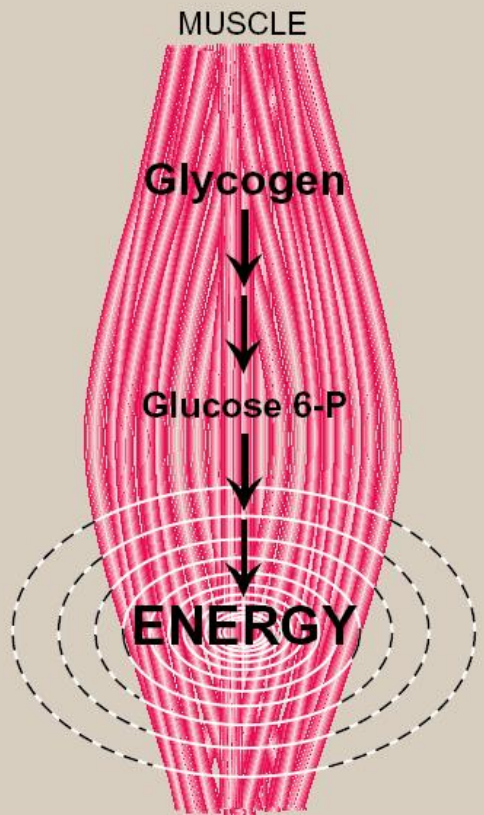
- In liver – The synthesis and breakdown of glycogen is regulated to maintain blood glucose levels.
- In muscle - The synthesis and breakdown of glycogen is regulated to meet the energy requirements of the muscle cell.

Remember!

•Liver contains Glu 6-phosphatase.

•Muscle does not have this enzyme.





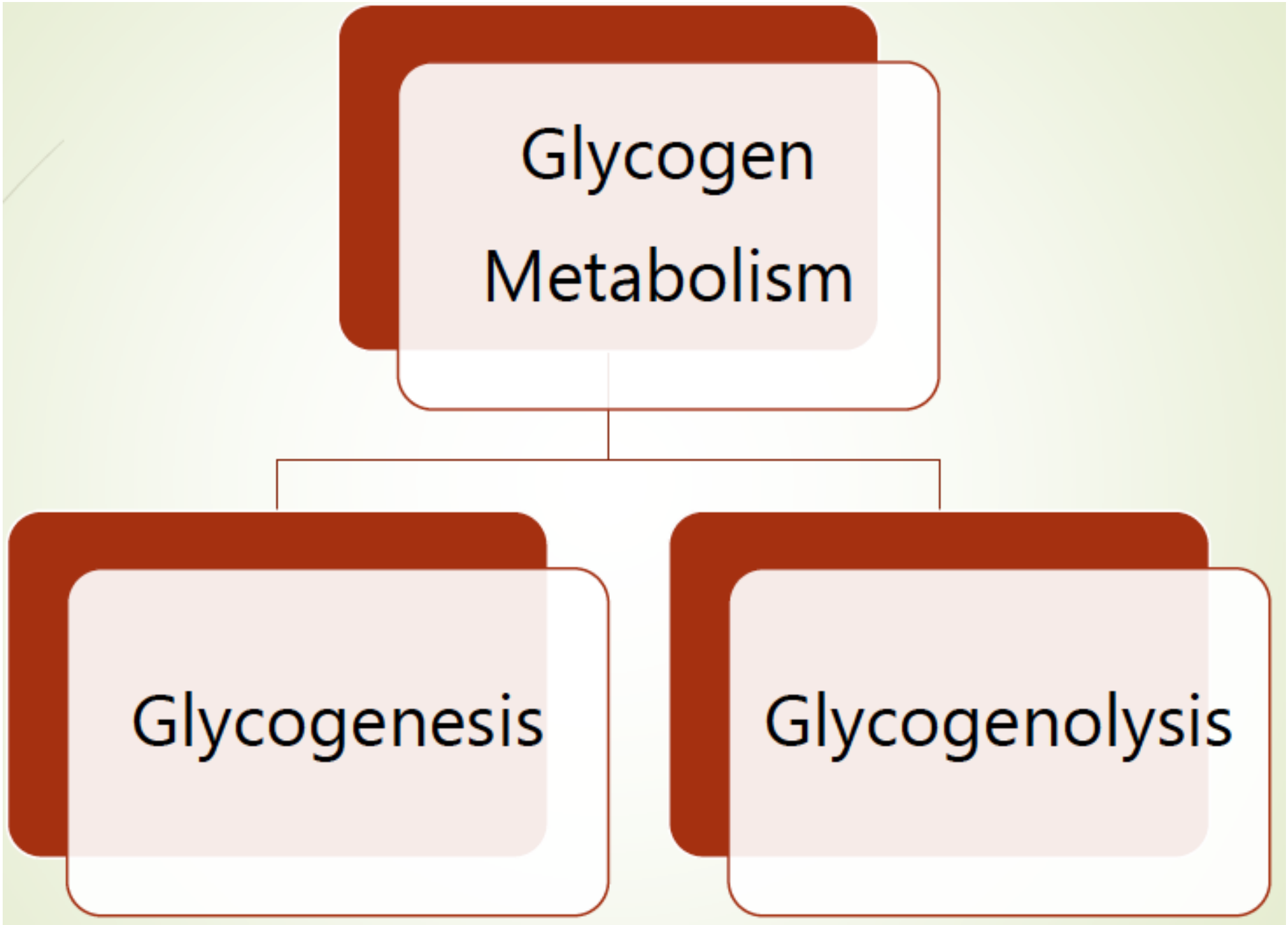
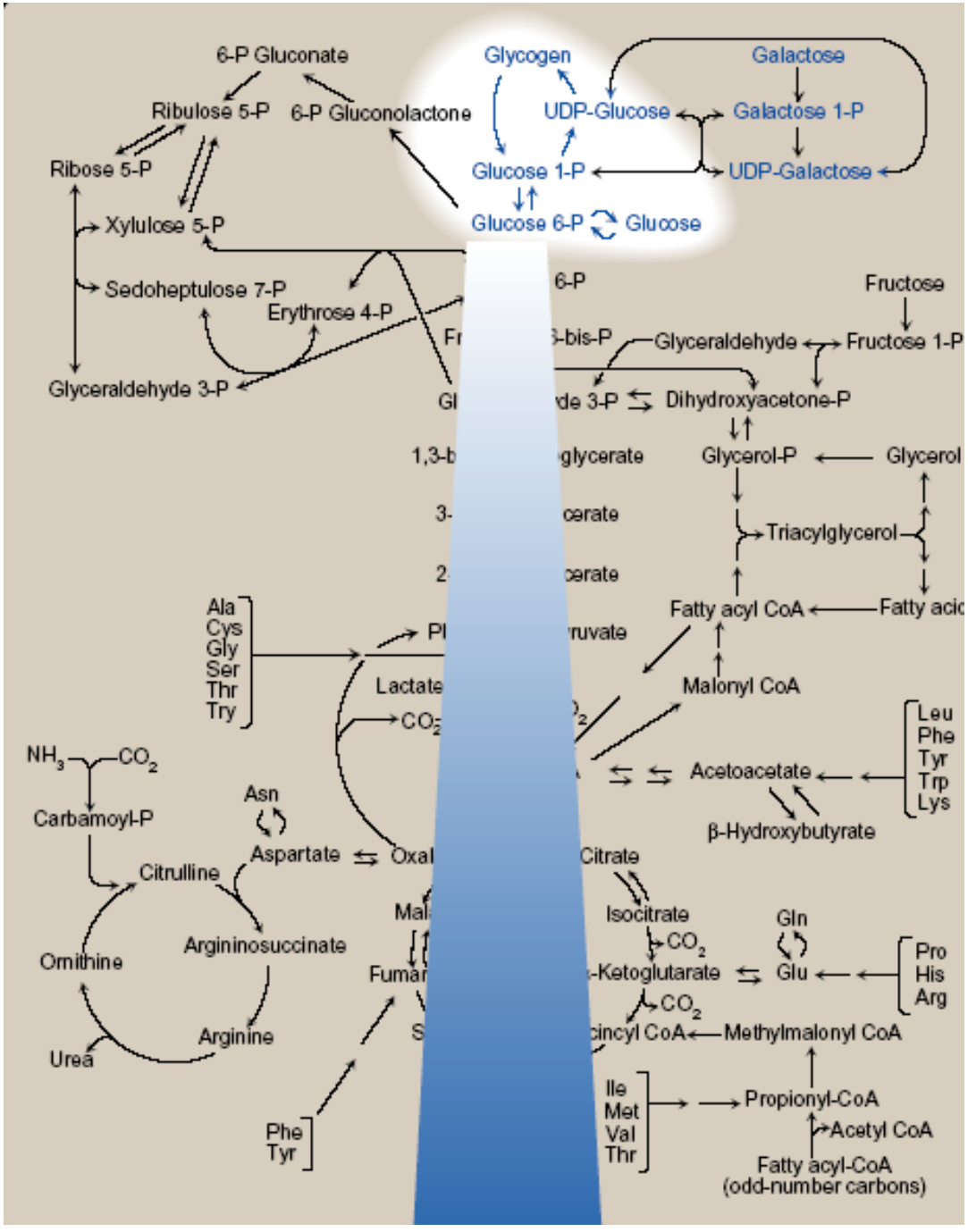

Glycogen Metabolism
Glycogenesis
Glycogenolysis

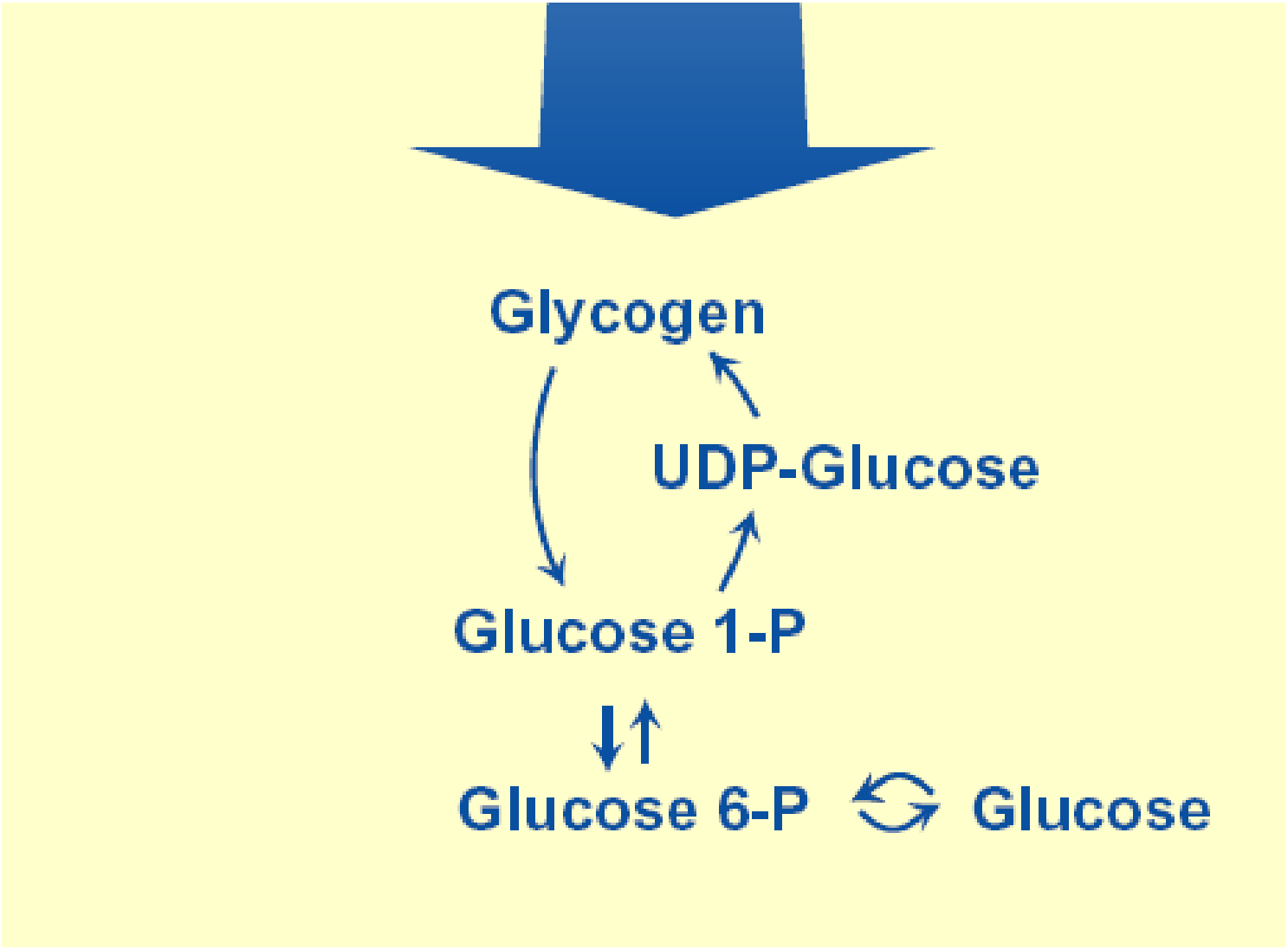
TABLE 21.1 Glycogen-storage diseases

Type	Defective enzyme	Organ affected	Glycogen in the affected organ	Clinical features
I Von Gierke disease	Glucose 6-phosphatase or transport system	Liver and kidney	Increased amount; normal structure.	Massive enlargement of the liver. Failure to thrive. Severe hypoglycemia, ketosis, hyperuricemia, hyperlipemia.
II Pompe disease	α-1,4-Glucosidase (lysosomal)	All organs	Massive increase in amount; normal structure.	Cardiorespiratory failure causes death, usually before age 2.
III Cori disease	Amylo-1,6-glucosidase (debranching enzyme)	Muscle and liver	Increased amount; short outer branches.	Like type I, but milder course.
IV Andersen disease	Branching enzyme (α-1,4 → α-1,6)	Liver and [illegible]	Normal amount; very long outer branches	Progressive cirrhosis of the liver. Liver failure causes death usually before age 2.
V McArdle disease	Phosphorylase	Muscle	Moderately increased amount; normal structure.	Limited ability to perform strenuous exercise because of painful muscle cramps. Otherwise patient is normal and well developed.
VI Hers disease	Phosphorylase	Liver	Increased amount.	Like type I, but milder course.
VII	Phosphofructokinase	Muscle	Increased amount; normal structure.	Like type V.
VIII	Phosphorylase kinase	Liver	Increased amount; normal structure.	Mild liver enlargement. Mild hypoglycemia.

Note: Types I through VII are inherited as autosomal recessives. Type VIII is sex linked.

GLYCOGEN STORAGE DISEASES


6-P Gluconate
Ribulose 5-P
6-P Gluconolactone
Ribose 5-P
Xylulose 5-P
Sedoheptulose 7-P
Erythrose 4-P
Glyceraldehyde 3-P
Glycogen
UDP-Glucose
Glucose 1-P
Glucose 6-P
Glucose
Galactose
Galactose 1-P
UDP-Galactose
Fructose
Fructose 1-P
Glyceraldehyde
Dihydroxyacetone-P
Glycerol-P
Glycerol
Triacylglycerol
Fatty acyl CoA
Fatty acid
Malonyl CoA
Ala
Cys
Gly
Ser
Thr
Try
Lactate
Leu
Phe
Tyr
Trp
Lys
Acetoacetate
β-Hydroxybutyrate
NH3
CO2
Carbamoyl-P
Asn
Aspartate
Citrulline
Argininosuccinate
Ornithine
Arginine
Urea
Citrate
Isocitrate
Gln
Glu
Pro
His
Arg
Methylmalonyl CoA
Ile
Met
Val
Thr
Propionyl-CoA
Acetyl CoA
Fatty acyl-CoA
(odd-number carbons)
Phe
Tyr



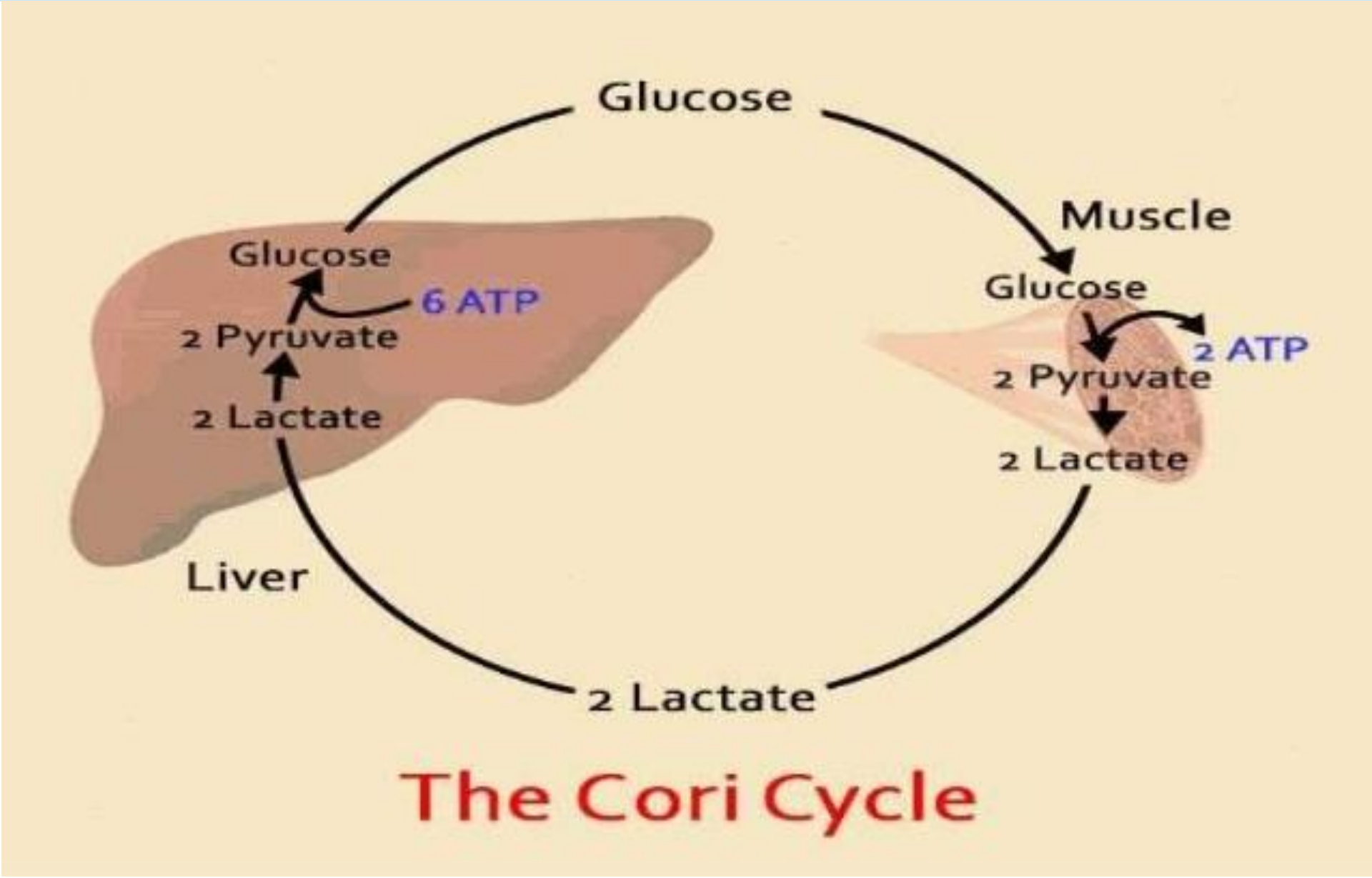
Glycogen synthesis and degradation shown as a part of the essential reactions of energy metabolism

Glycogenesis

- Glycogenesis is the process of glycogen synthesis, in which glucose molecules are added to chains of glycogen for storage.

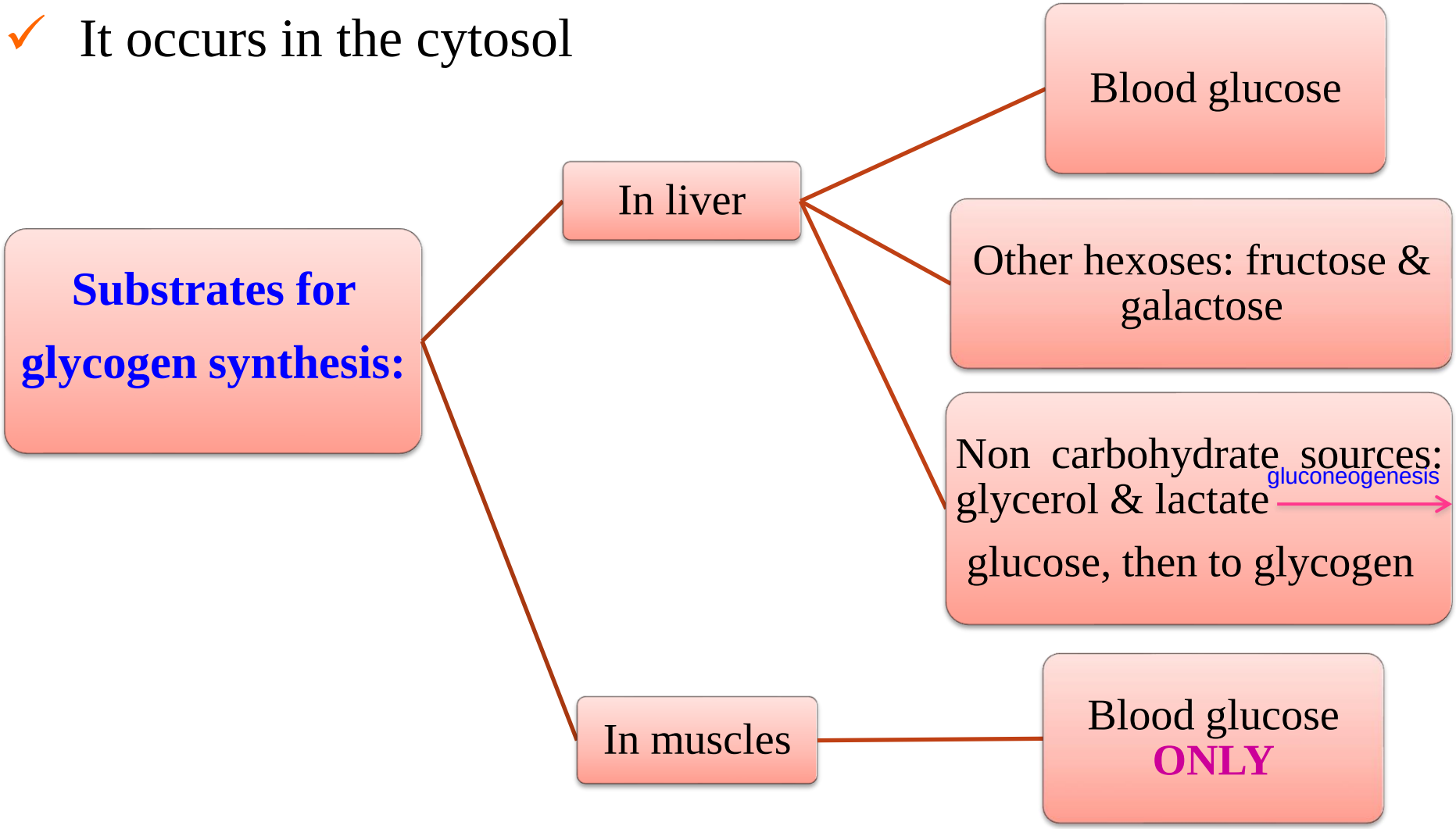
- This process is activated during rest periods in well-fed state (also following the Cori cycle!!!)

Cori Cycle


Glucose
Muscle
Glucose
2 ATP
2 Pyruvate
2 Lactate
Glucose
6 ATP
2 Pyruvate
2 Lactate
Liver
2 Lactate
The Cori Cycle

GLYCOGENESIS:

- ✓ Glycogenesis is the formation of glycogen in liver and muscles
- ✓ It occurs in the cytosol



Phases of Glycogenesis

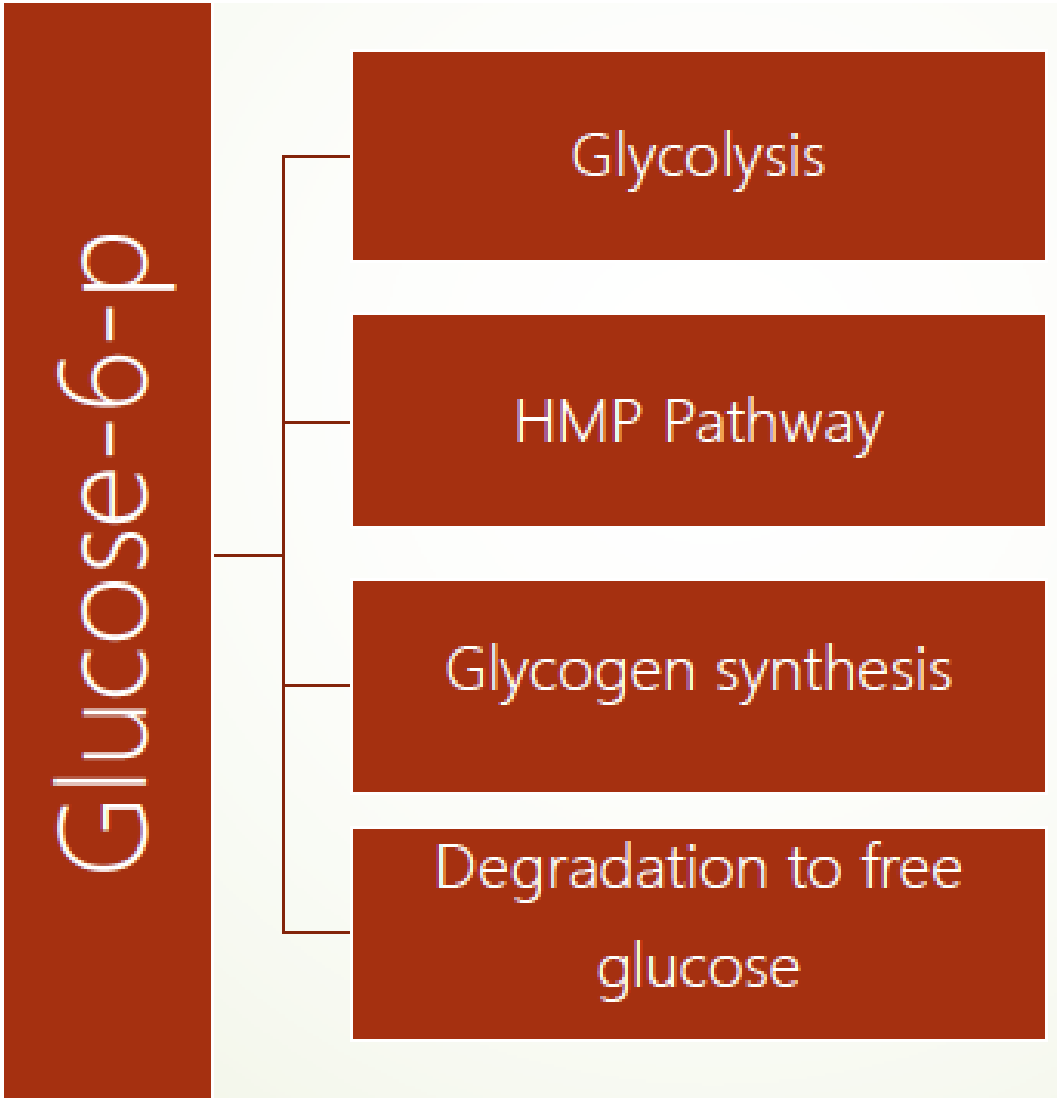
Steps of Glucose Activation

Step-1- Phosphorylation of Glucose

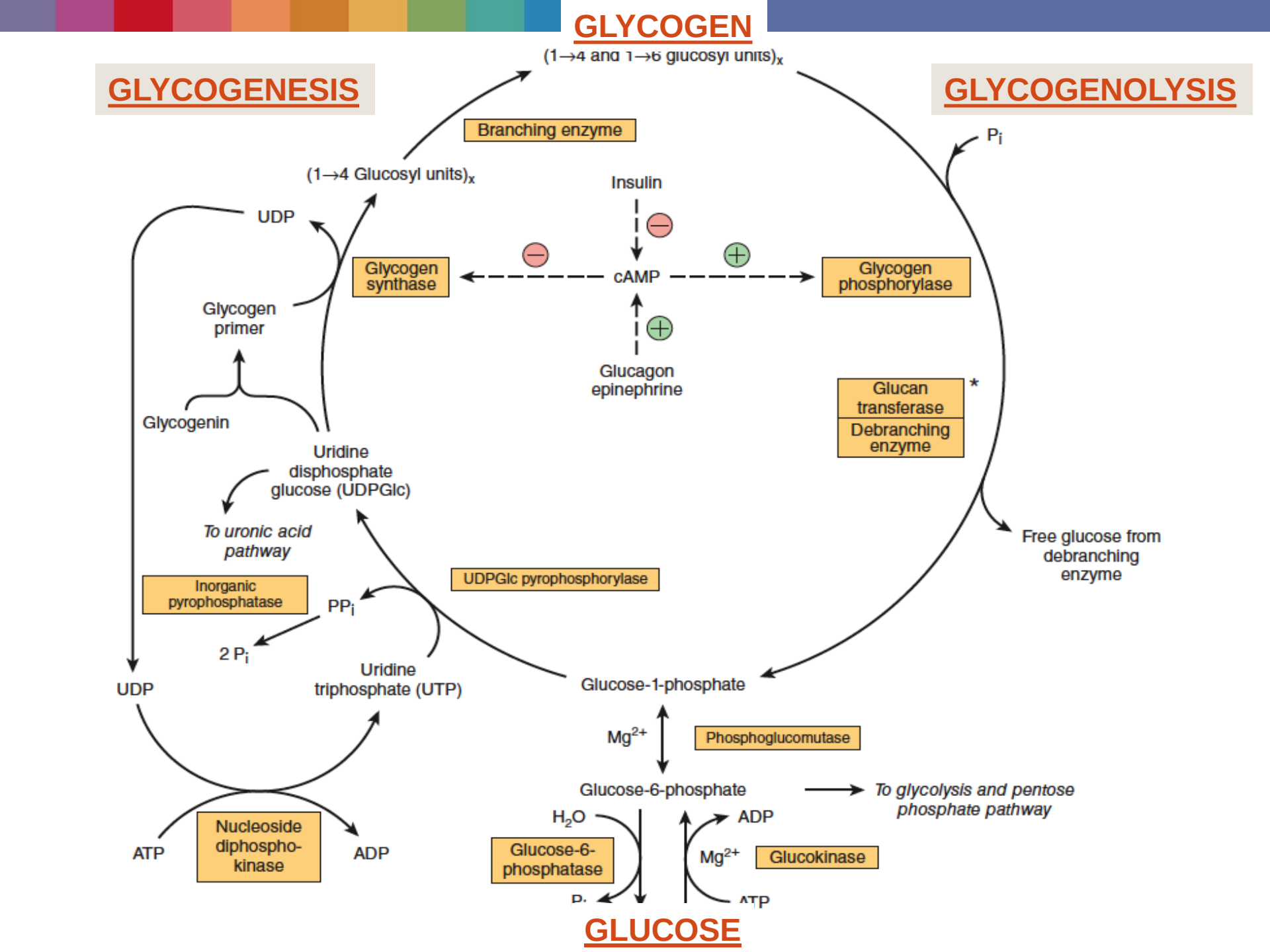
Step-2- Conversion of Glucose-6-P to Glucose-1-P

Step-3- Conversion of Glucose-1-P to UDP-Glucose

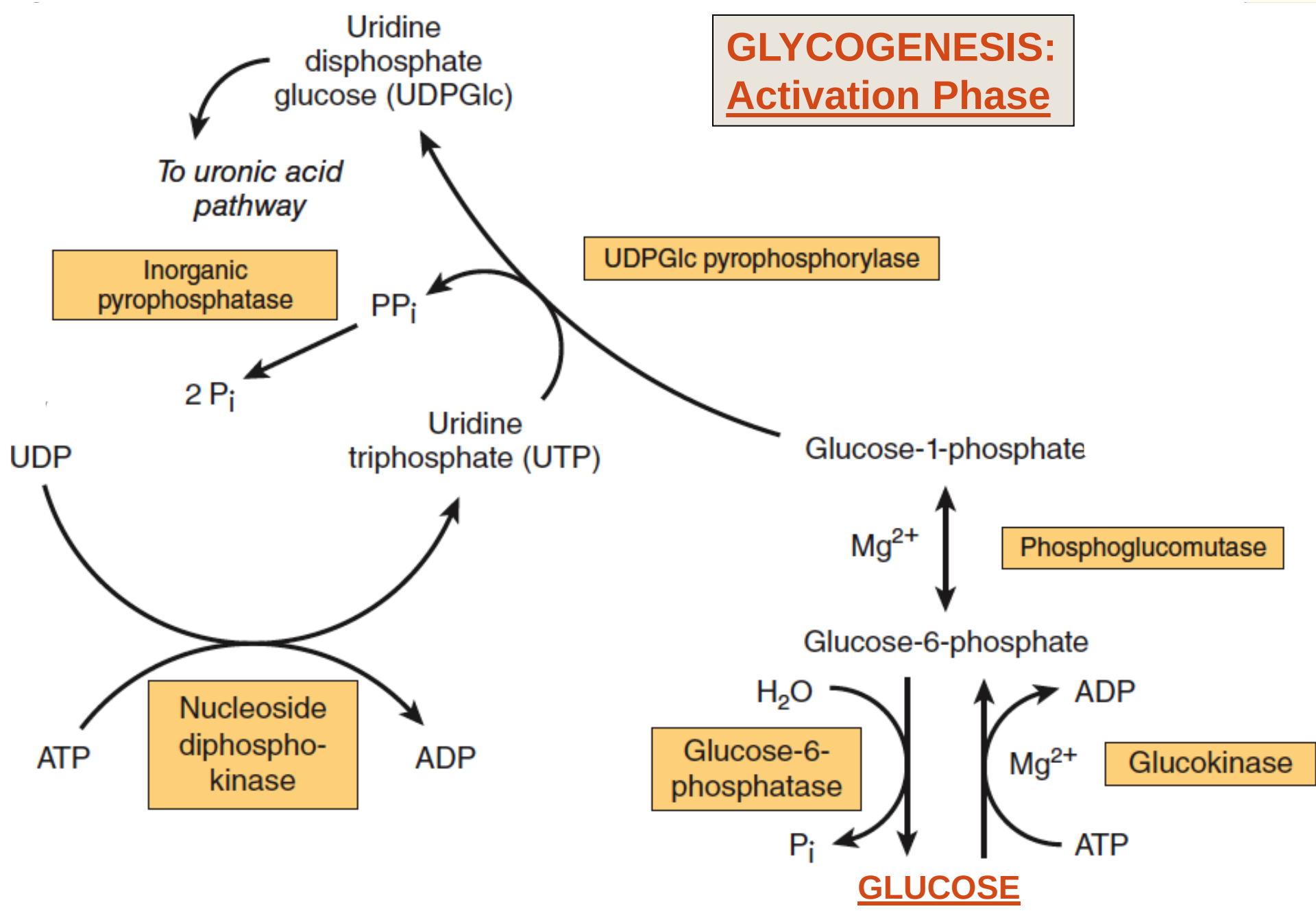
Fate of Glucose-6-P



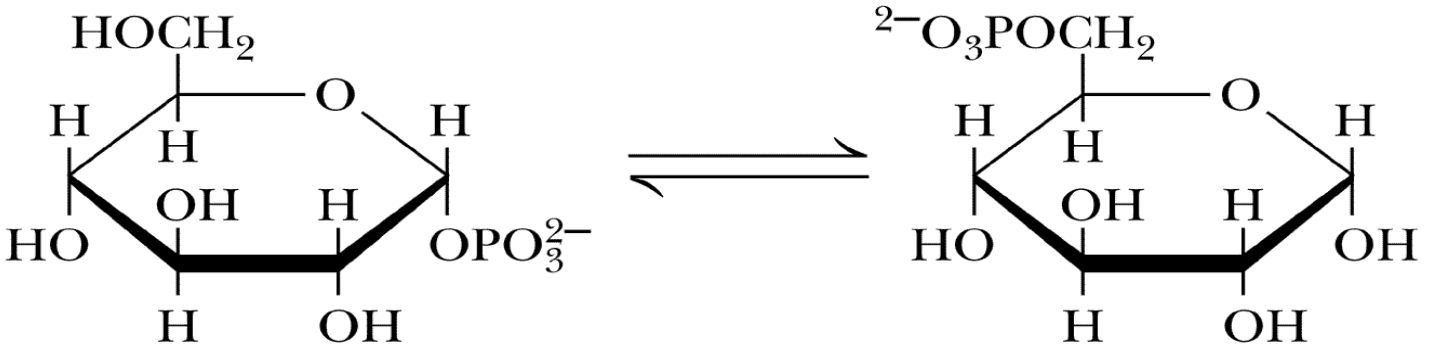
Step-1- Phosphorylation of Glucose


GLYCOGEN
GLYCOGENESIS
GLYCOGENOLYSIS
(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
Glycogenin
Glucan transferase
Debranching enzyme
*
Uridine disphosphate glucose (UDPGlc)
To uronic acid pathway
Free glucose from debranching enzyme
Inorganic pyrophosphatase
UDPGlc pyrophosphorylase
PPi
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
ATP
Nucleoside diphospho-kinase
ATP
ADP
GLUCOSE

GLYCOGENESIS: Activation Phase



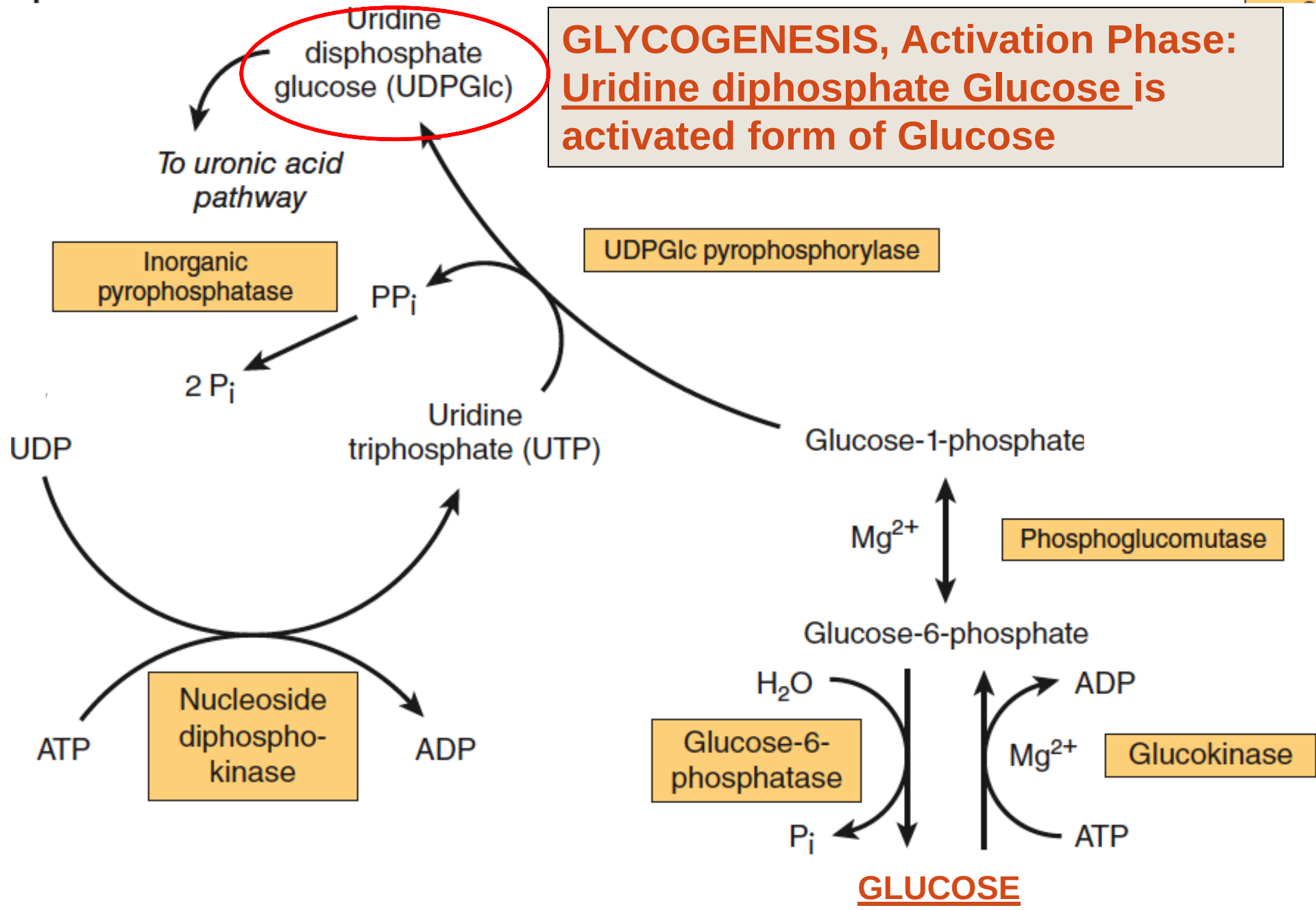
The phosphoglucomutase reaction



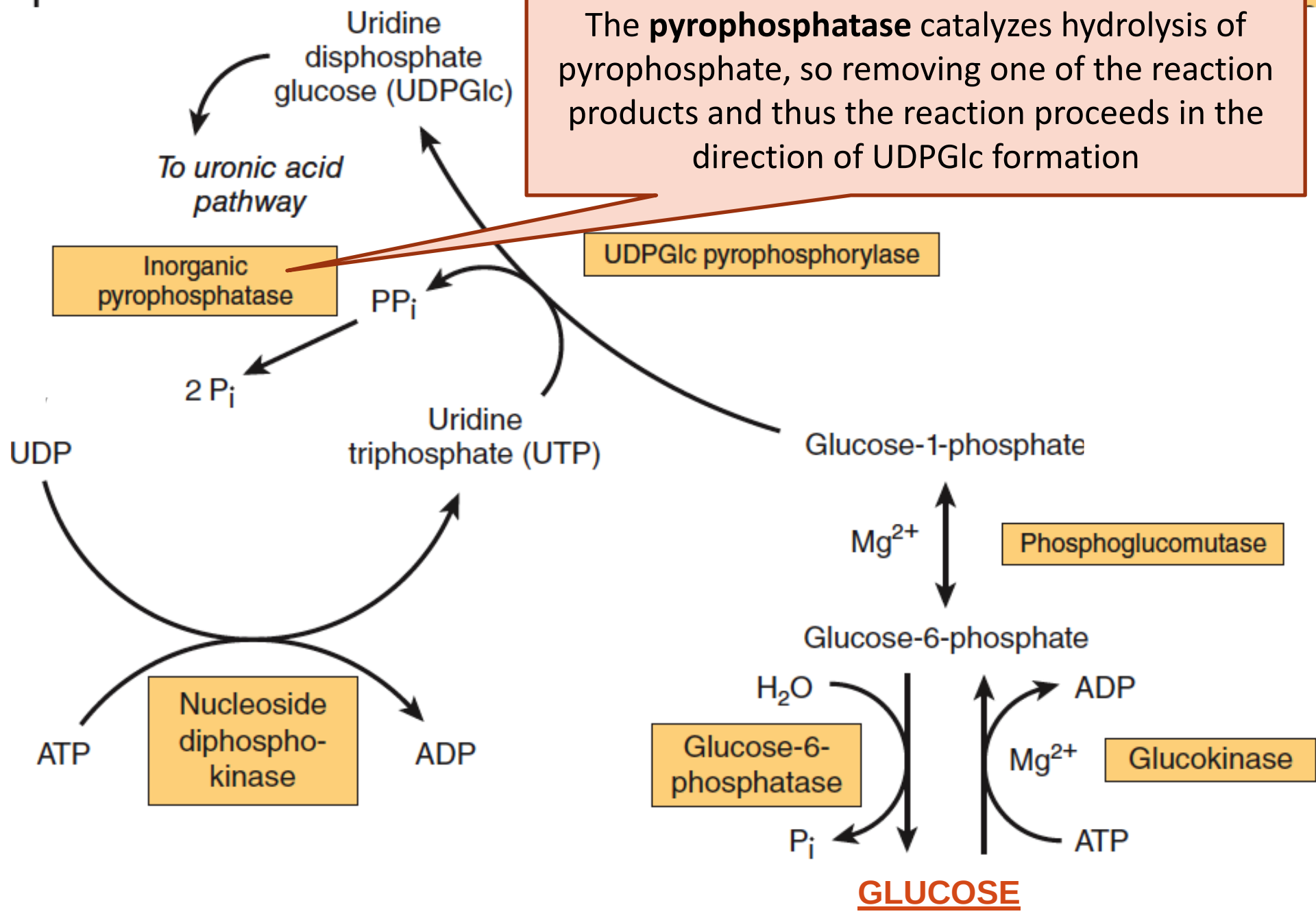
Glucose-1-phosphate

Glucose-6-phosphate

GLYCOGENESIS, Activation Phase: Uridine diphosphate Glucose is activated form of Glucose



The **pyrophosphatase** catalyzes hydrolysis of pyrophosphate, so removing one of the reaction products and thus the reaction proceeds in the direction of UDPGlc formation



GLUCOSE

Uridine Disphosphate Glucose (UDPGlc)

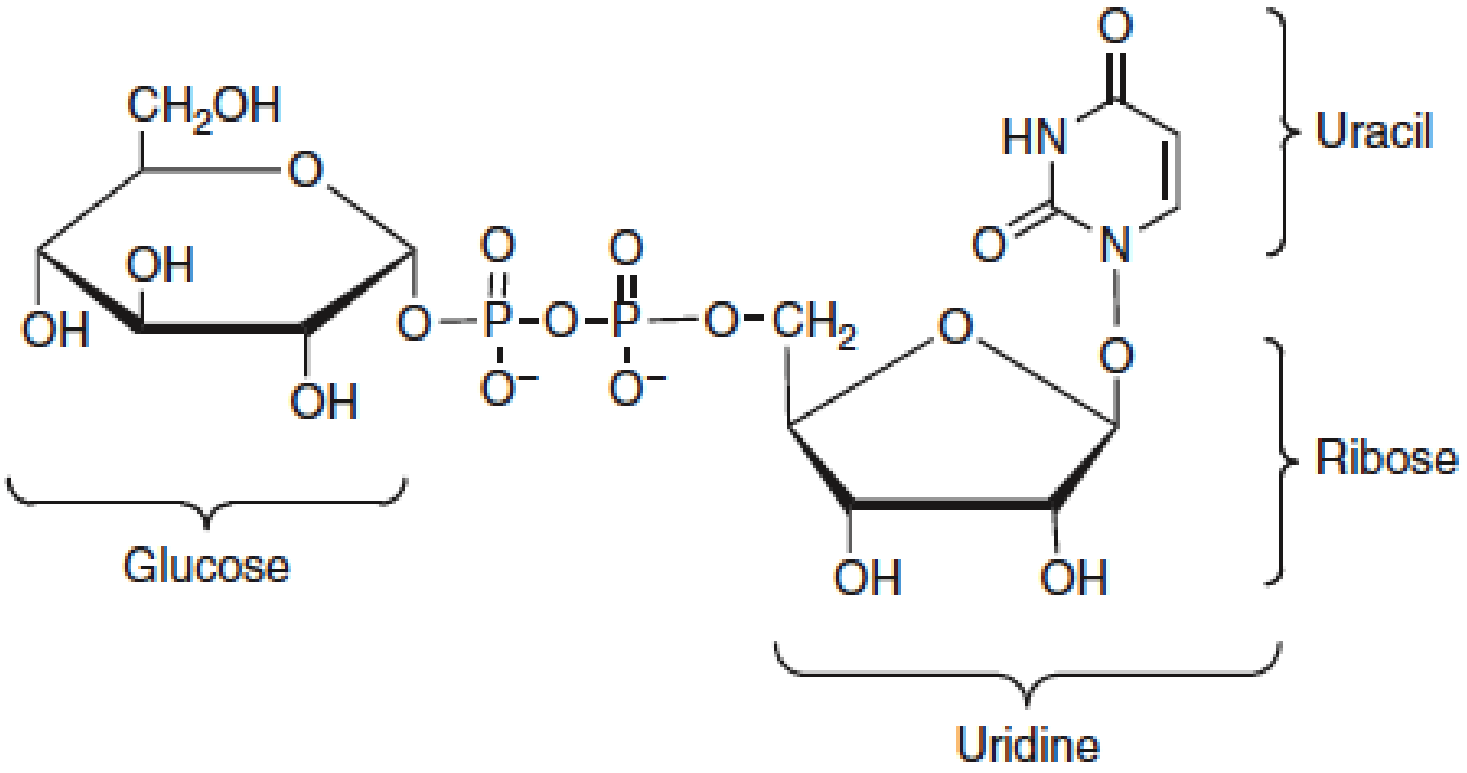
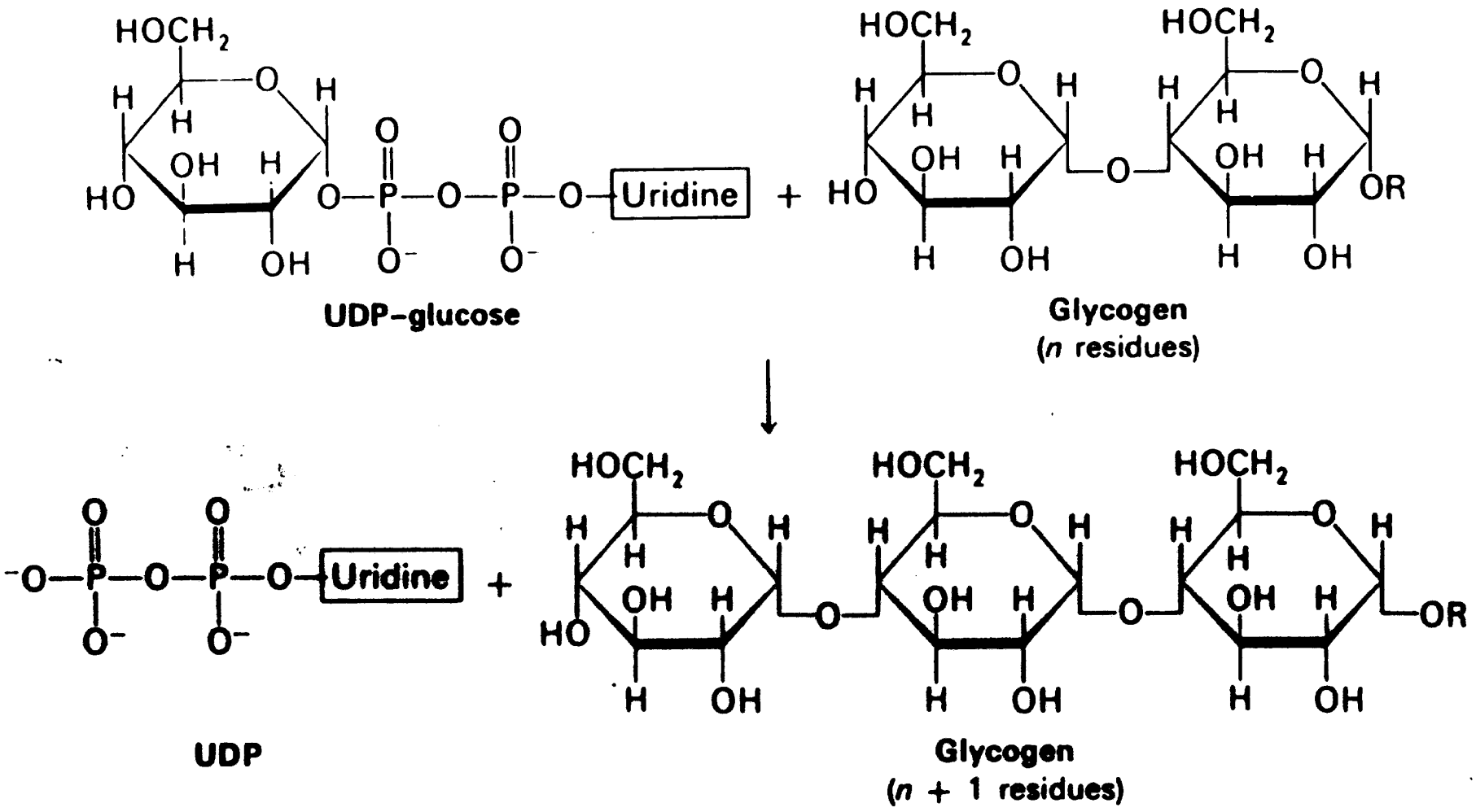


FIGURE 18–2 **Uridine diphosphate glucose (UDPGlc).**

GLYCOGENESIS

- **UDP-glucose, the glucose donor in biosynthesis of glycogen, is an activated form of glucose.**
- **Synthesis of glycogen from glucose is carried out by the enzyme Glycogen Synthase.**
- **Glycogen synthase is the key regulatory enzyme in glycogen synthesis.**
- **This enzyme utilizes UDP-glucose as one substrate added to the non-reducing end of newly growing glycogen chain.**

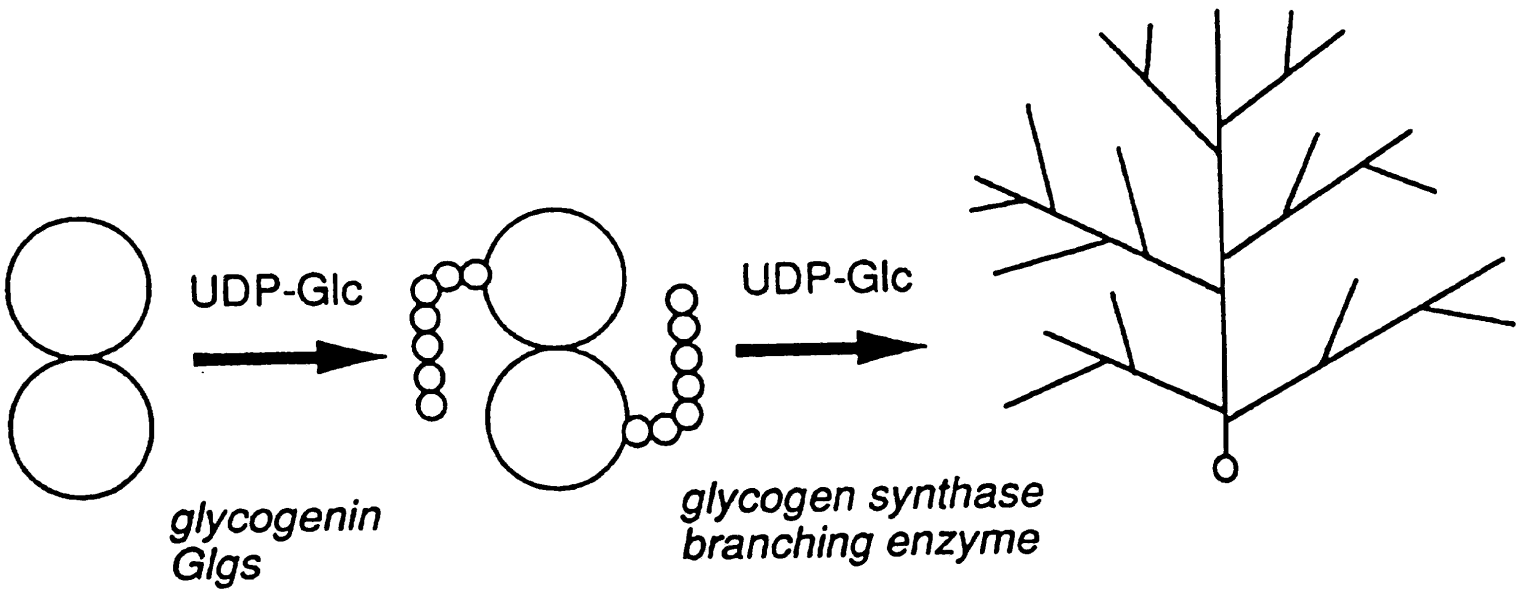


Glycogen Synthase Reaction

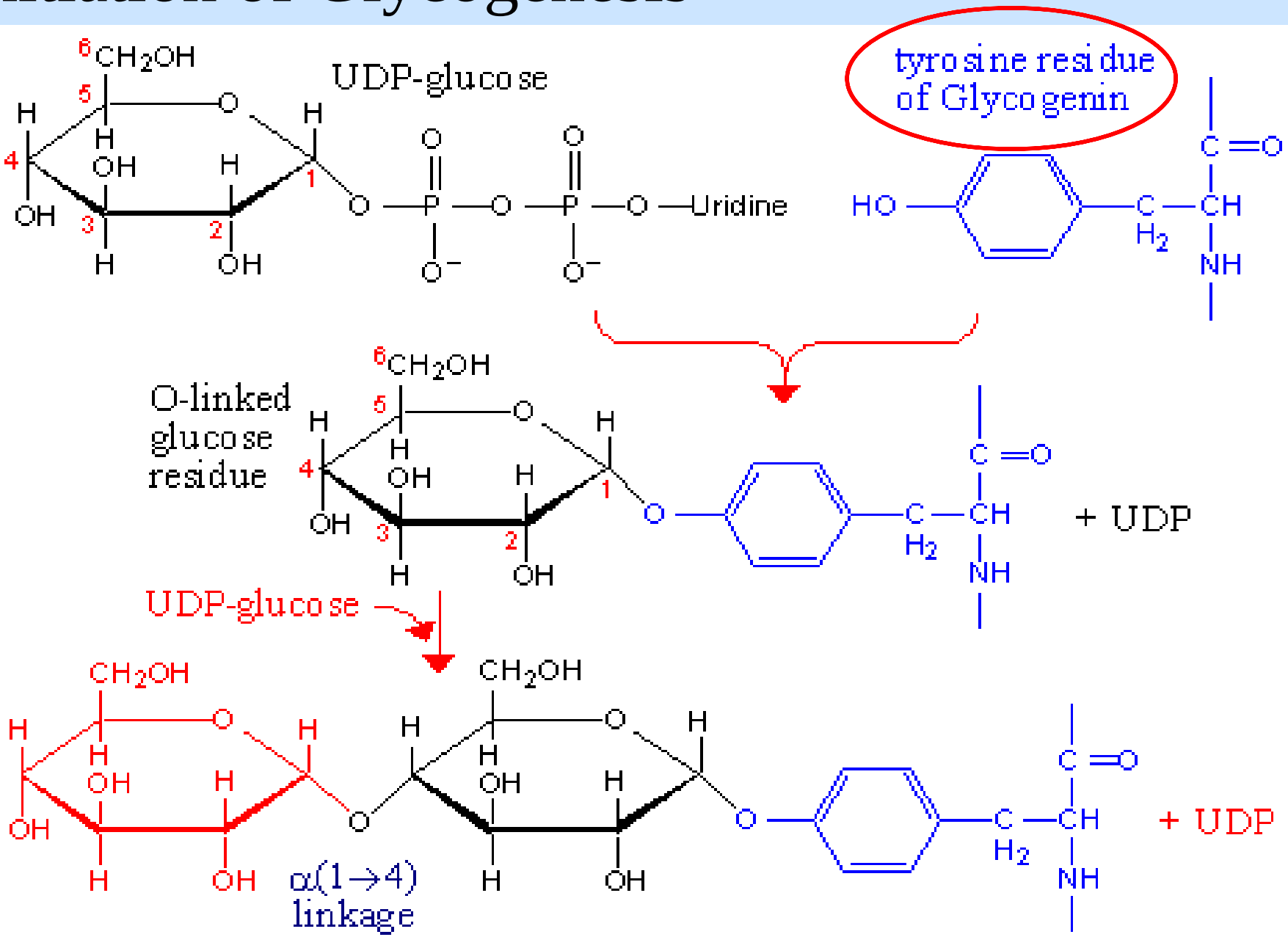
Initiation of Glycogenesis

- Glycogen synthesis requires a primer.
- Glycogen synthase can add glucosyl residues only if the polysaccharide chain already contains eight glucose residues.
- This priming function is carried out by GLYCOGENIN, a protein composed of two identical subunits (dimeric protein), each bearing an oligosaccharide of alpha-1,4-linked glucose units.

Glycogen Synthesis is Initiated on Glycogenin



Initiation of Glycogenesis



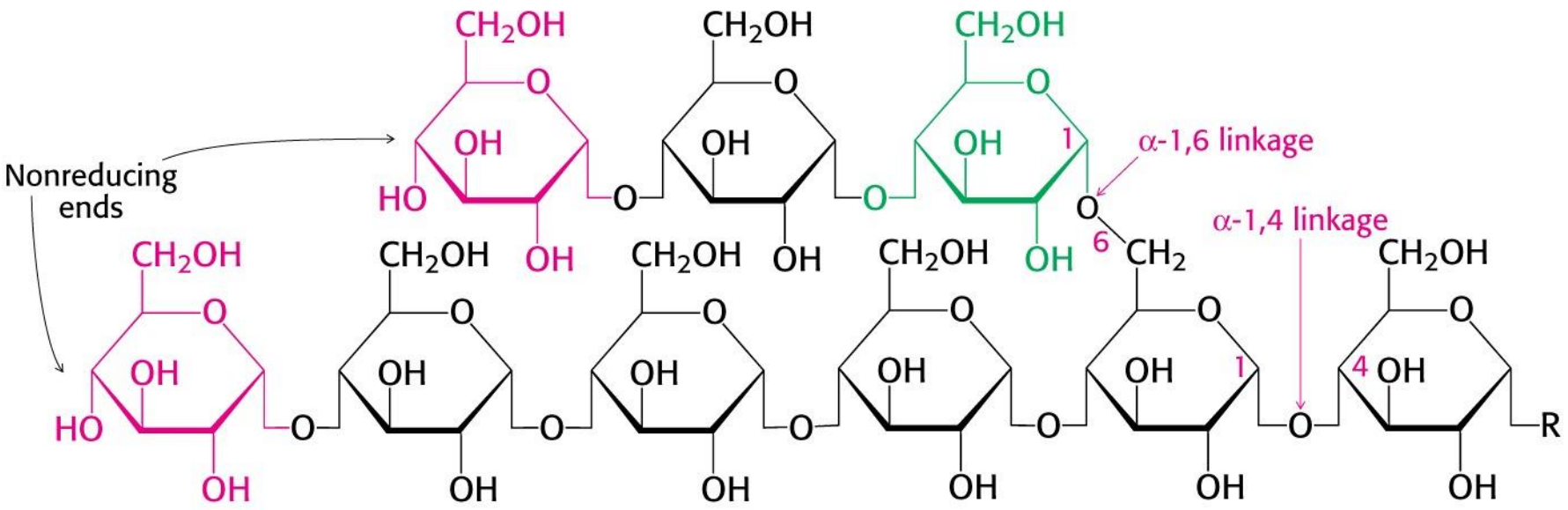
Elongation phase of Glycogenesis

- 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, liberating uridine diphosphate (UDP).

- This addition of a glucose residue occurs to a preexisting glycogen chain, or “primer” at the nonreducing, outer end of the molecule, as successive 1 → 4 linkages.

- **Glycogen synthase is the key regulatory enzyme in glycogen synthesis**.

The α-1,4-linkage.



Synthesis requires the addition of glucose to the non-reducing ends of glycogen via UDP-glucose.

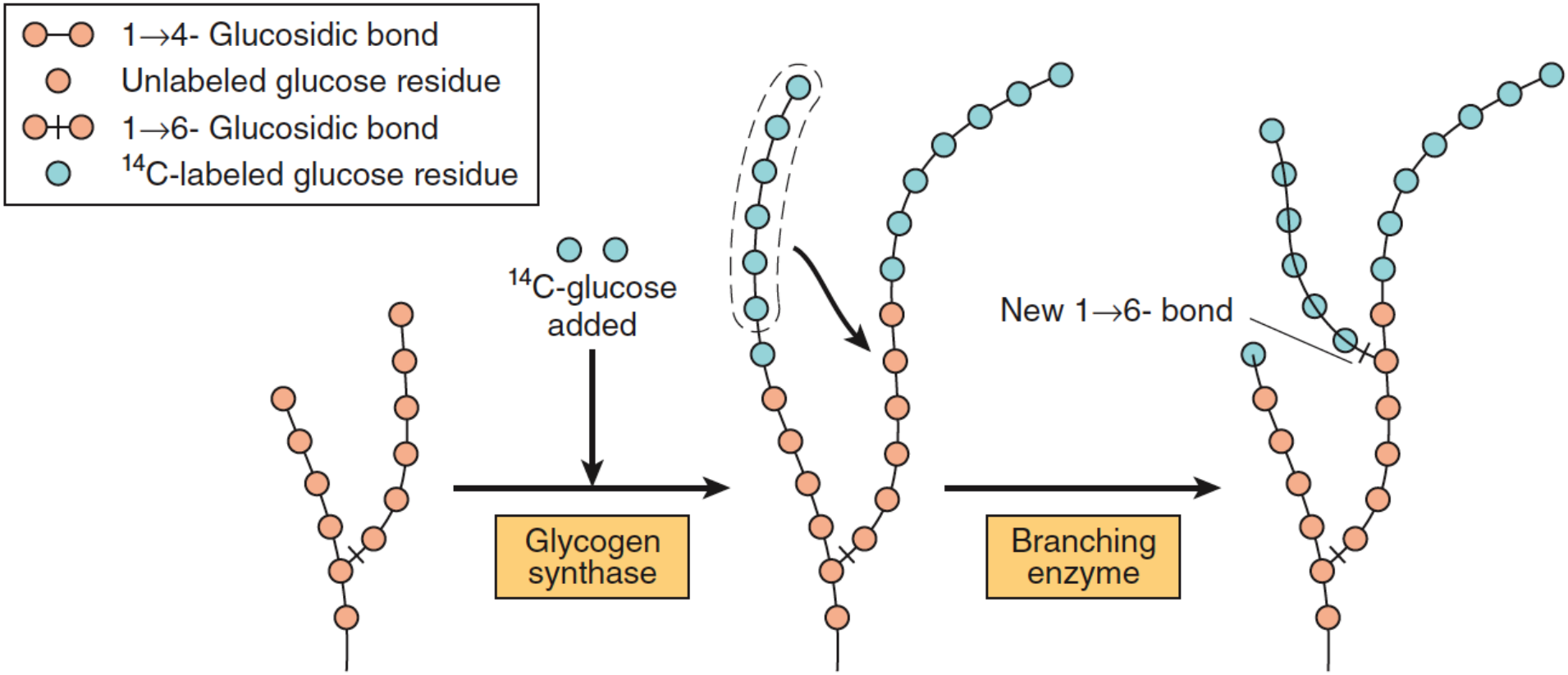
Branching and further elongation phase

- Branching is important because it increases the solubility of glycogen.
- Furthermore, branching creates a large number of terminal residues, the sites of action of glycogen synthase and phosphorylase.
- Thus, branching increases the rate of glycogen synthesis and degradation.

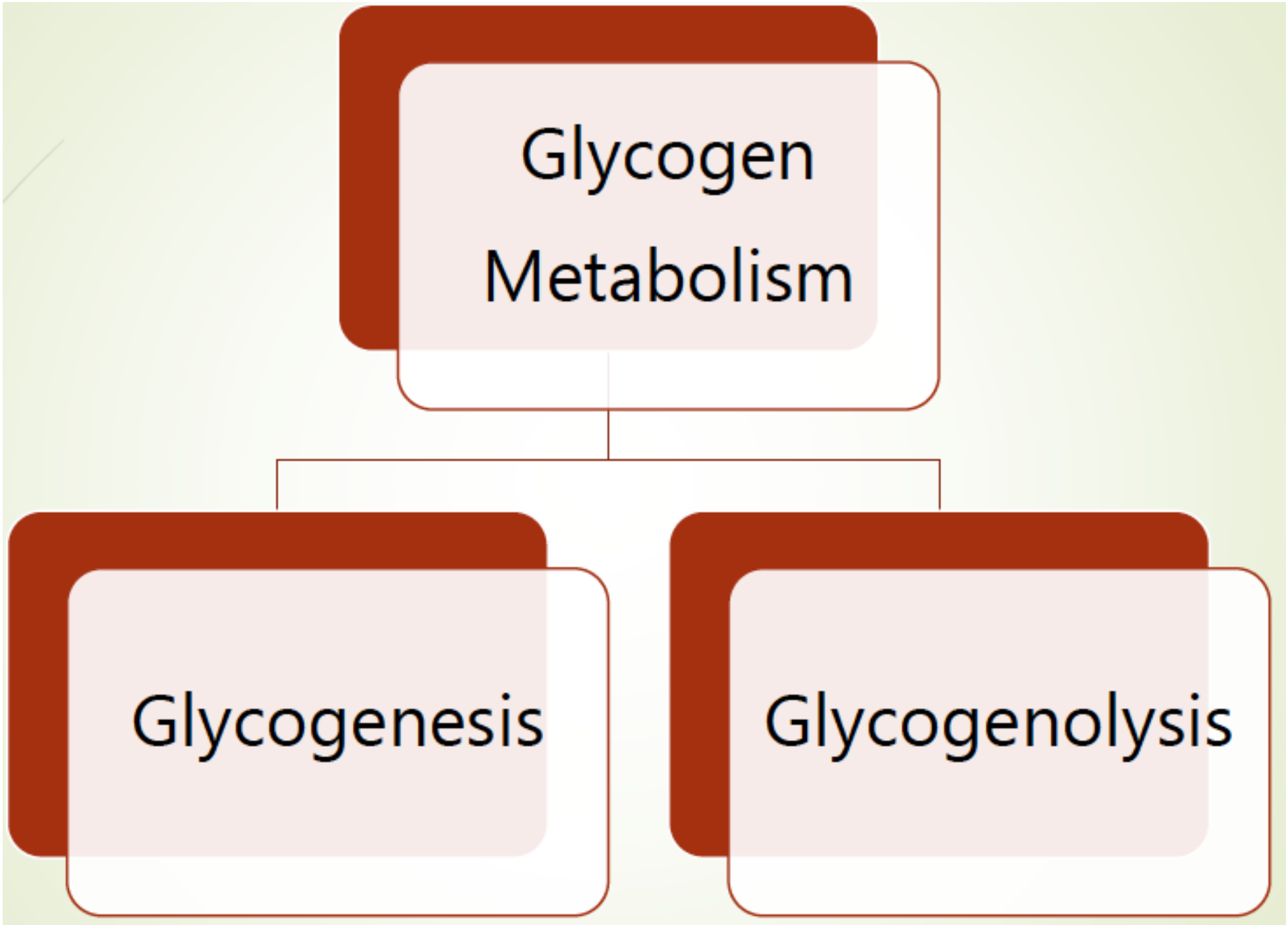
Branching and further elongation phase

- When the growing chain reaches at least 11 glucose residues long.
- The **branching enzyme** transfers a part of the 1 → 4-chain (at least 6 glucose residues) to a neighboring chain to form a 1 → 6 linkage, establishing a branch point.
- The α-1,4-glucosidase activity and the transferase (glycosyltransferase) activity are within one bifunctional protein.

Branching and further elongation phase



Phases of Glycogenesis


Glycogen Metabolism
Glycogenesis
Glycogenolysis

Glycogenolysis:

- **Glycogenolysis is the breakdown of glycogen into glucose (in liver) and lactic acid (Glu-6-P going into anerobic glycolysis in exercising muscles –** recall importance of Cori cycle**).**

- **It occurs in the cytosol.**

Glycogenolysis:

Two major enzymes participate in all glycogen degradation:

- Glycogen phosphorylase
- Glycogen de-branching enzyme → has 2 independent active sites:
  - **Transferase**
  - **α (1→6) glucosidase**

Purpose of Glycogenolysis

- The controlled breakdown of glycogen – release/ availability of glucose between meals – glycogen serves as a buffer to maintain blood-glucose levels.
- Maintaining blood glucose levels is especially important – glucose is virtually the only fuel used by the brain.
- The glucose from glycogen is readily mobilized – a good source of rapid energy for sudden, strenuous activity.
- The released glucose can provide energy in the absence of oxygen and can thus supply energy for anaerobic activity.

Glycogenolysis vs Glycogenesis

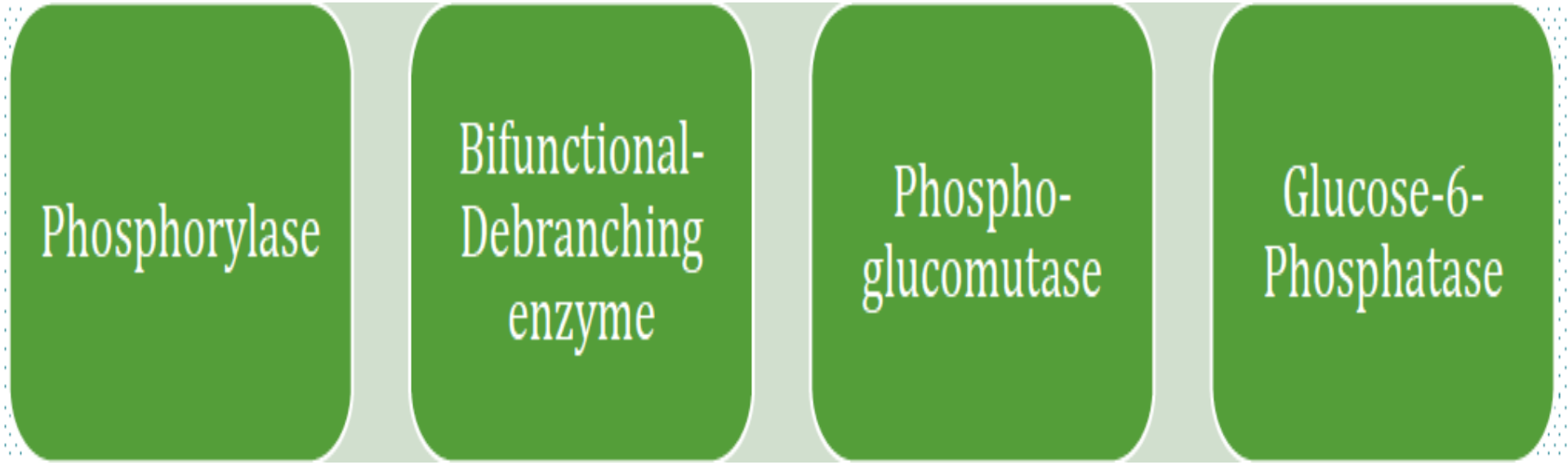
Glycogenesis

- Glucose-> Glucose-6-P
- Glucose-6-P –> Glucose-1-P
- Polymerization
- Branching
- Polymerization

Glycogenolysis

- De-polymerization
- De-branching
- De-polymerization
- Glucose-1-P –> Glucose-6-P
- Glucose-6-P –> Glucose

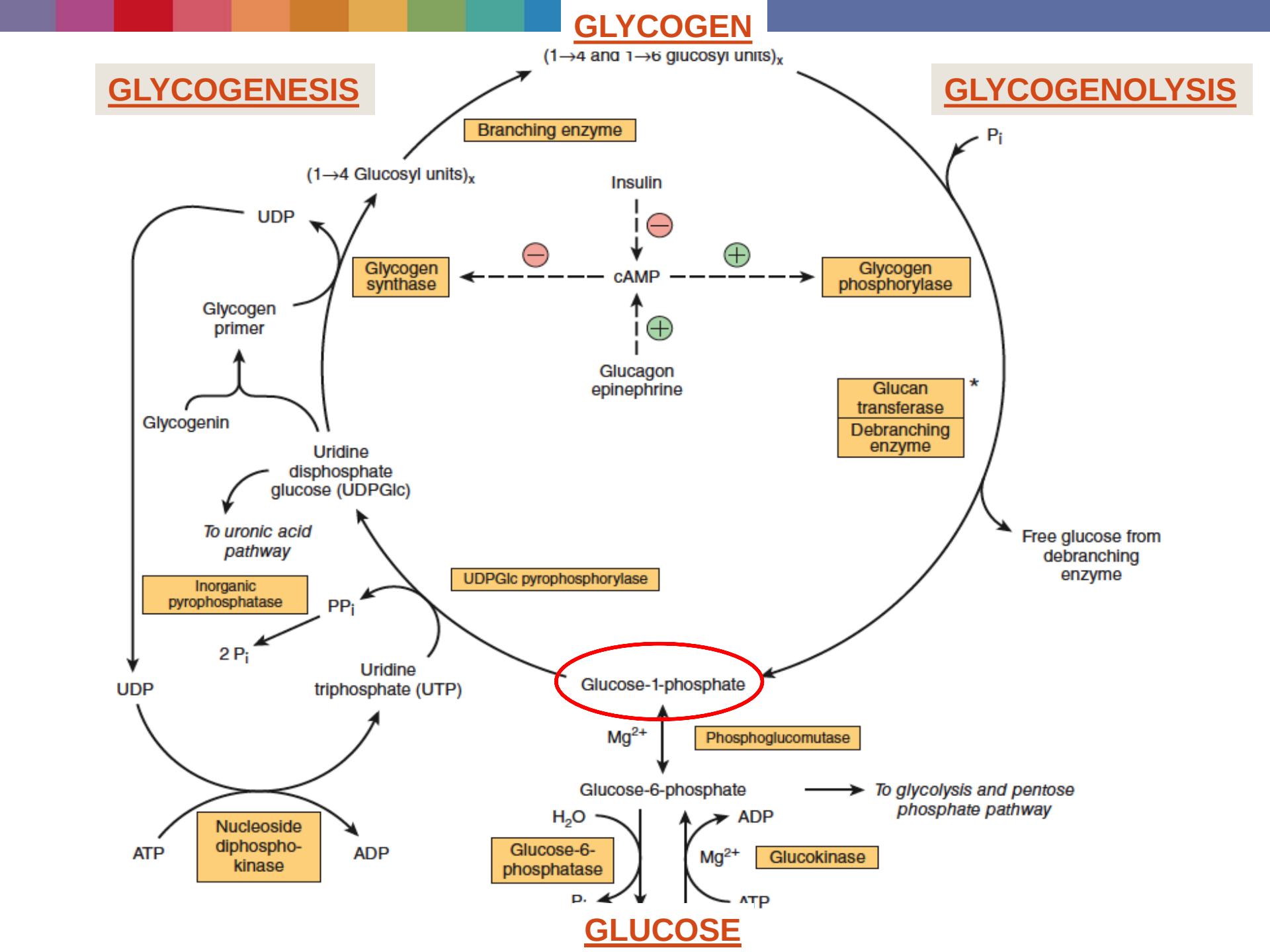
Enzymes of Glycogenolysis



Reaction catalyzed by Phosphorylase

Glycogen Phosphorylase (the rate limiting enzyme) catalyzes the sequential removal of glucosyl residues from the nonreducing ends (the ends with a free 4-OH group) of the glycogen molecule to release phosphorylated glucose (Glucose-1P) – the process known as **Phosphorolytic cleavage**

- Glycogen phosphorylase requires pyridoxal phosphate (Vit B6).


GLYCOGEN
GLYCOGENESIS
GLYCOGENOLYSIS
(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
Glycogenin
Glucan transferase
Debranching enzyme
*
Uridine disphosphate glucose (UDPGlc)
To uronic acid pathway
Free glucose from debranching enzyme
UDPGlc pyrophosphorylase
Inorganic pyrophosphatase
PPi
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
ATP
Nucleoside diphospho-kinase
ATP
ADP
GLUCOSE

Advantages of Phosphoroyltic cleavage

- The phosphoroylytic cleavage of glycogen is energetically advantageous - the released sugar is already phosphorylated.
- In contrast, a hydrolytic cleavage would yield glucose, which would then have to be phosphorylated at the expense of the hydrolysis of a molecule of ATP to enter the glycolytic pathway.
- An additional advantage of phosphorolytic cleavage for muscle cells is that glucose 1-phosphate, negatively charged under physiological conditions, cannot diffuse out of the cell.

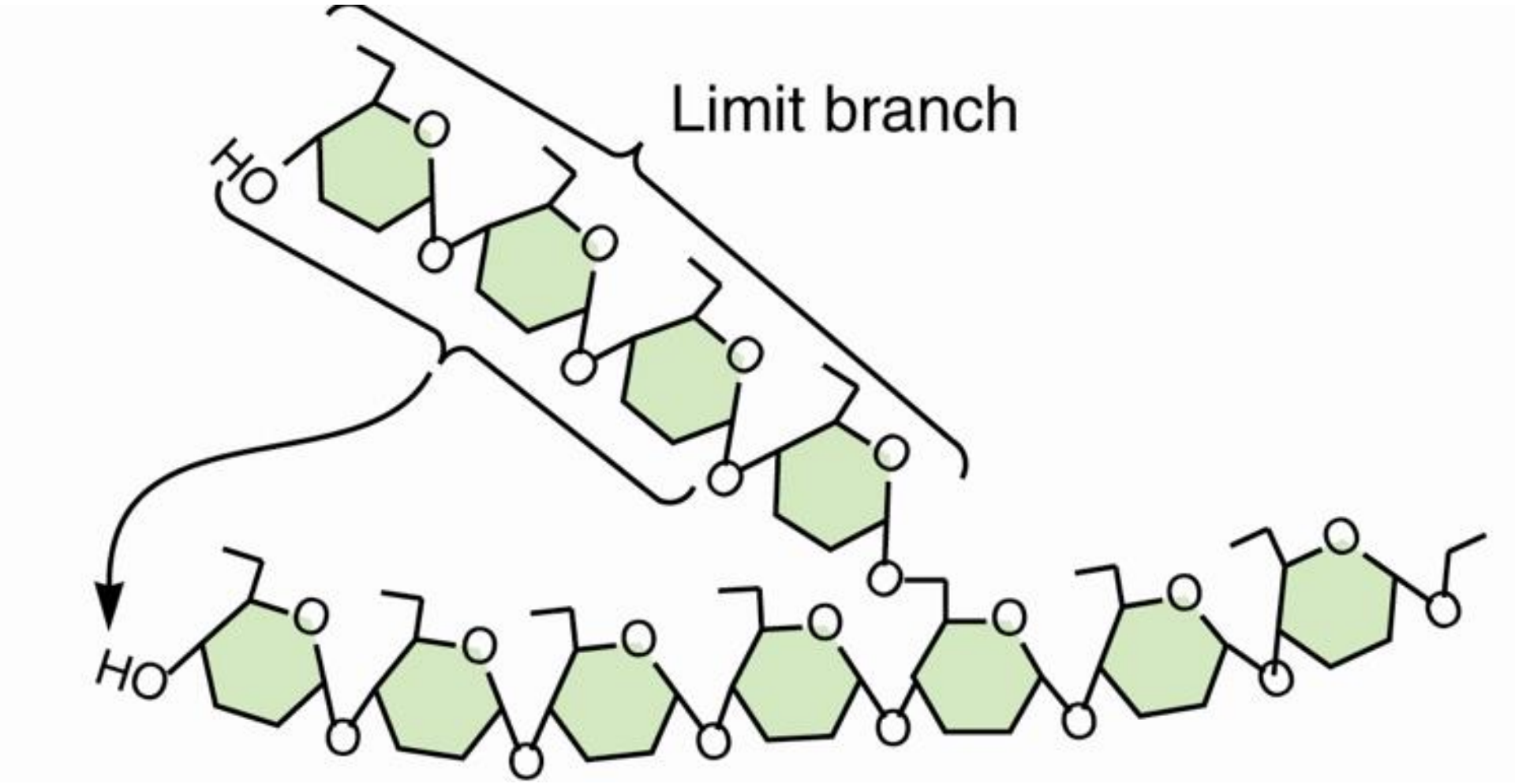
Phosphorolytic cleavage

- **Glycogen phosphorylase stops cleaving α -1,4 linkages when it reaches a terminal residue four residues away from a branch point.**

- **Having about 10 residues in a branch, glycogen degradation by the phosphorylase alone would come to a halt after the release of six glucose molecules per branch.**

- **Also, the α-1,6-glycosidic bonds at the branch points are not susceptible to cleavage by phosphorylase.**

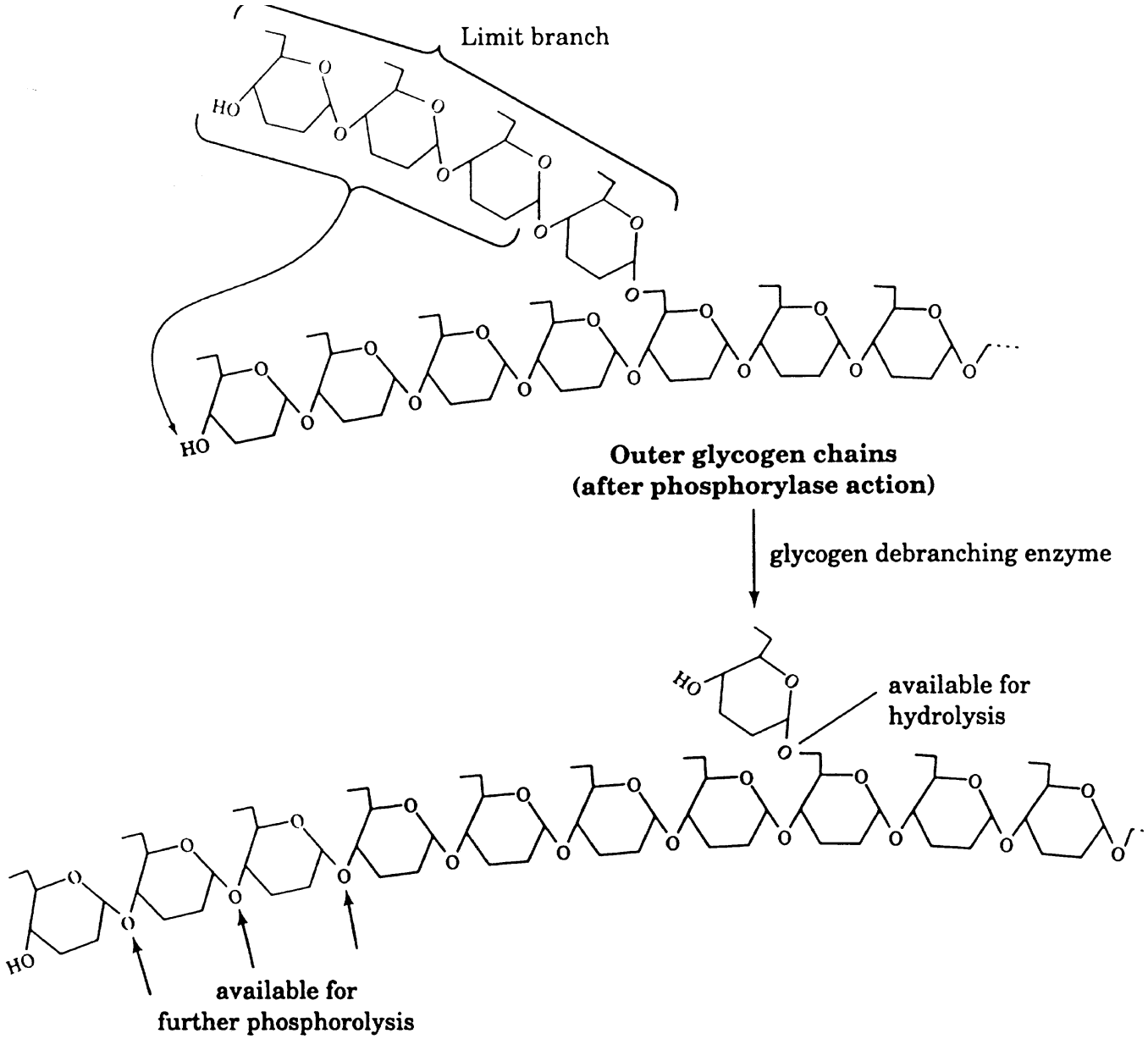
Concept of Limit Branch

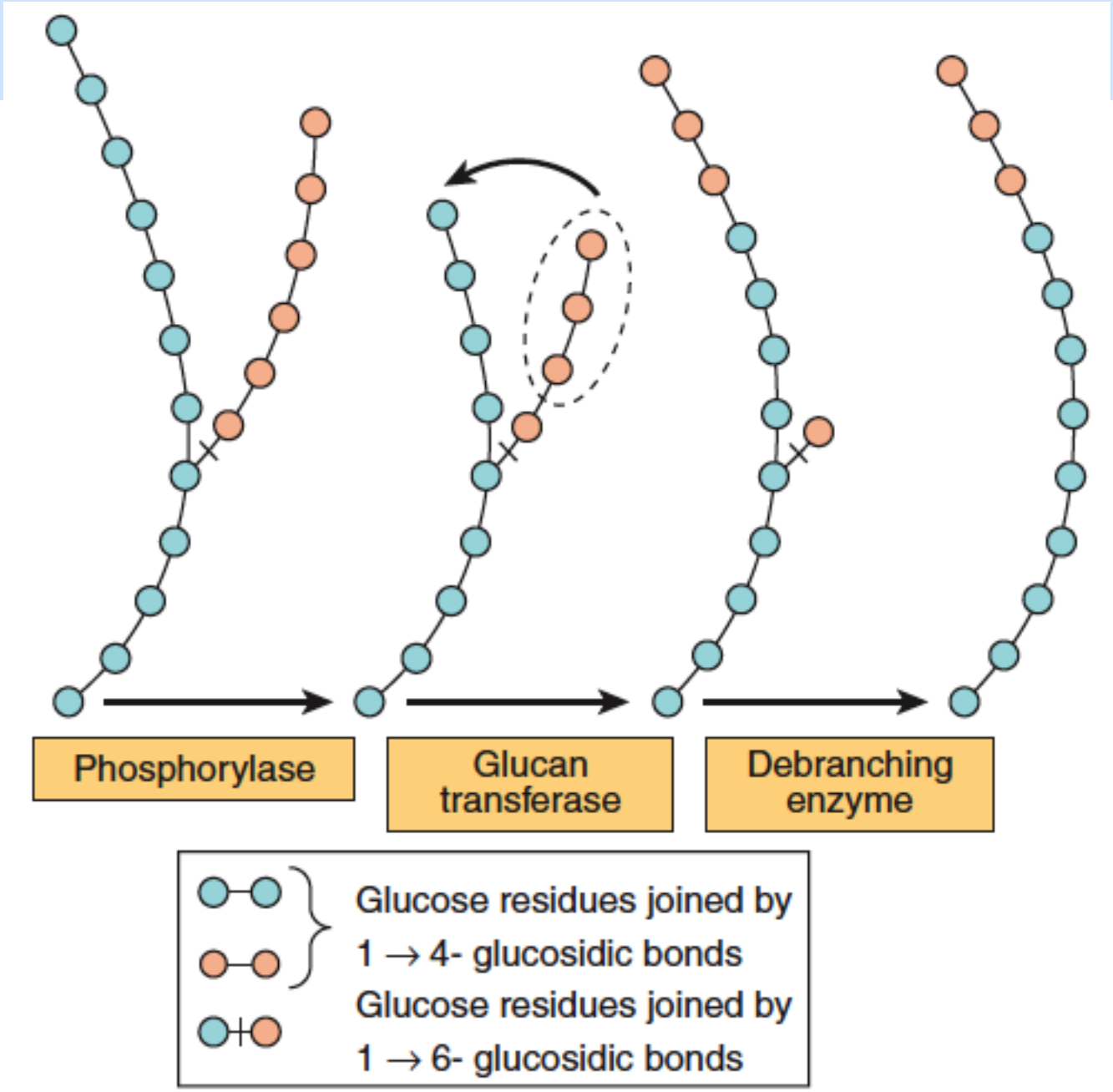


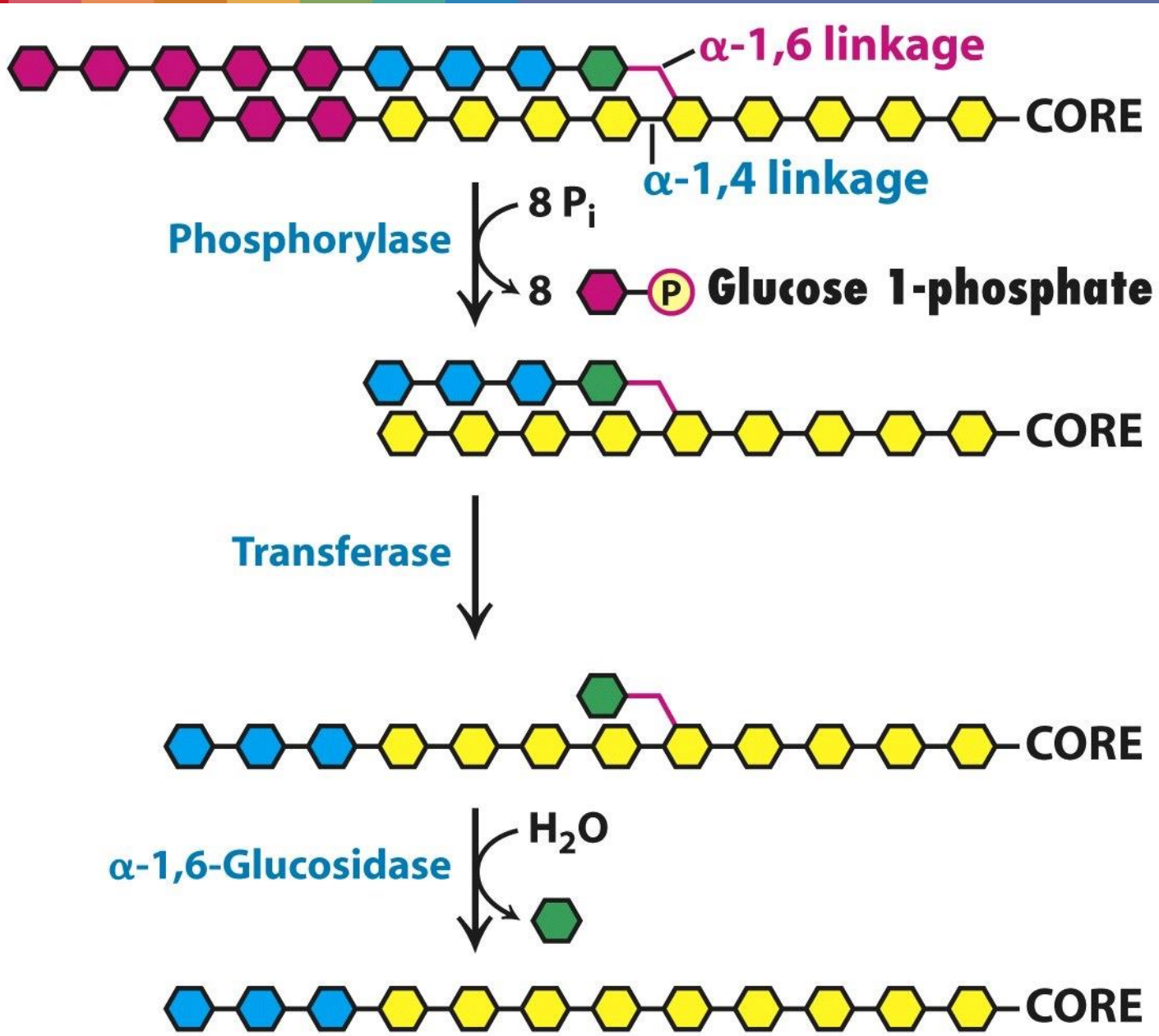
- The **transferase activity of branching enzyme** transfers 3 glucose residues from a 4-residue limit branch to the end of another branch, diminishing the limit branch to a single glucose residue .

- The **α(1→6) glucosidase activity of branching enzyme** then catalyzes hydrolysis of the **α(1→6)** linkage by adding H_2O, yielding free **glucose**

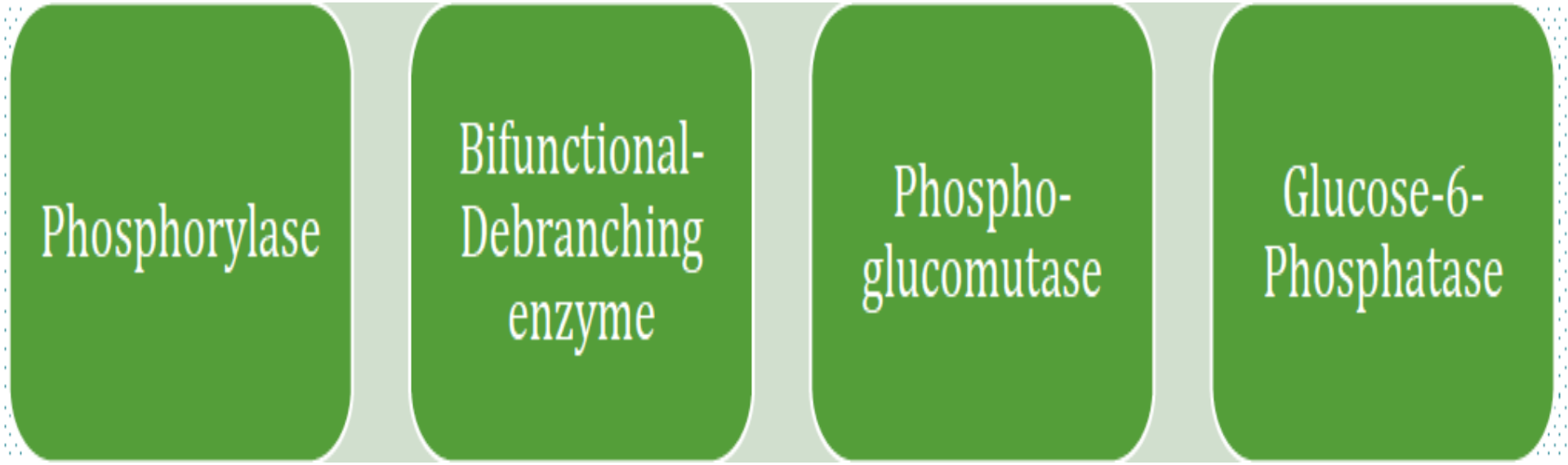
- The major product of glycogen breakdown is **glucose-1-phosphate**, from Phosphorylase activity.


Limit branch
HO
HO
Outer glycogen chains
(after phosphorylase action)
glycogen debranching enzyme
HO
available for
hydrolysis
HO
available for
further phosphorolysis

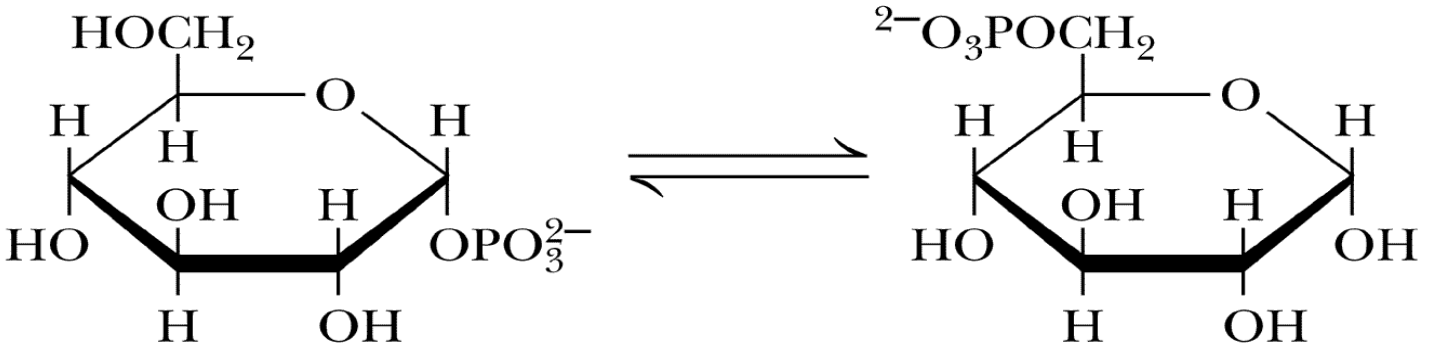

Phosphorylase
Glucan transferase
Debranching enzyme
Glucose residues joined by
1 → 4- glucosidic bonds
Glucose residues joined by
1 → 6- glucosidic bonds


α-1,6 linkage
CORE
α-1,4 linkage
Phosphorylase
8 P_i
8
P
Glucose 1-phosphate
CORE
Transferase
CORE
α-1,6-Glucosidase
H_2O
CORE

Enzymes of Glycogenolysis



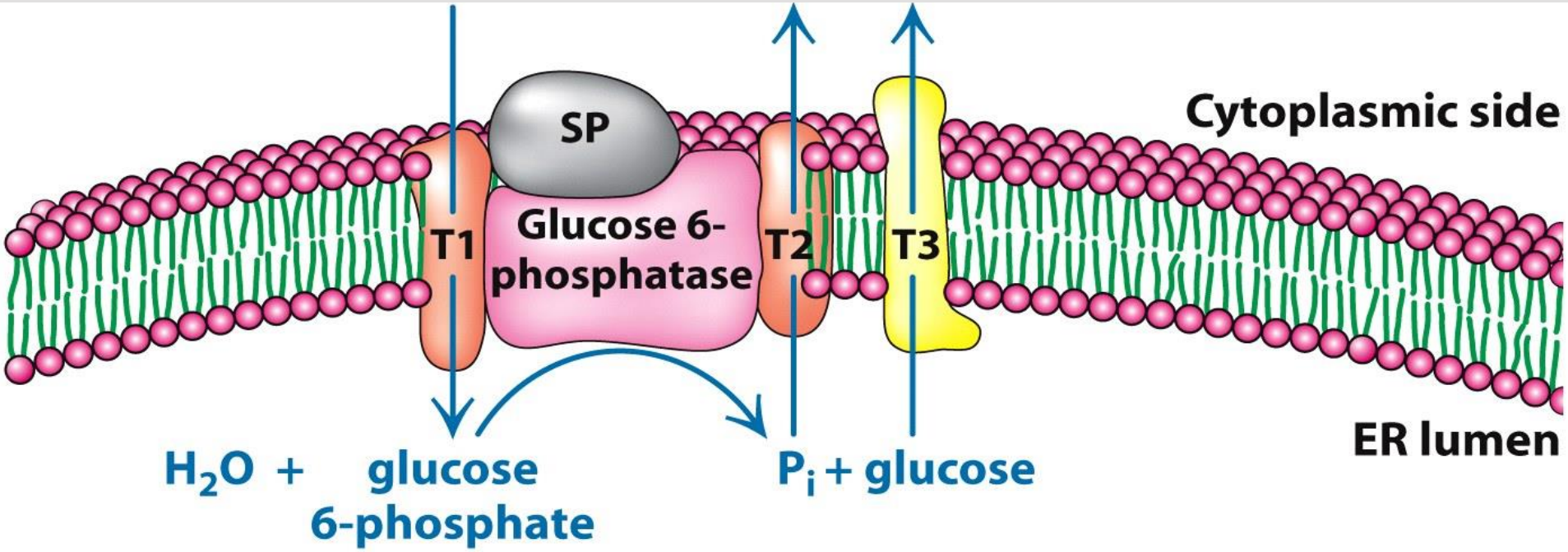
The phosphoglucomutase reaction



Glucose-1-phosphate

Glucose-6-phosphate

Glucose 6 Phosphatase Enzyme



Glucose-6-phosphatase is in the lumen of the smooth ER

- In **liver**, but not muscle, **glucose-6-phosphatase** catalyzes hydrolysis of glucose-6-phosphate, yielding glucose.
- Genetic defects of the glucose-6- phosphate transporter can cause different variants of type-I glycogen storage disease.

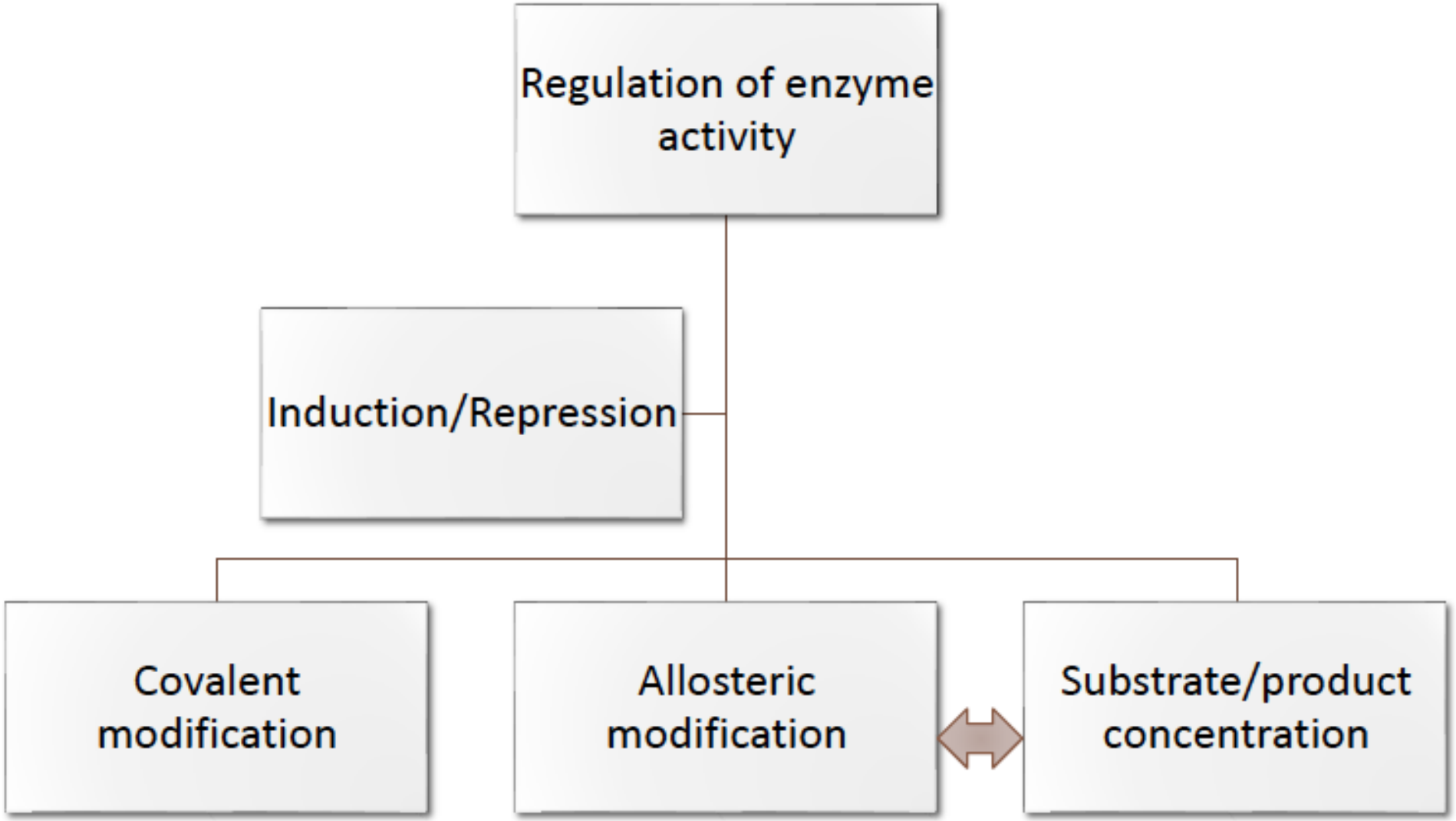
Lysosomal degradation of Glycogen

- A small amount of glycogen is continuously degraded by lysosomal enz, *α(1→4)-glucosidase* (acid maltase).
- Purpose of this pathway is unknown.
- However, a deficiency of this enz causes accumulation of glycogen in vacuoles in the cytosol, resulting in the serious glycogen storage disease type II (Pompe disease).

Regulation of Glycogen Metabolism

- Glycogenesis and glycogenolysis are reciprocally regulated.
- Insulin promotes glycogenesis.
- Glucagon and epinephrine promote glycogenolysis.
- Glycogenesis is the process of well-fed state.
- Glycogenolysis is the process of Fasting or starvation.
- Both these processes are meant for maintaining the blood glucose concentration within the normal range.

REGULATION OF GLYCOGEN METABOLISM



Glycogen Synthase & Phosphorylase activity are reciprocally regulated

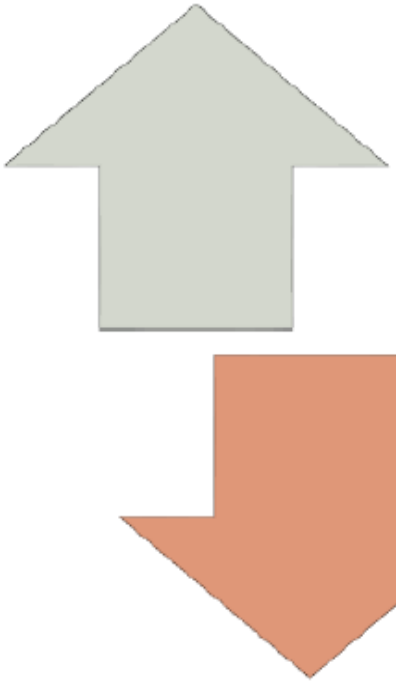
- At the same time as phosphorylase is activated by a rise in concentration of cAMP (via phosphorylase kinase), glycogen synthase is converted to the inactive form.

- Thus, inhibition of glycogenolysis enhances net glycogenesis, and inhibition of glycogenesis enhances net glycogenolysis

- Both processes do not occur at the same time.

REGULATION OF GLYCOGEN METABOLISM

Key enzymes involved in the regulation of glycogen metabolism



Glycogen synthase-
For Glycogenesis

Glycogen
Phosphorylase
(Glycogenolysis)

Both these enzymes are reciprocally regulated.

Substrate concentration and allosteric modification

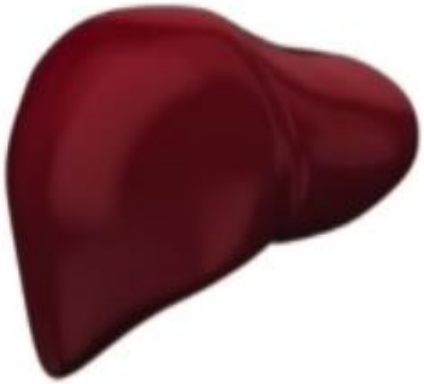
- Certain metabolites that allosterically regulate the activities of glycogen synthase & glycogen phosphorylase.
- The glycogen synthesis is increased when substrate availability and energy levels are high.
- Glycogen breakdown is enhanced when glucose concentration & energy levels are low.
- In a well-fed state, the availability of glucose 6 – phosphate is high which allosterically activates glycogen synthase for more glycogen synthesis.

Substrate concentration and allosteric modification

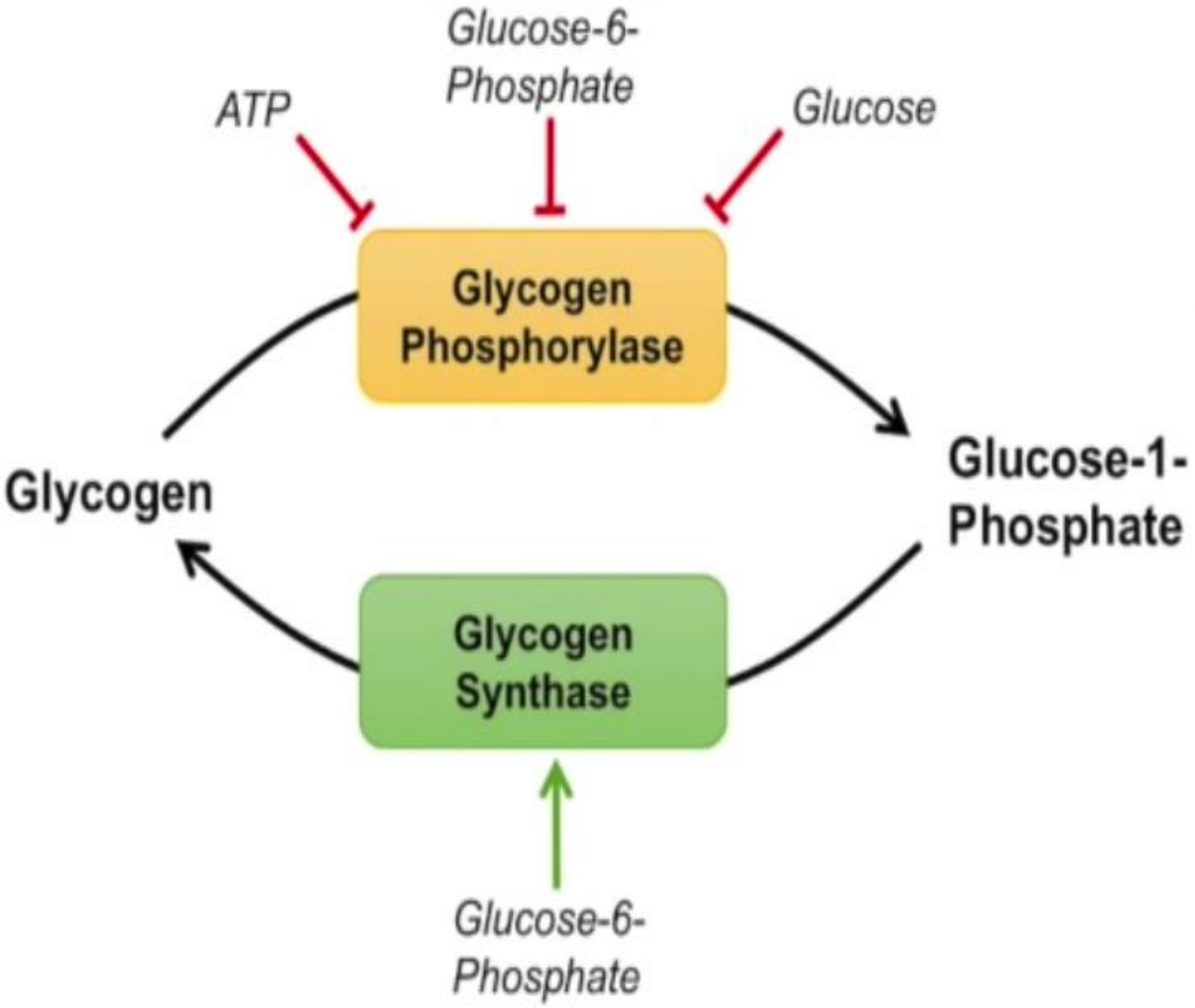
- Glycogen Synthase is allosterically activated by glucose-6-P.
- High blood glucose concentration leads to elevated intracellular glucose-6-P.
- When glycolytic pathway is saturated, excess glucose-6-P activates Glycogen synthase and thus is stored as glycogen.
- Glucose 6-phosphate & ATP allosterically inhibit glycogen phosphorylase.
- Free glucose in liver also acts as an allosteric inhibitor of glycogen phosphorylase.

Allosteric regulation of glycogen synthesis and degradation

Effects of Insulin??



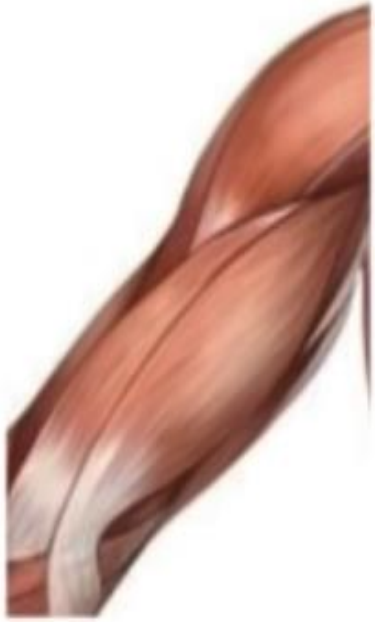
Liver



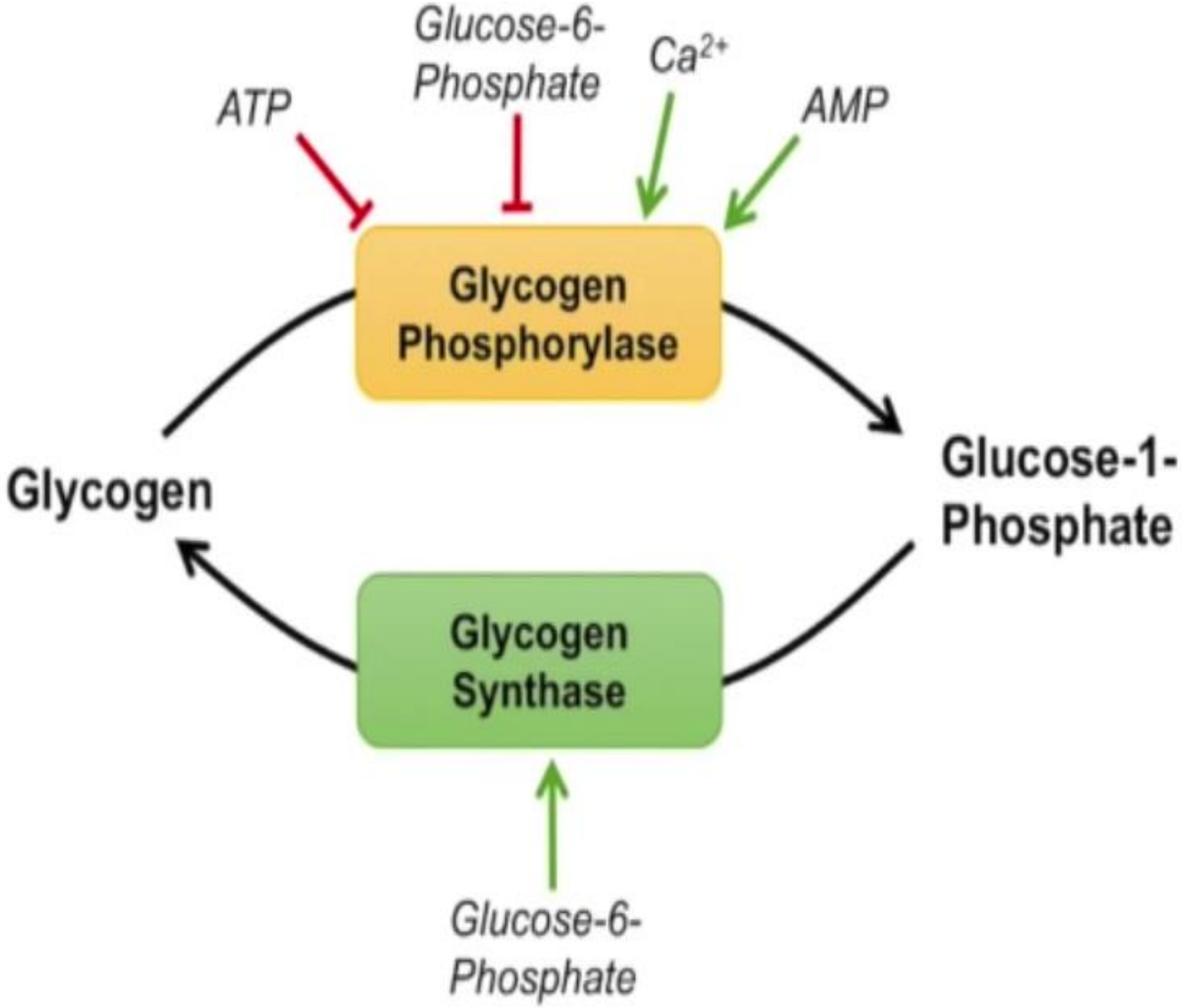
Glycogen Phosphorylase Regulation Is Different in Liver & Muscle

Allosteric regulation of glycogen synthesis and degradation

Effects of Insulin??

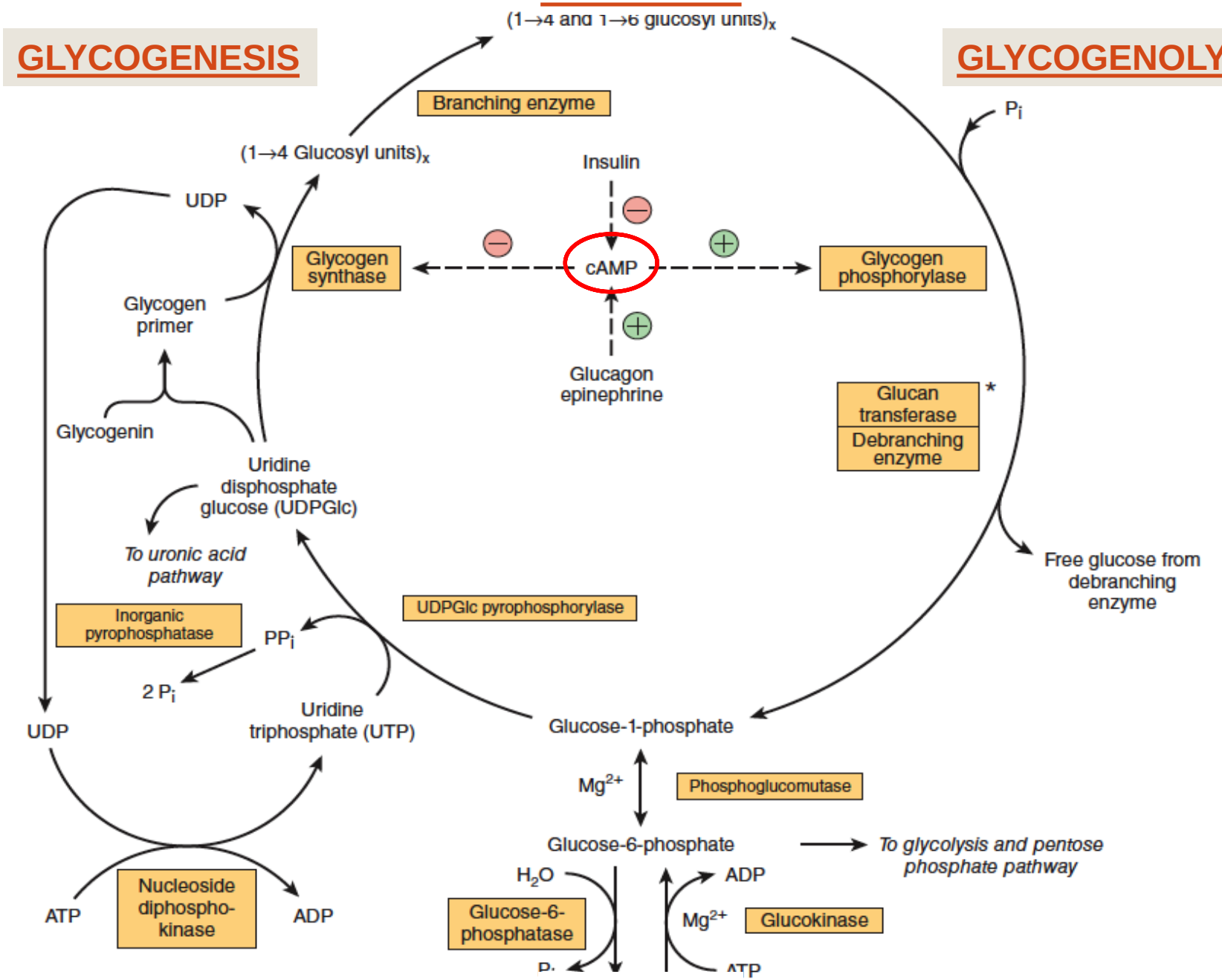


Skeletal Muscle



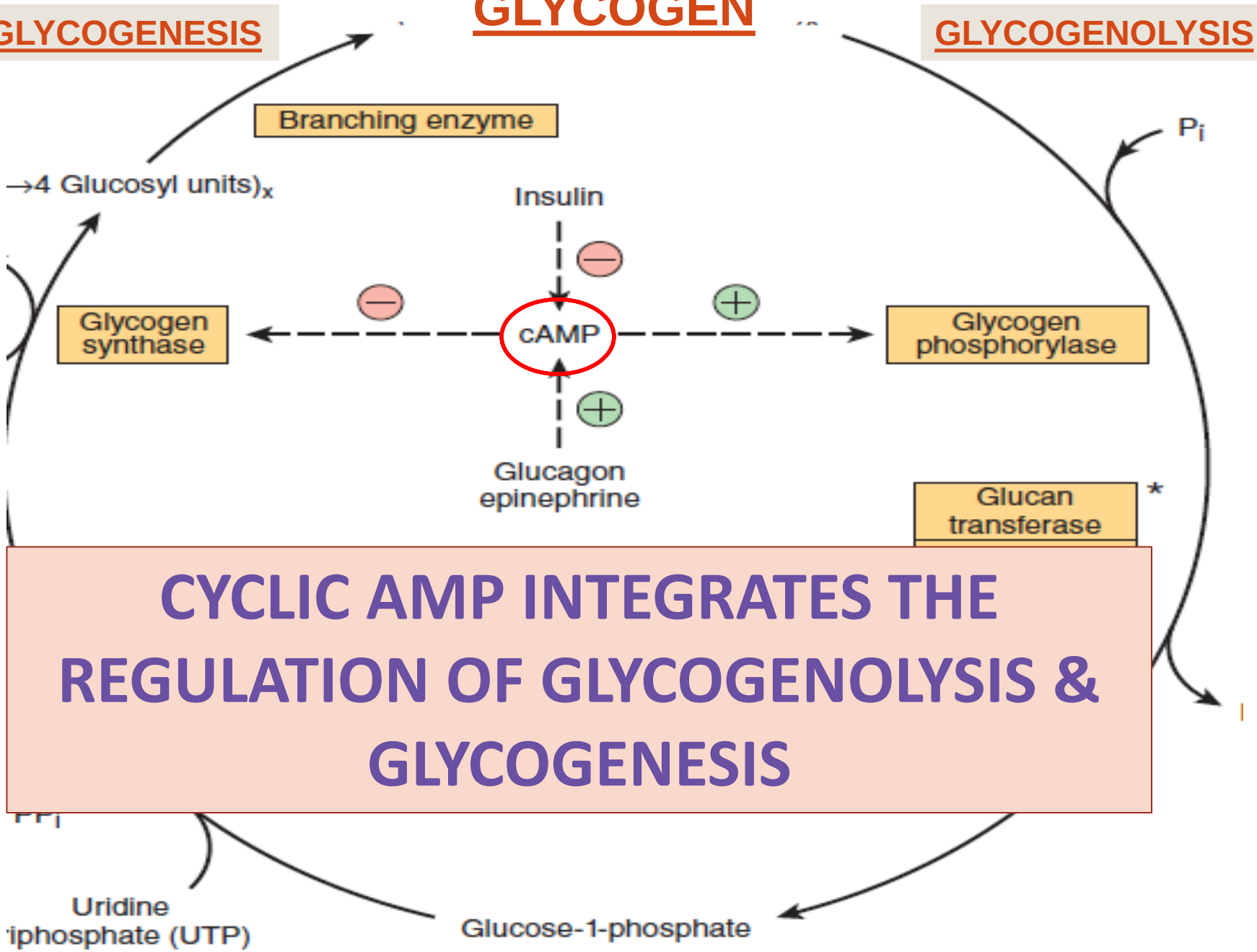
Glycogen Phosphorylase Regulation Is Different in Liver & Muscle

GLYCOGEN



GLUCOSE

GLYCOGEN



CYCLIC AMP INTEGRATES THE REGULATION OF GLYCOGENOLYSIS & GLYCOGENESIS

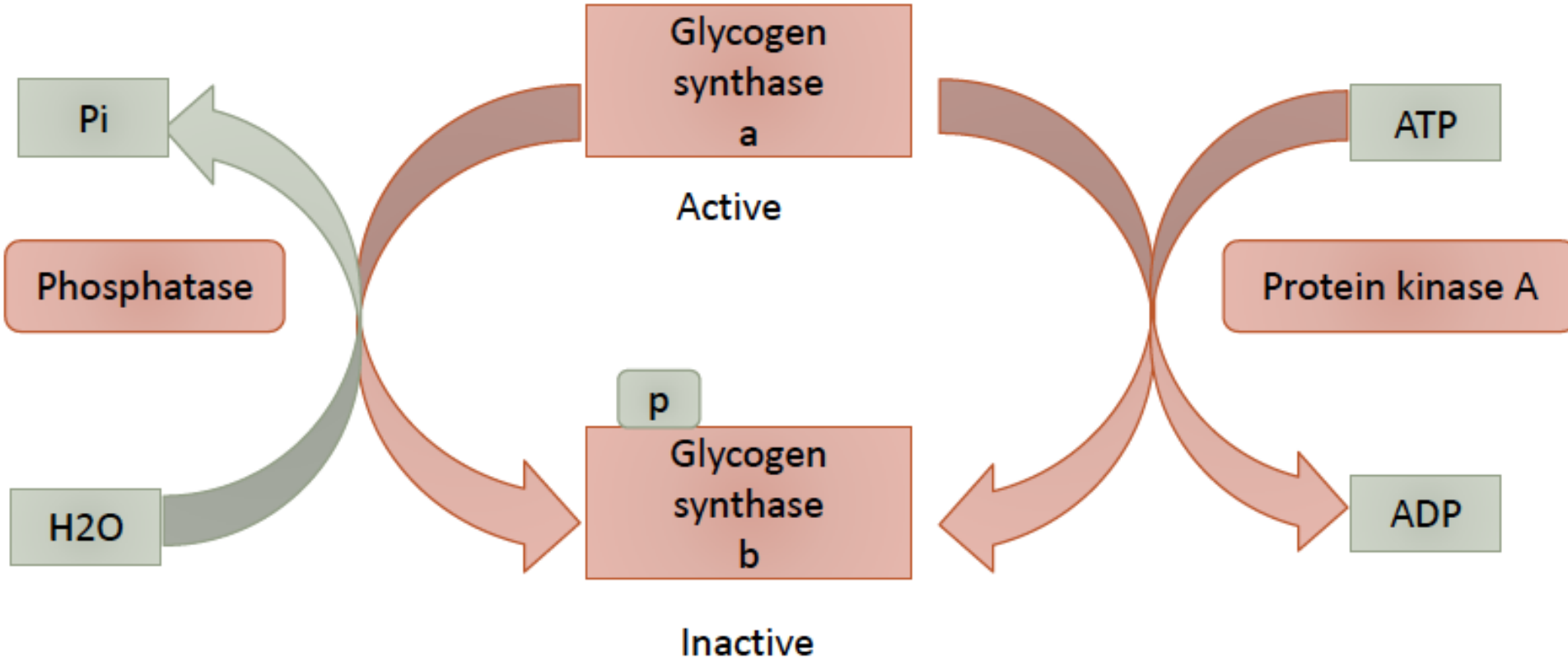
Hormonal regulation of glycogen metabolism

- The hormones bring about covalent modification
- Via Reversible phosphorylation and dephosphorylation
- Hormone mediated C-AMP mediated cascade
- Phosphorylation is mediated by Protein kinase A
- Dephosphorylation is carried out by Phosphatase
- Insulin causes dephosphorylation by stimulating Phosphatase, and by stimulating Phosphodiesterase (in liver) to break down cAMP
- Epinephrine (and norepinephrine) and Glucagon causes phosphorylation by activating adenylate cyclase to increase the production of cAMP and Protein kinase A

Glycogen synthase & covalent modification

- Glycogen synthase exists in both phosphorylated or dephosphorylated forms/states
- Active glycogen synthase-a is dephosphorylated and inactive glycogen synthase-b is phosphorylated
- Phosphorylation is catalysed by a cAMP dependent protein kinase.
- Protein kinase phosphorylates & inactivates glycogen synthase.
- The glycogen synthase 'b' can be converted back to synthase' a' by protein phosphatase.

Covalent modification of glycogen synthase



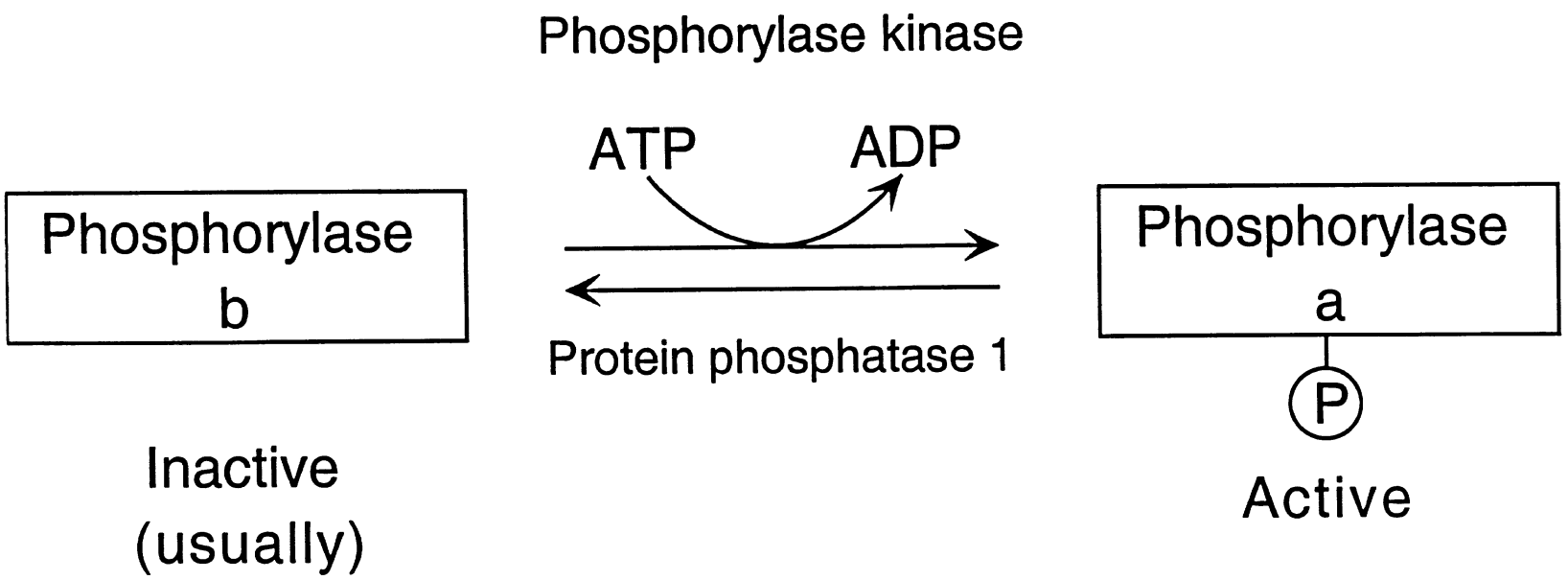
Regulation of glycogenesis by cAMP

- The inhibition of glycogen synthesis brought by epinephrine (also norepinephrine) & glucagon through cAMP by converting active glycogen synthase 'a' to inactive synthase ‘b’.
- The hormones like epinephrine & glucagon bring about glycogenolysis by their action on glycogen phosphorylase through cAMP.
- Glycogen phosphorylase exists in two forms:
  - An active 'a‘ form – phosphorylated
  - Inactive form 'b' – dephosphorylated

Regulation of glycogen Phosphorylase by covalent modification

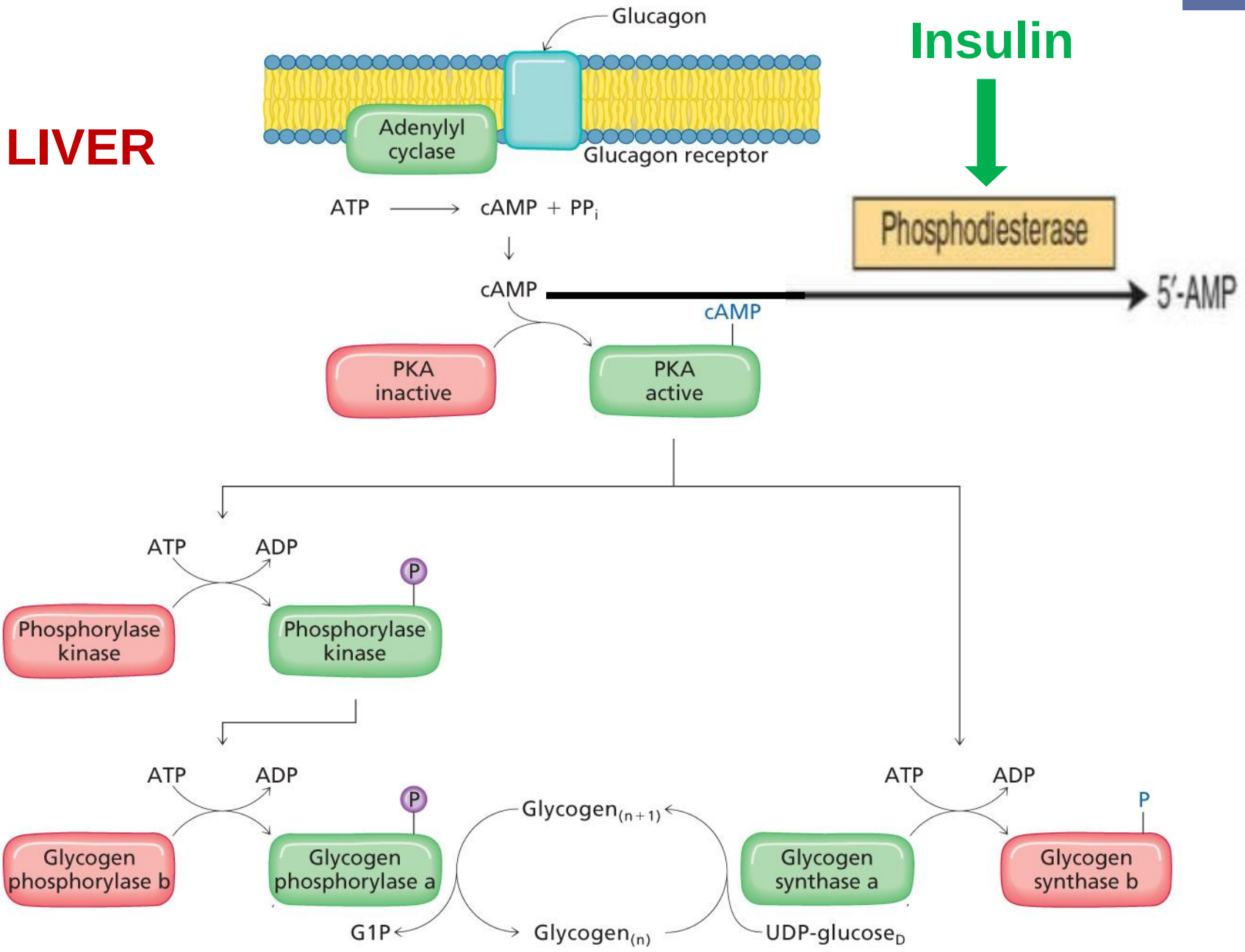
Glycogen Phosphorylase

Skeletal muscle phosphorylase can exist in two forms, an active **phosphorylase a** and a usually inactive **phosphorylase b**.



- The cAMP - activates cAMP dependent protein kinase.
- Protein kinase phosphorylates inactive form of glycogen phsophorylase kinase to active form.
- The enzyme protein phosphatase removes phosphate & inactivates phosphorylase kinase.
- The Phosphorylase kinase phosphorylates inactive glycogen phosphorylase 'b' to active glycogen phosphorylase 'a' which degrades glycogen.
- The enzyme protein phosphatase I can dephosphorylate & convert active glycogen phosphorylase 'a' to inactive 'b' form.

LIVER

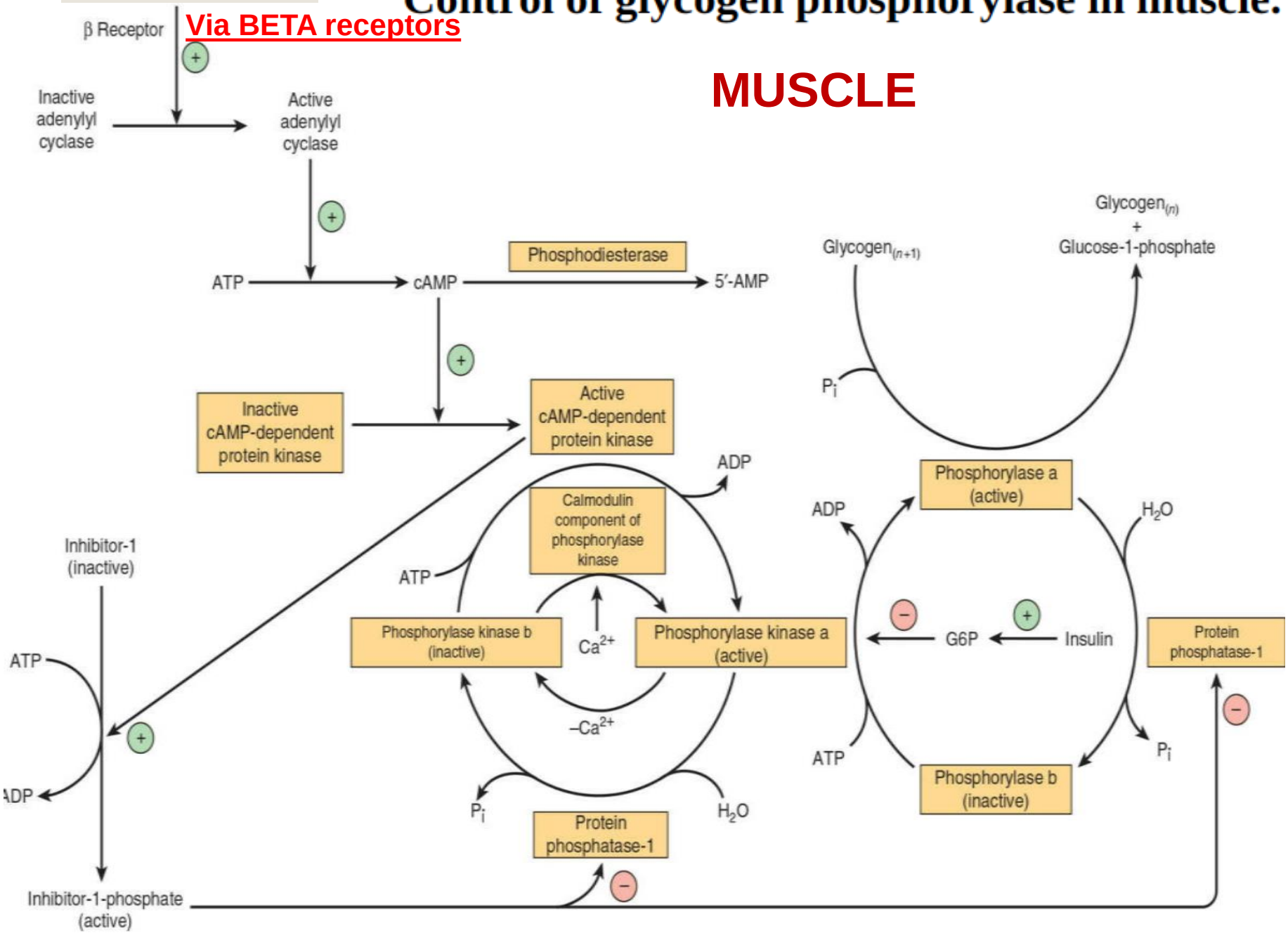


EPINEPRINE

Control of glycogen phosphorylase in muscle.

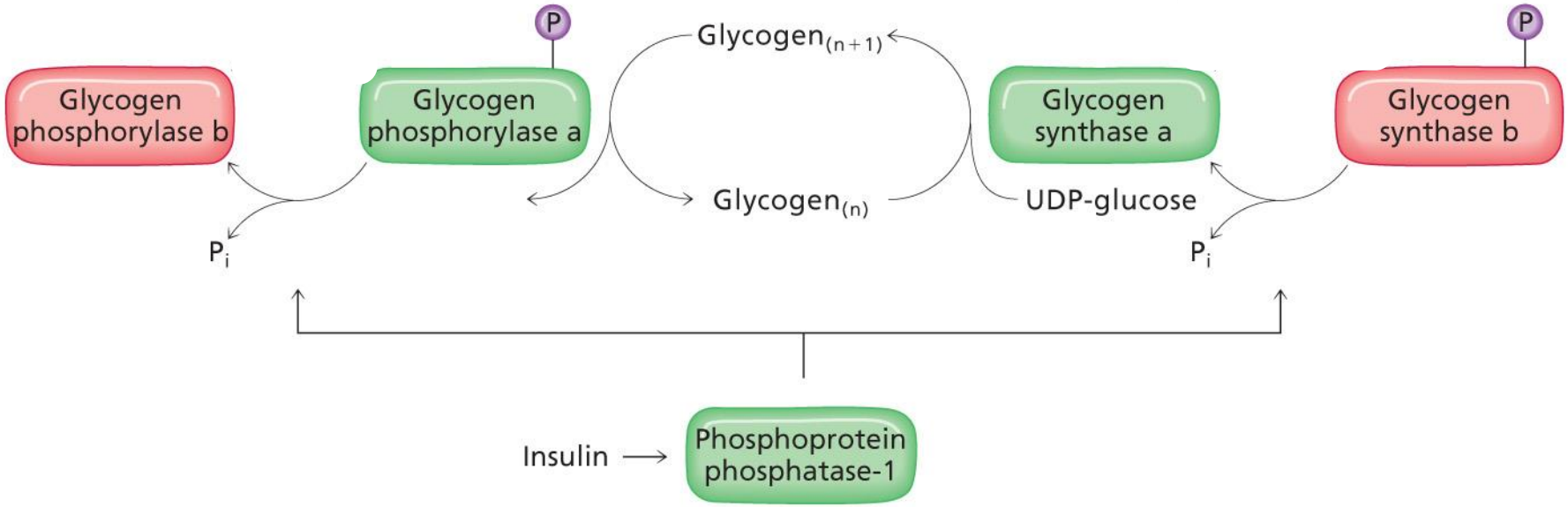
Via BETA receptors

MUSCLE



Insulin vs Glucagon

- Act Reciprocally on Glycogen synthase and Glycogen phosphorylase



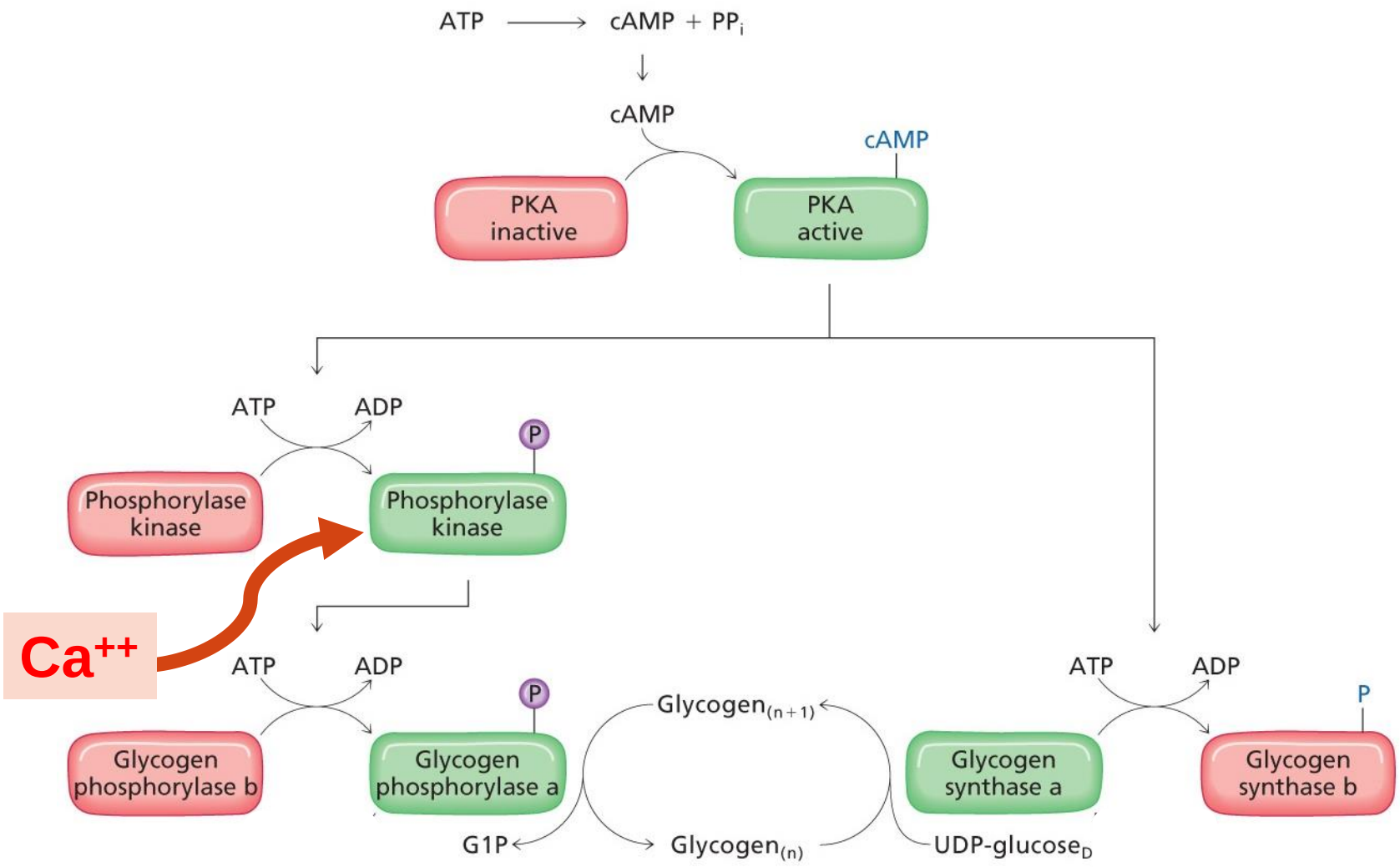
Role of Ca^{++} in glycogen degradation

- Glycogenolysis in muscle increases several 100-fold at the onset of contraction.

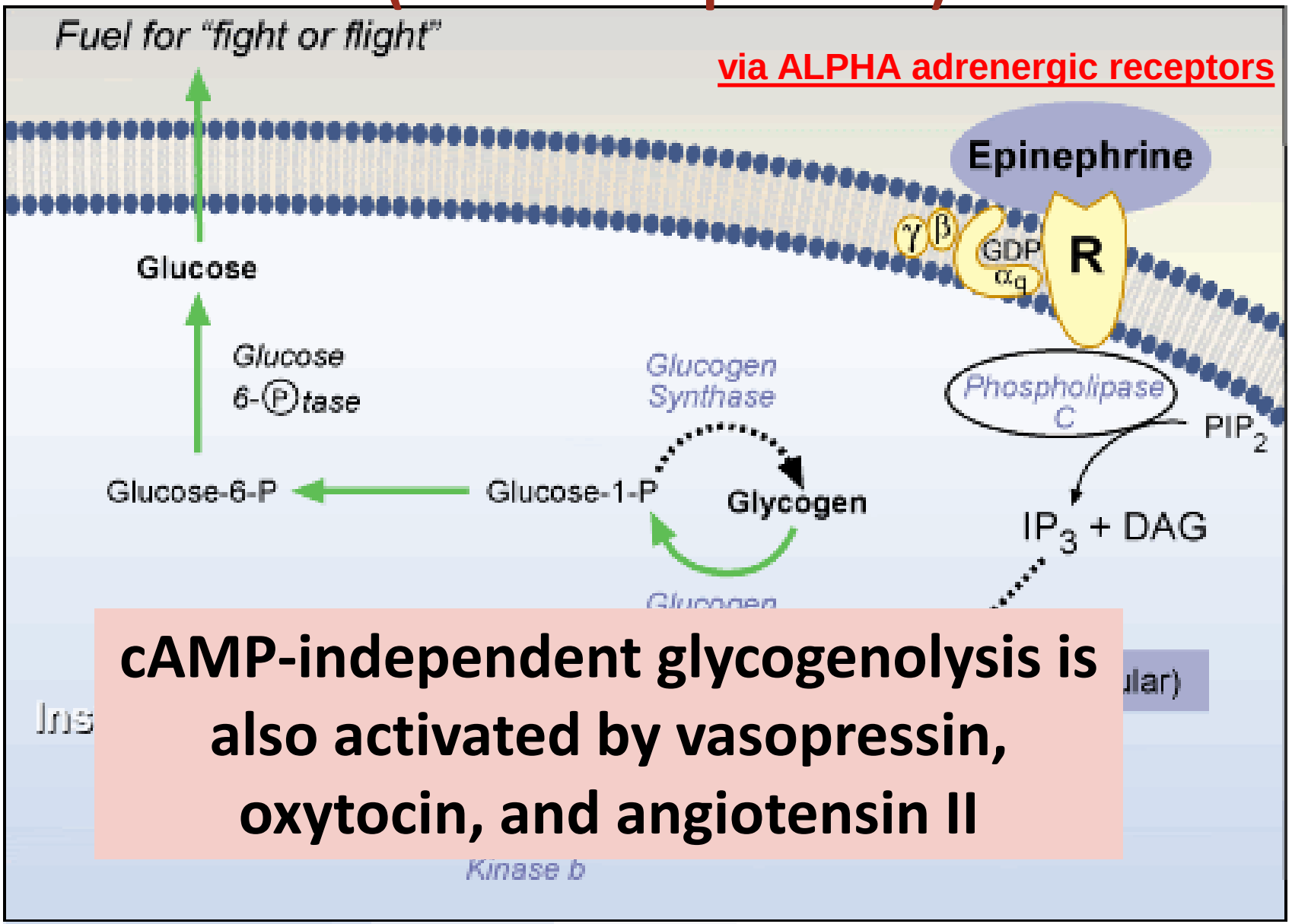
- During activation of contraction in skeletal muscle, Ca^{++} is released from the sarcoplasmic reticulum to promote actin/myosin interactions & glycogen breakdown in muscle

- The released Ca^{++} activates Phosphorylase Kinase, which activates glycogen phosphorylase in muscle (as δ subunit of phosphorylase kinase binds to calcium).

MUSCLE

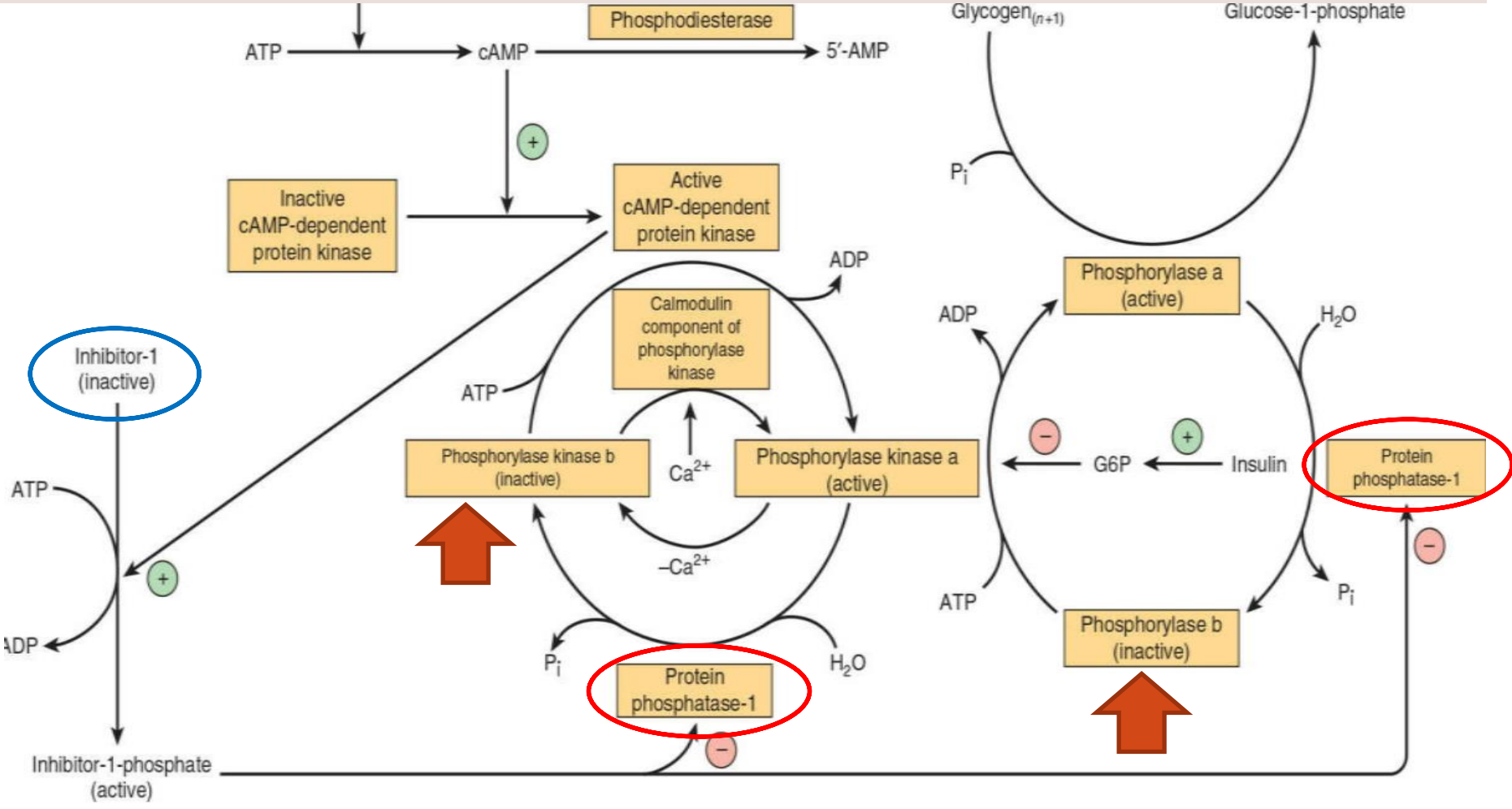


Glycogenolysis in Liver Can Be Calcium Dependent (cAMP-Independent)



cAMP-independent glycogenolysis is also activated by vasopressin, oxytocin, and angiotensin II

- Phosphorylase-a and phosphorylase kinase-a are dephosphorylated and inactivated by **protein phosphatase-1**.
- Protein phosphatase-1 is inhibited by **inhibitor-1**, which is active only after it has been phosphorylated by cAMP-dependent protein kinase.

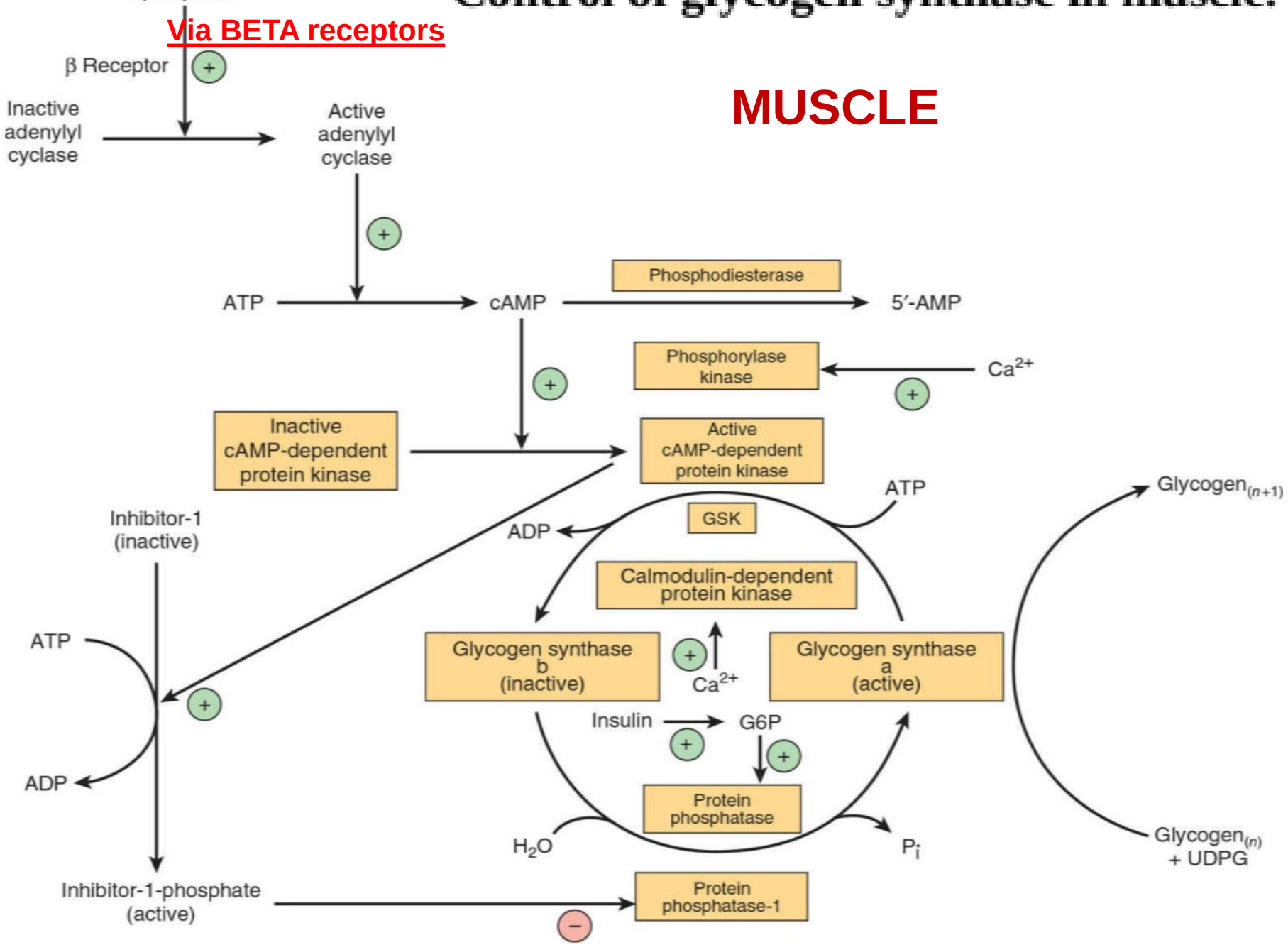


EPINEPRINE

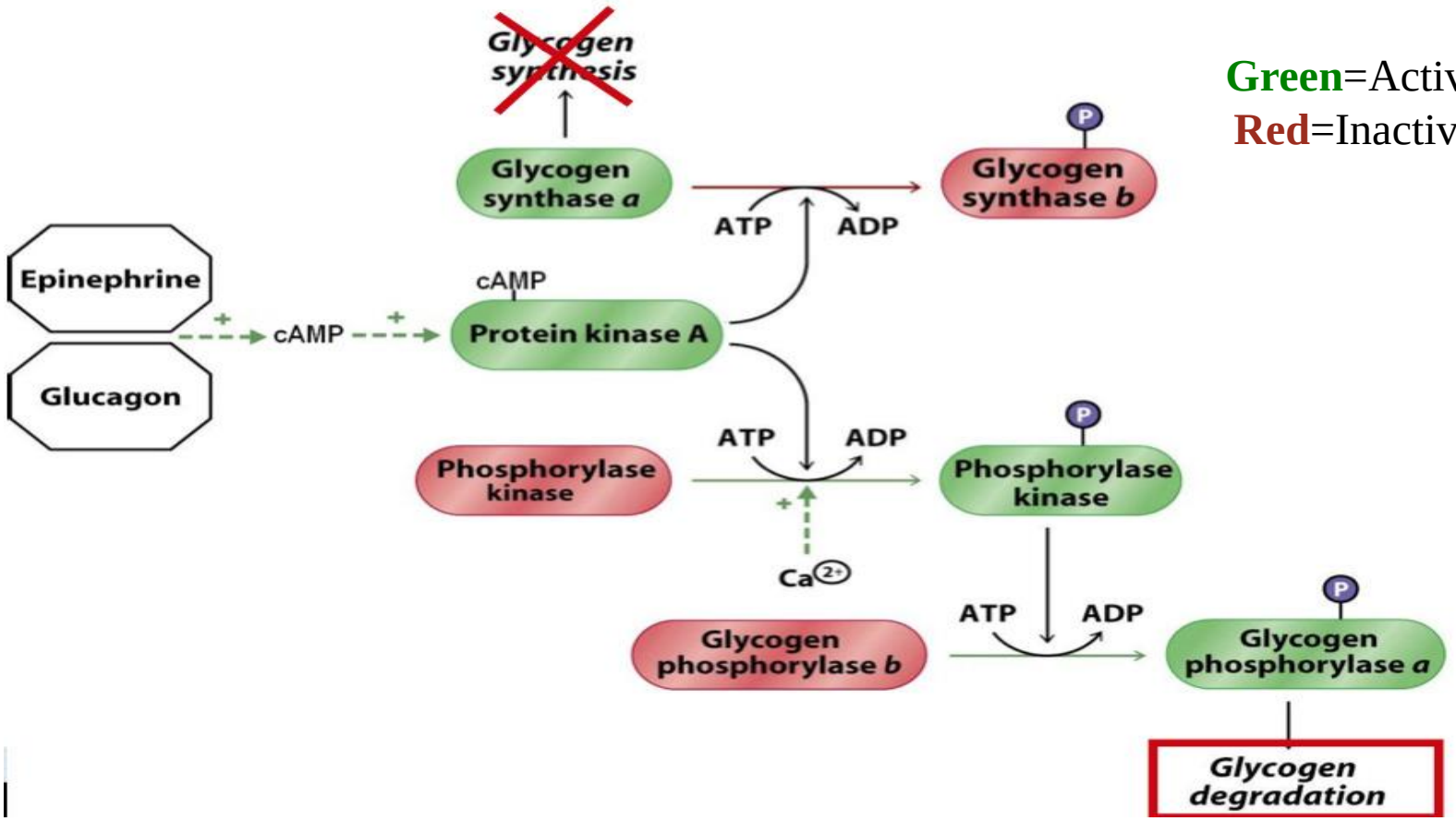
Control of glycogen synthase in muscle.

Via BETA receptors

MUSCLE

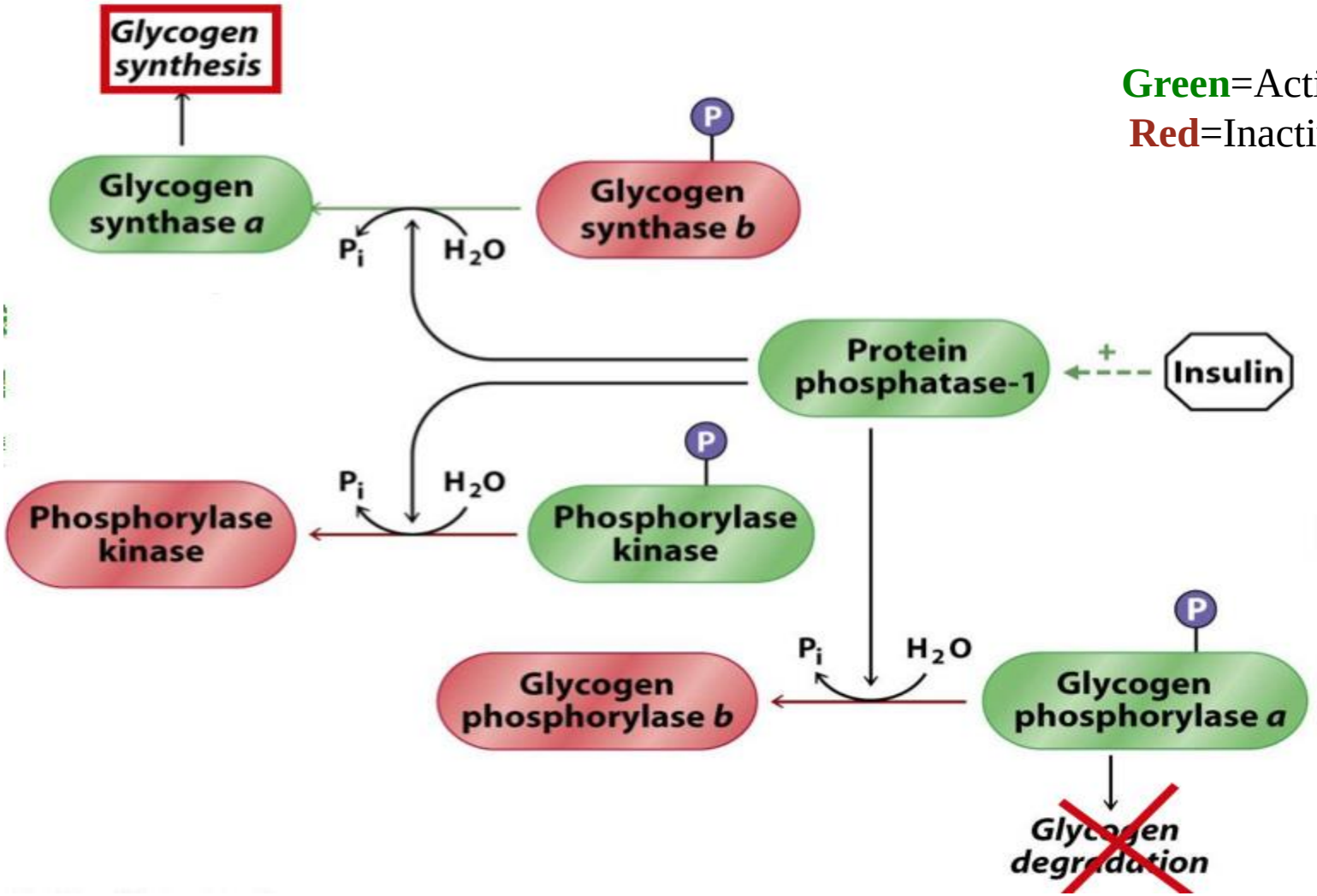


Glucagon & Epinephrine.....



Green=Active
Red=Inactive

Insulin.....



Green=Active
Red=Inactive

Regulation by Covalent Modification

Glucagon:

-Low levels of glucose induce release of glucagon

-Acts primarily on **liver** cells.

Epinephrine:

- Low levels of glucose induce release of Epinephrine

- Acts primarily on **skeletal muscle.**

They BOTH **Stimulates** glycogen breakdown & **inhibits** glycogenesis.

Insulin:

-High levels of glucose induce release of insulin from β- cells of islets of Langerhan in the pancreas.

-Detected by receptors at surface of **muscle** and **liver** cells.

Stimulates glycogenesis & **inhibits** glycogenolysis

Thanks for your attention!