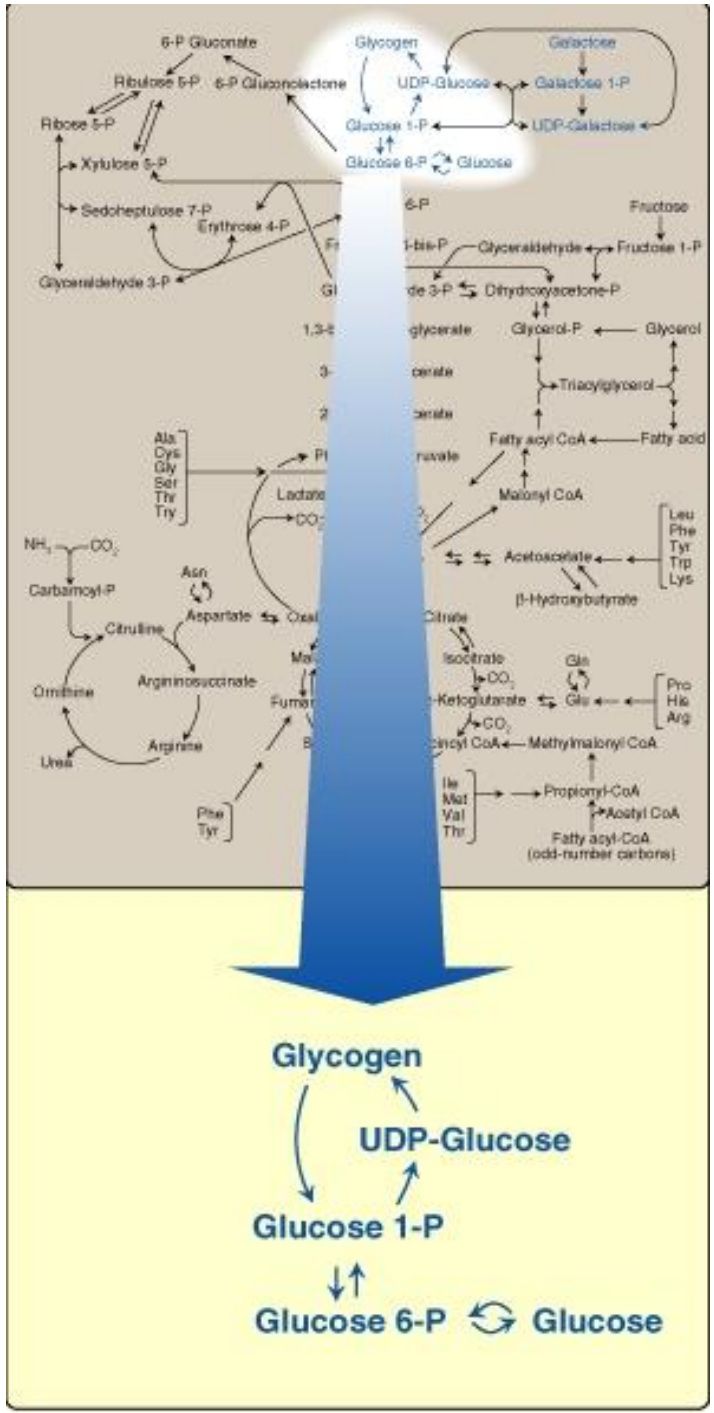
Glycogen Metabolism

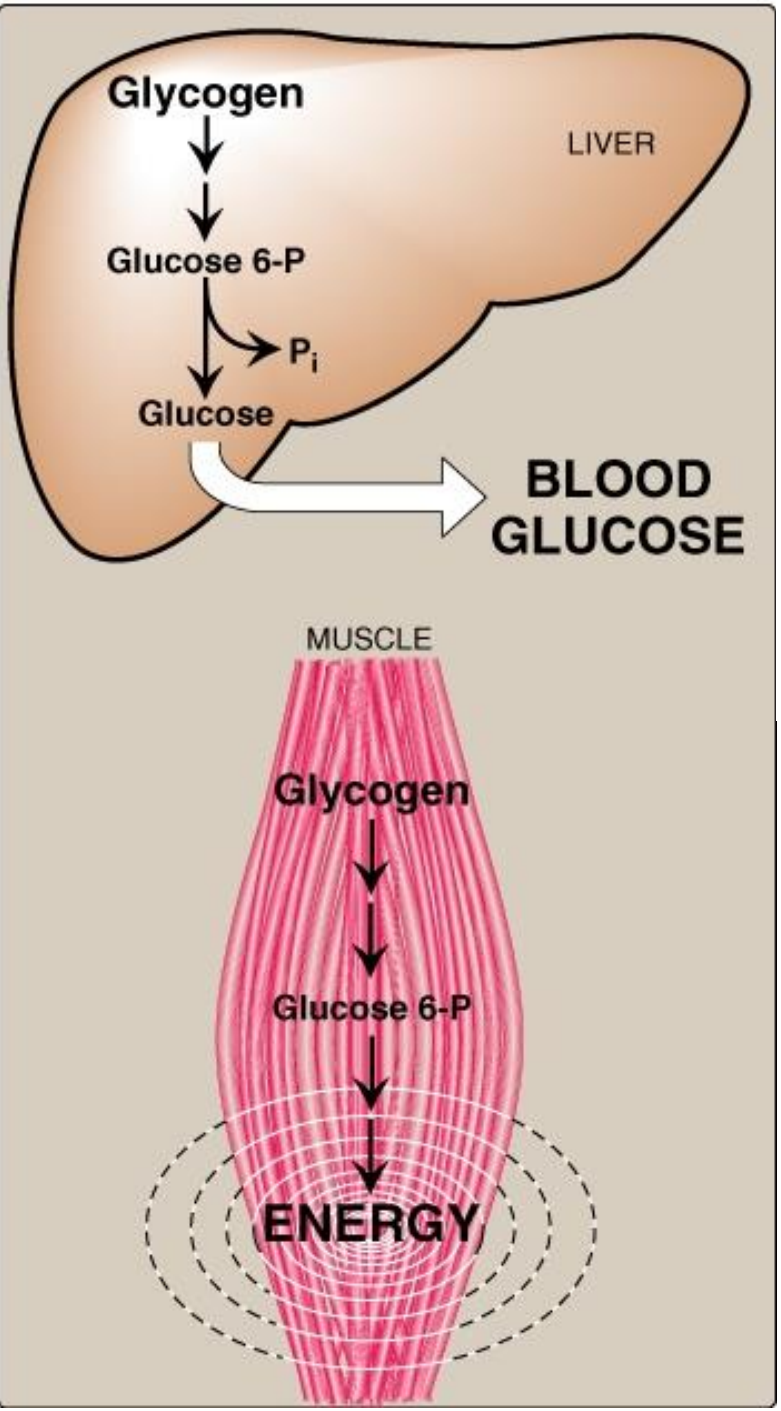
Suggested Reading:

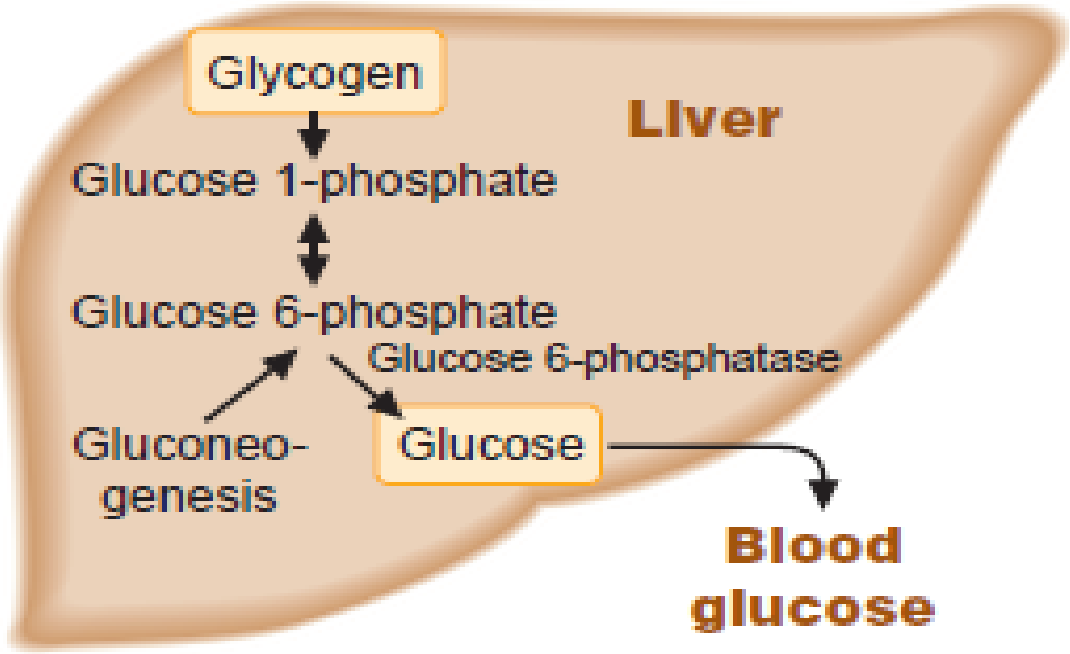
Lippincott's Illustrated reviews: Biochemistry

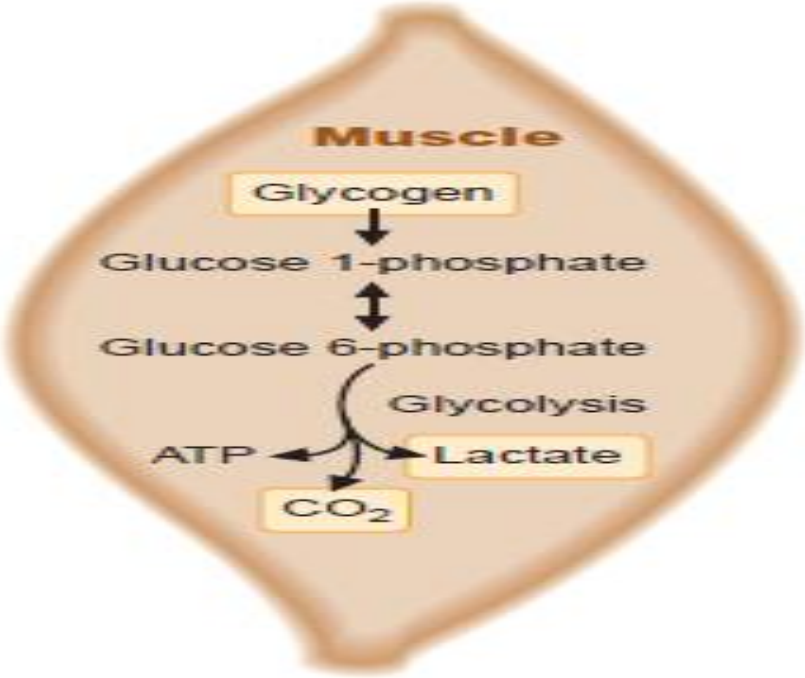


Glycogen
UDP-Glucose
Glucose 1-P
Glucose 6-P
Glucose

Glycogen
UDP-Glucose
Glucose 1-P
Glucose 6-P
Glucose

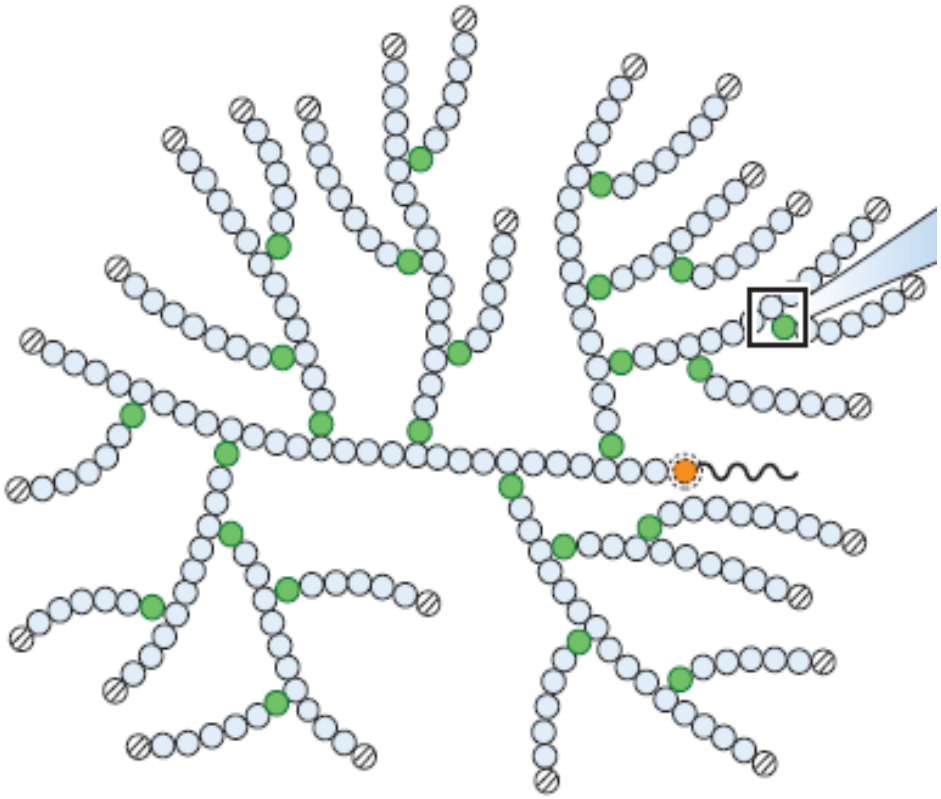

Glycogen
LIVER
Glucose 6-P
P_i
Glucose
BLOOD GLUCOSE
MUSCLE
Glycogen
Glucose 6-P
ENERGY


Glycogen
Liver
Glucose 1-phosphate
Glucose 6-phosphate
Glucose 6-phosphatase
Gluconeo-genesis
Glucose
Blood glucose


Muscle
Glycogen
Glucose 1-phosphate
Glucose 6-phosphate
Glycolysis
ATP
Lactate
CO_2

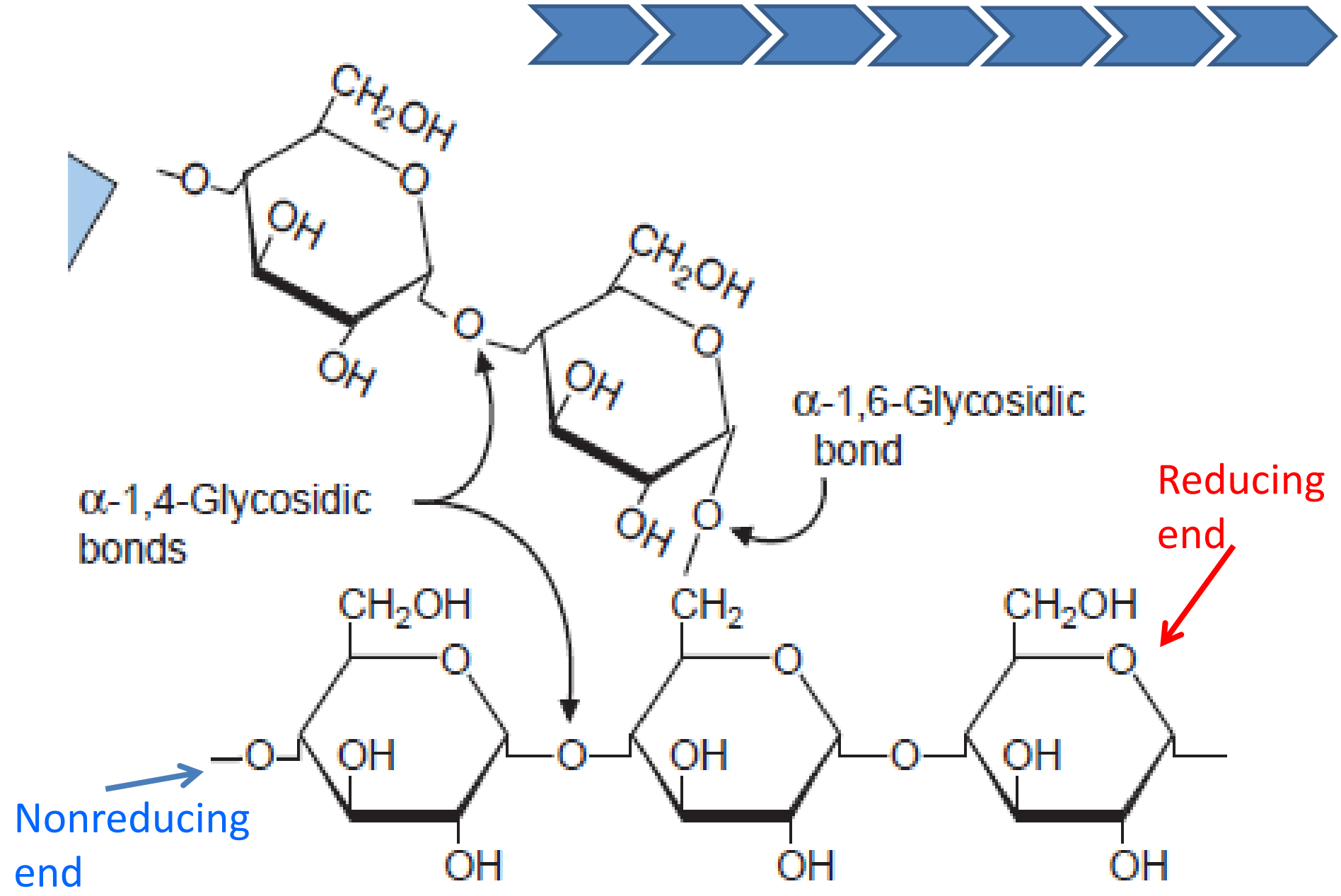
Sources of Blood Glucose

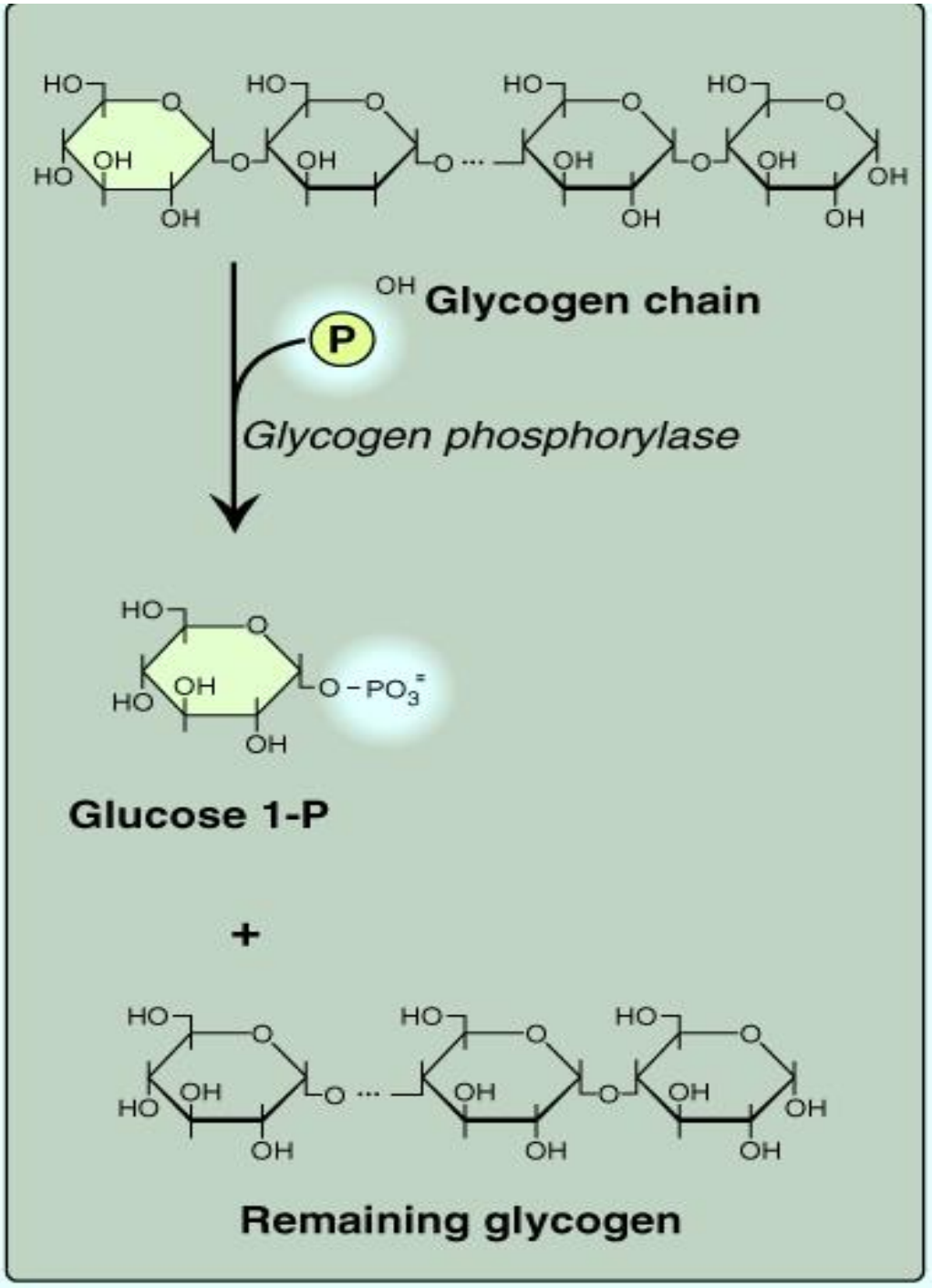
- Diet
  - Starch, mono and disahccarides, glucose
  - Sporadic, depend on diet,
- Gluconeogenesis
  - Sustained synthesis
  - Slow in responding to falling blood glucose level
- Glycogen
  - Storage form of glucose
  - Rapid response and mobilization.
  - Limited amount
  - Important energy source for exercising muscle.



* Extensively branched homopolysaccharide

* One molecule consists of hundreds of thousands of glucose units- up to M.W. of 100,000,000.


α-1,6-Glycosidic bond
α-1,4-Glycosidic bonds
Reducing end
Nonreducing end

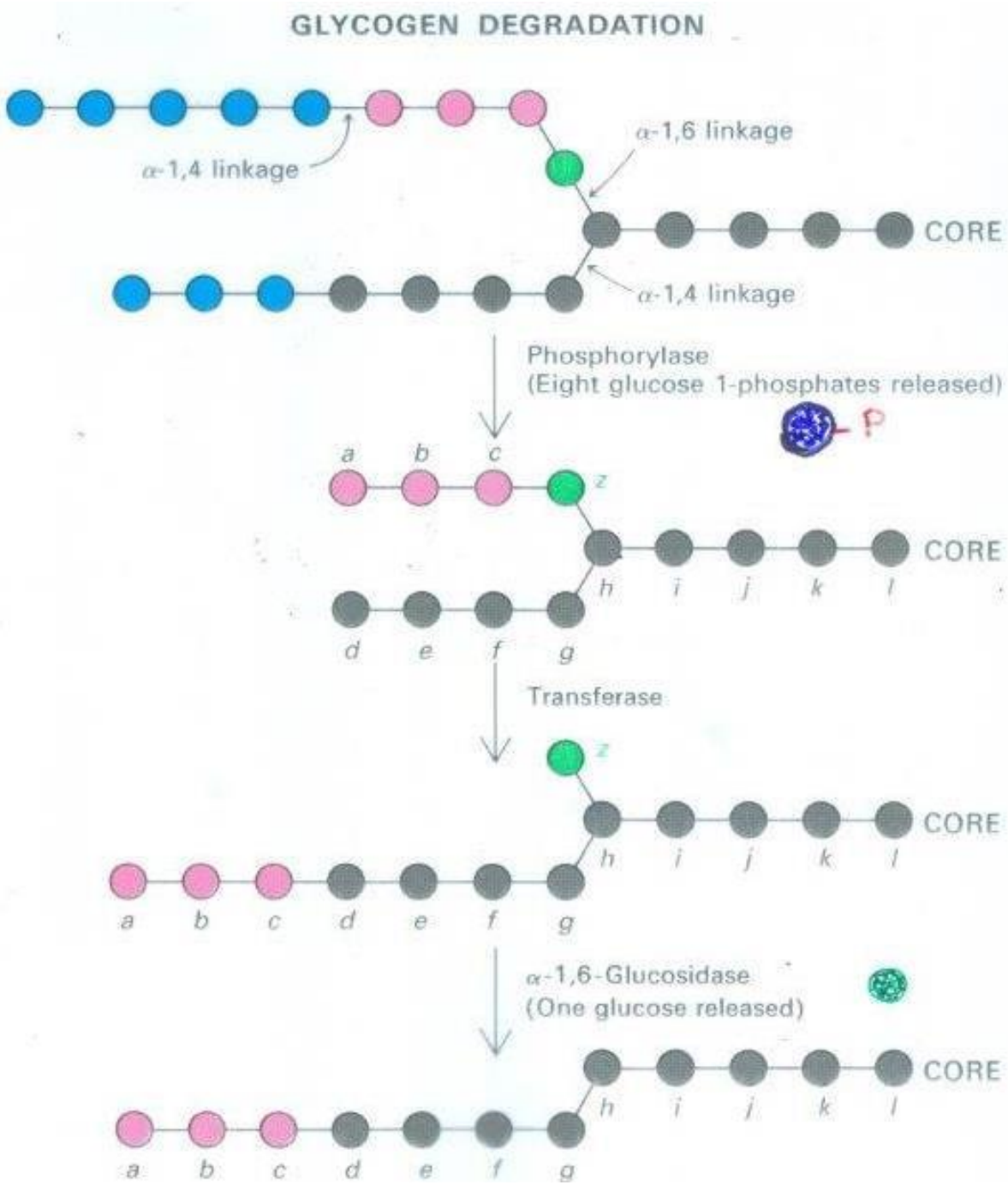


Degradation of glycogen

Degradation of glycogen
One glucose unit is removed at a time

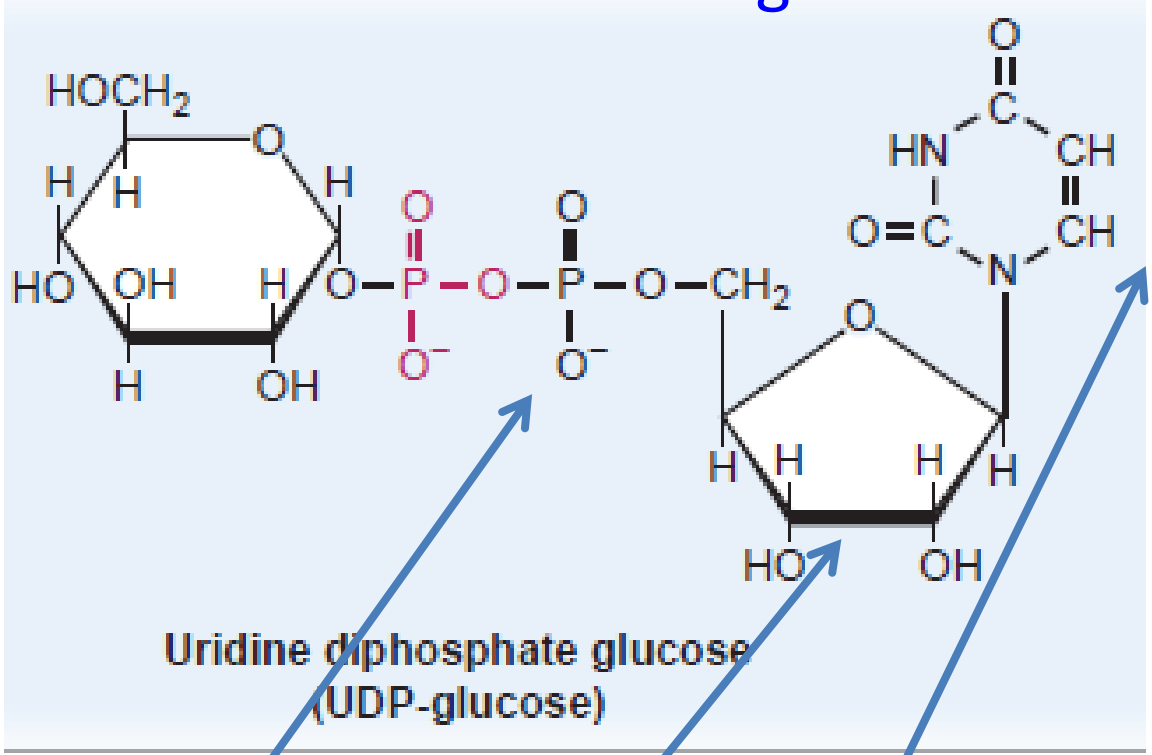
From the nonreducing ends

Released in the form of glucose 1-phosphate


GLYCOGEN DEGRADATION
α-1,4 linkage
α-1,6 linkage
CORE
α-1,4 linkage
Phosphorylase
(Eight glucose 1-phosphates released)
P
a b c z
CORE
h i j k l
d e f g
Transferase
z
CORE
h i j k l
a b c d e f g
α-1,6-Glucosidase
(One glucose released)
CORE
h i j k l
a b c d e f g

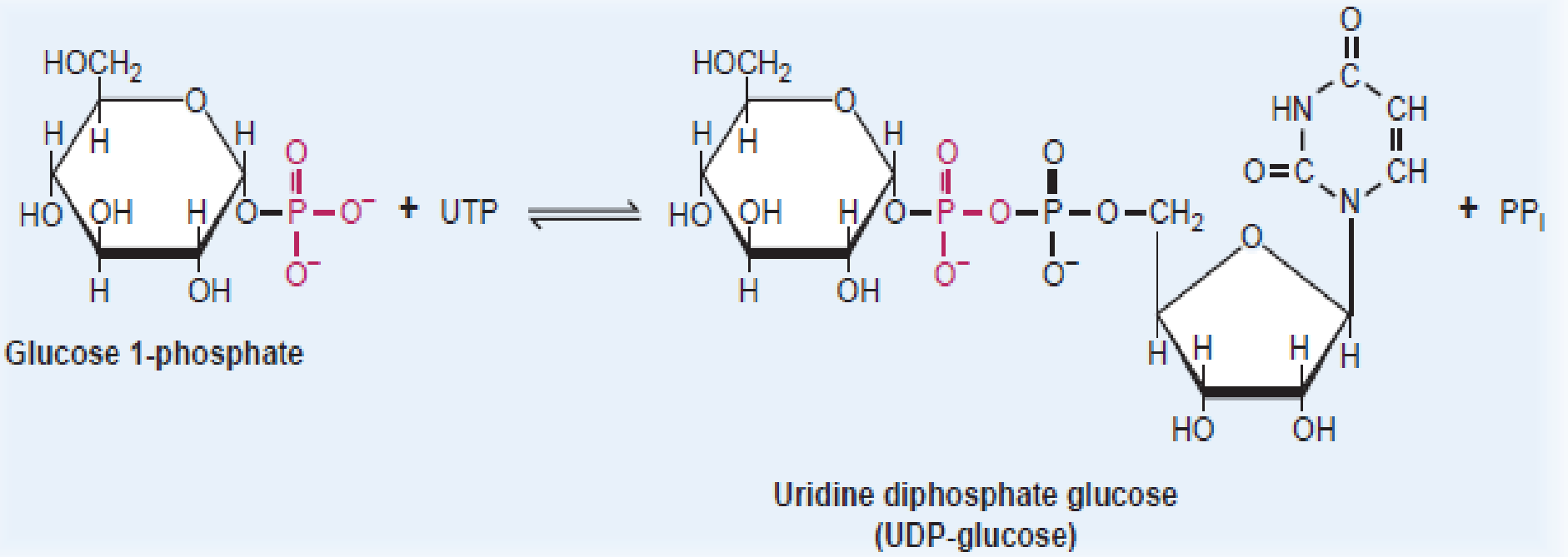
Glycogen is synthesized by adding glucose one by one

UDP-Glucose s the active donor of glucose units

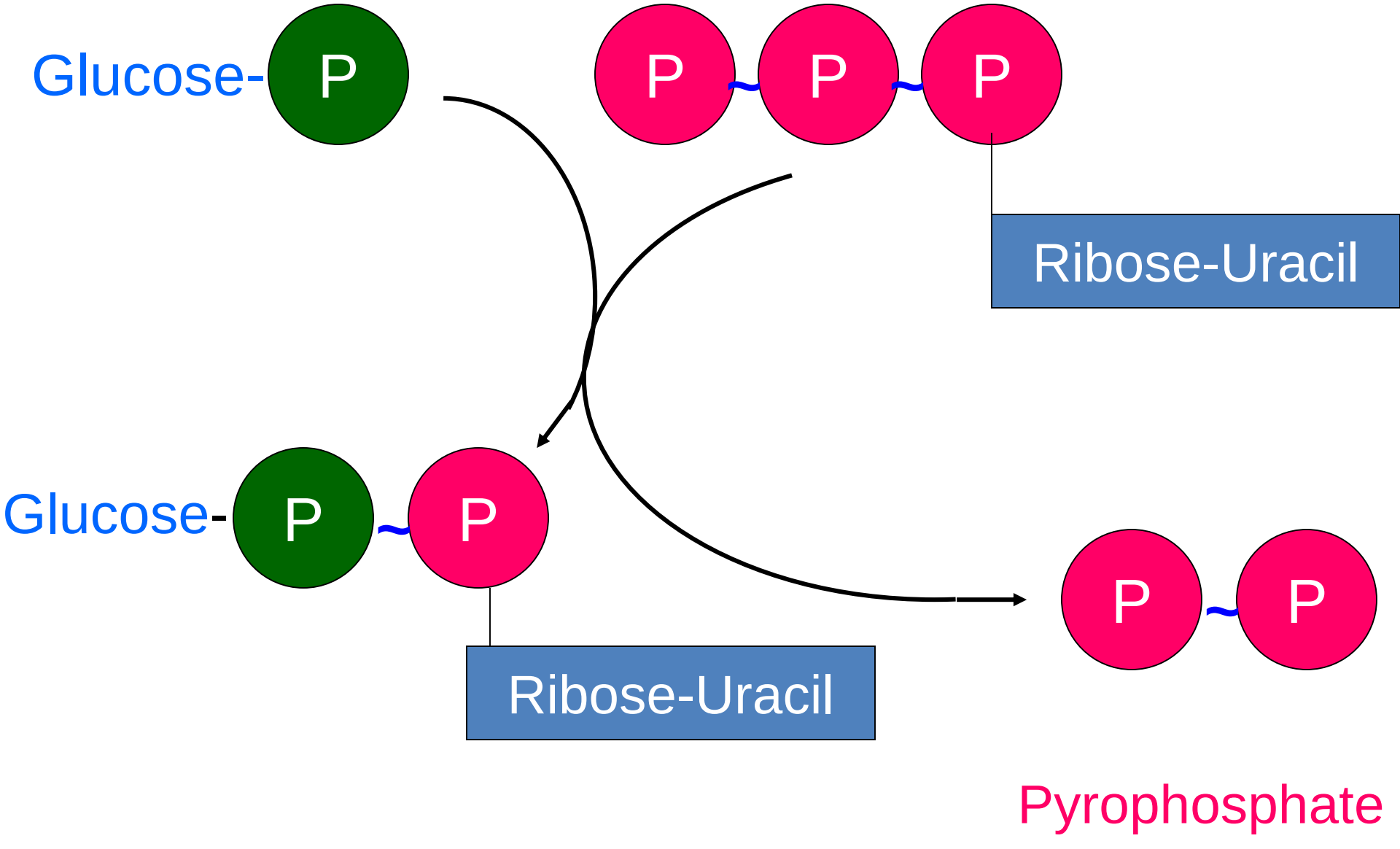


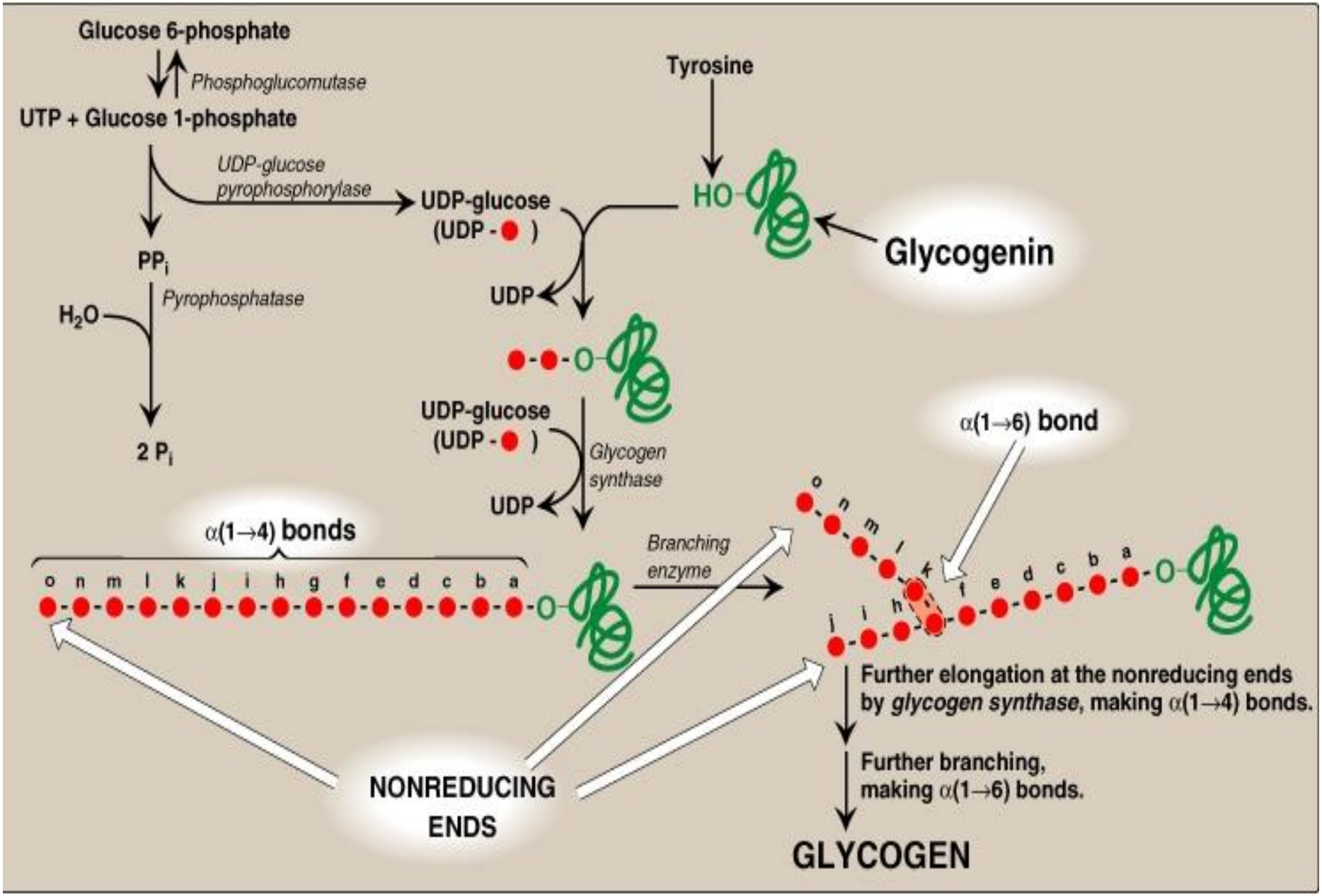
Phosphate Ribose Uracil

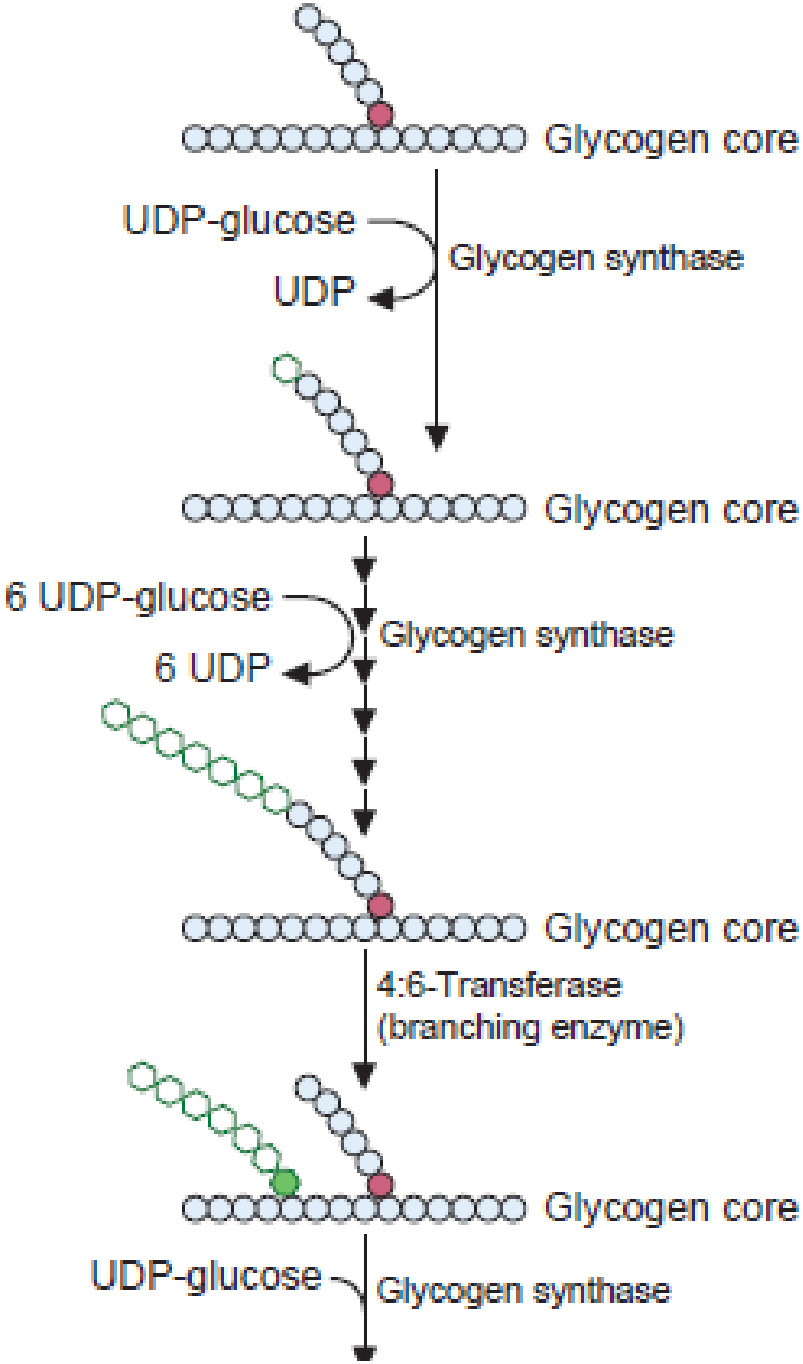
Formation of UDP-Glucose



Formation of UDP-Glucose




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


Glycogen core
UDP-glucose
UDP
Glycogen synthase
Glycogen core
6 UDP-glucose
6 UDP
Glycogen synthase
Glycogen core
4:6-Transferase
(branching enzyme)
Glycogen core
UDP-glucose
Glycogen synthase

Glycogen Storage Diseases

- Genetic diseases
- Defect in an enzyme required for synthesis or degradation ➔
- Accumulation of excessive amount of glygcogen
- In one or more tissue
- Severity: FATAL in Infancy……. Mild disorder

Glycogen Storage Diseases (examples)

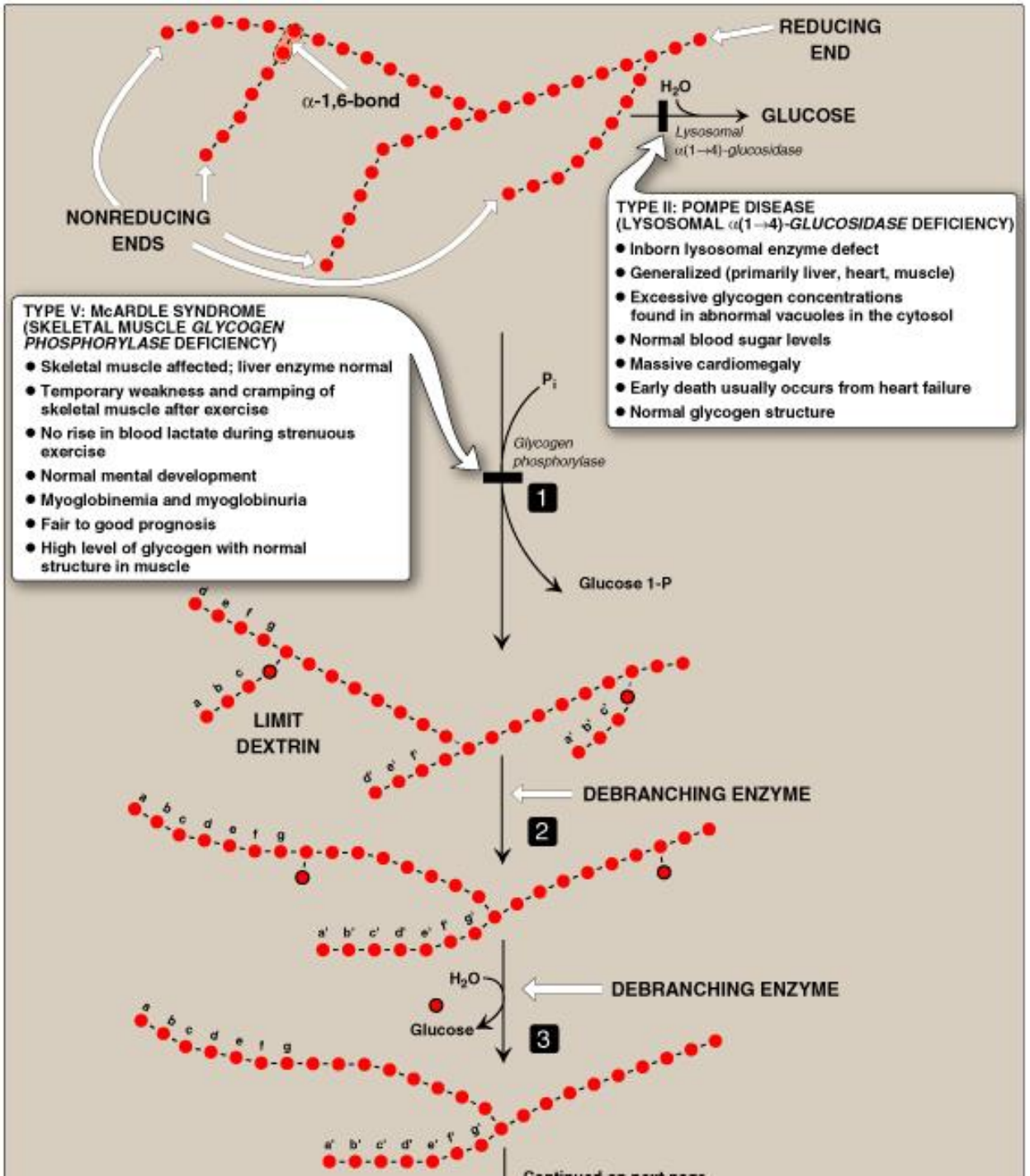
- I Glucose-6-phosphatase (von Gierk's) disease
  - Liver, kidney and intestine.
  - Severe fasting hypoglycemia
  - Hepatomegaly fatty liver.
  - Normal glycogen structure.
  - Progressive renal disease.
  - Growth retardation.

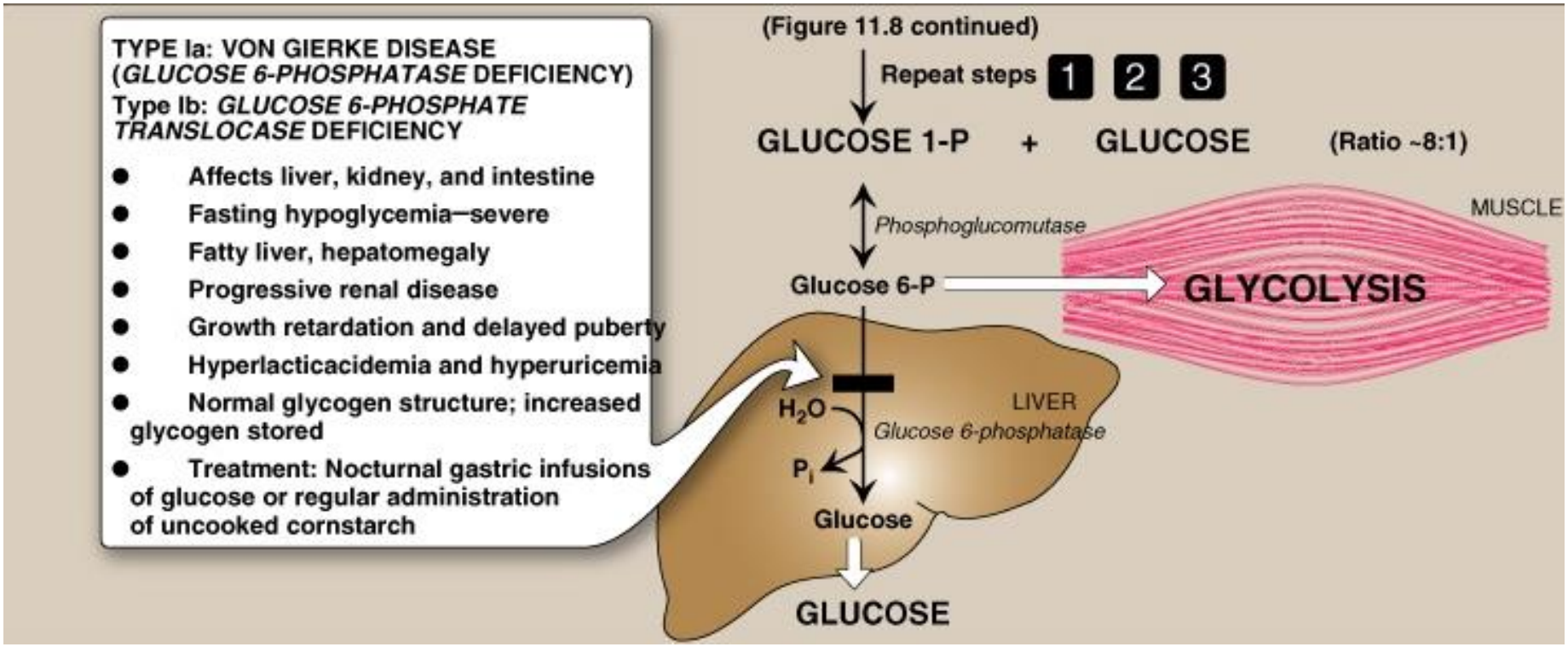
Glycogen Storage Diseases (examples)

- V Muscle glycogen phosphorylase (McArdle syndrome)
  - Only muscle is affected;
  - Weakness and cramping of muscle after exercise
  - no increase in [lactate] during exercise

Glycogen Storage Diseases (examples)

- II Lysosomes α (1→4) glucosidase ➔ POMP Disease
- Degradation of glycogen in the lysosomes
- ≈ 3% of glycogen is degraded in the lysosomes
- Affects liver, heart and muscle
- Excessive glycogen in abnormal vacuoles in the lysosomes
- Massive cardiomegaly
- Normal blood sugar, normal glycogen structre
- Early death from heart failure.


REDUCING END
α-1,6-bond
H_2O
GLUCOSE
Lysosomal α(1→4)-glucosidase
NONREDUCING ENDS
TYPE II: POMPE DISEASE (LYSOSOMAL α(1→4)-GLUCOSIDASE DEFICIENCY)
• Inborn lysosomal enzyme defect
• Generalized (primarily liver, heart, muscle)
• Excessive glycogen concentrations found in abnormal vacuoles in the cytosol
• Normal blood sugar levels
• Massive cardiomegaly
• Early death usually occurs from heart failure
• Normal glycogen structure
TYPE V: McARDLE SYNDROME (SKELETAL MUSCLE GLYCOGEN PHOSPHORYLASE DEFICIENCY)
• Skeletal muscle affected; liver enzyme normal
• Temporary weakness and cramping of skeletal muscle after exercise
• No rise in blood lactate during strenuous exercise
• Normal mental development
• Myoglobinemia and myoglobinuria
• Fair to good prognosis
• High level of glycogen with normal structure in muscle
P_i
Glycogen phosphorylase
1
Glucose 1-P
LIMIT DEXTRIN
DEBRANCHING ENZYME
2
H_2O
Glucose
DEBRANCHING ENZYME
3


TYPE Ia: VON GIERKE DISEASE
(GLUCOSE 6-PHOSPHATASE DEFICIENCY)
Type Ib: GLUCOSE 6-PHOSPHATE TRANSLOCASE DEFICIENCY
Affects liver, kidney, and intestine
Fasting hypoglycemia—severe
Fatty liver, hepatomegaly
Progressive renal disease
Growth retardation and delayed puberty
Hyperlacticacidemia and hyperuricemia
Normal glycogen structure; increased glycogen stored
Treatment: Nocturnal gastric infusions of glucose or regular administration of uncooked cornstarch
(Figure 11.8 continued)
Repeat steps 1 2 3
GLUCOSE 1-P + GLUCOSE (Ratio ~8:1)
Phosphoglucomutase
MUSCLE
Glucose 6-P
GLYCOLYSIS
LIVER
H2O
Glucose 6-phosphatase
Pi
Glucose
GLUCOSE

Energy needed for glycogen synthesis

Glucose + ATP $\longrightarrow$ Glucose 6-phosphate + ADP

Glucose 6-phosphate $\rightleftharpoons$ Glucose 1-phosphate

Glucose 1-phosphate UTP $\rightleftharpoons$ UDP-Glucose PP_i

PP_i + H_2O $\longrightarrow$ $2P_i$

UDP-Glucose + $Glycogen_{(n)}$ $\longrightarrow$ UDP + $Glycogen_{(n+1)}$

Glc. + ATP + UTP+$Glycogen_{(n)}$ $\longrightarrow$ ADP + UDP +$Glycogen_{(n+1}$

The net reaction in glycogen synthesis and degradation

Glucose 1-phosphate + UTP $\rightleftharpoons$ UDP-Glucose + PP_i

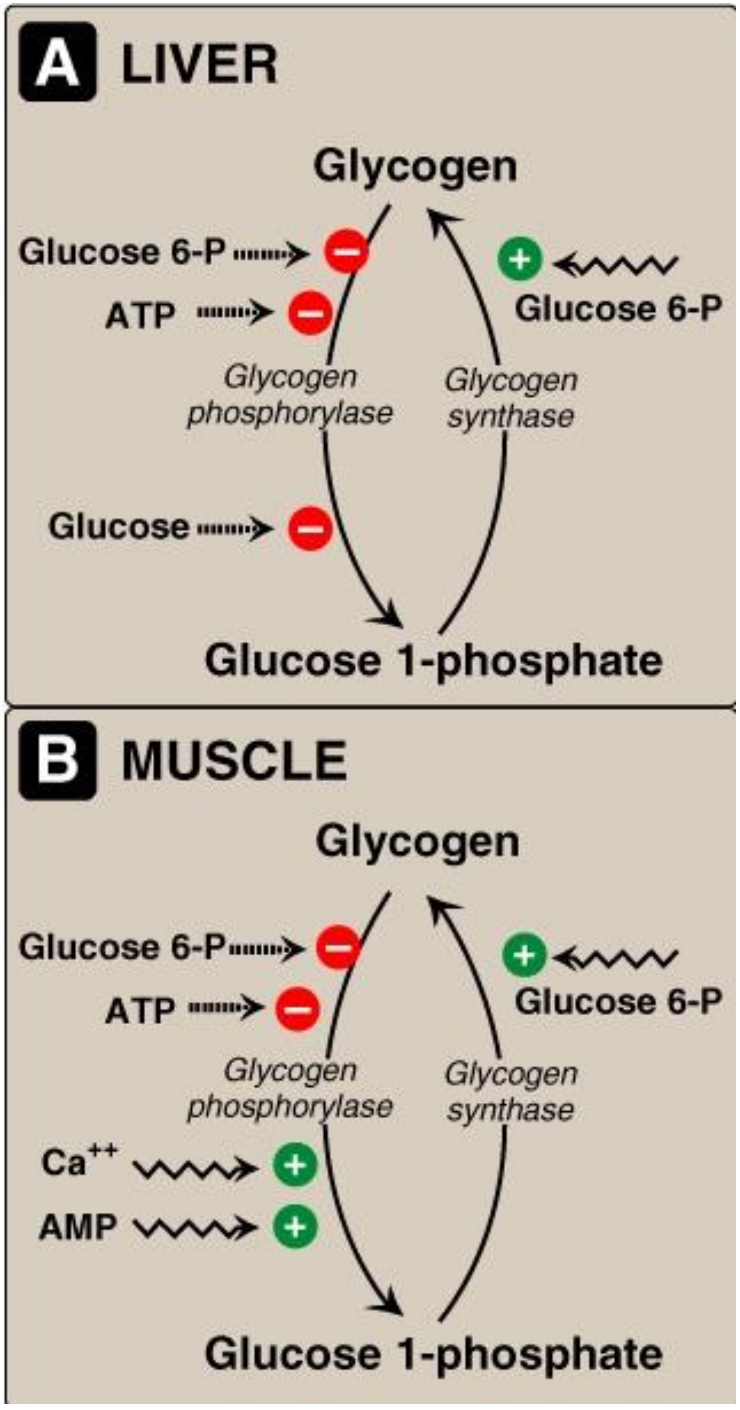
PP_i + H_2O $\longrightarrow$ $2P_i$

UDP-Glucose + $Glycogen_{(n)}$ $\rightleftharpoons$ UDP + $Glycogen_{(n+1)}$

Glc. 1-phosph. + UTP+$Glycogen_{(n)}$ $\longrightarrow$ UDP +$Glycogen_{(n+1}$

Degradation

$Glycogen_{(n)}$ + P_i $\rightleftharpoons$ $Glycogen_{(n-1)}$ +Glc. 1-phosphate

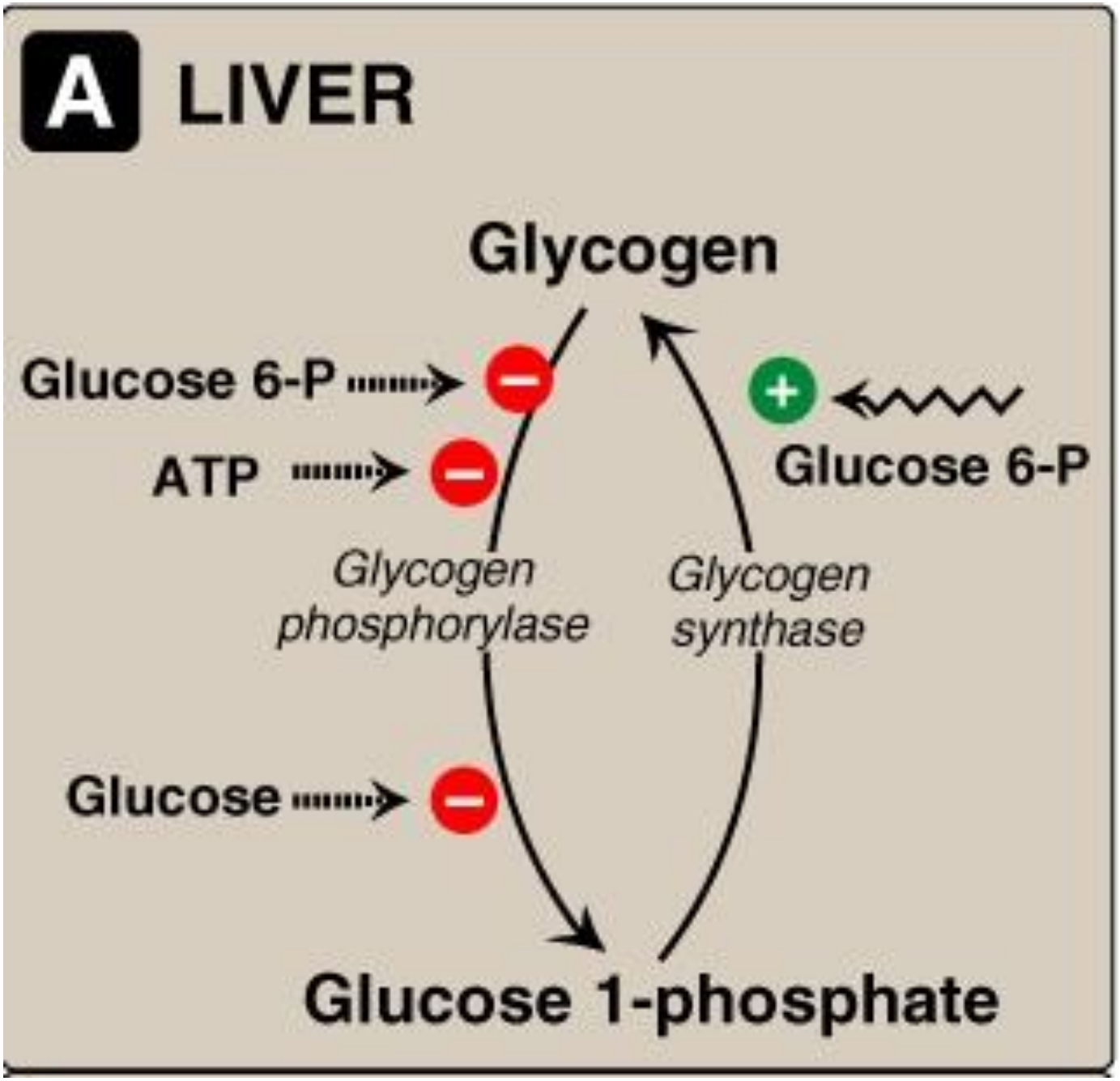


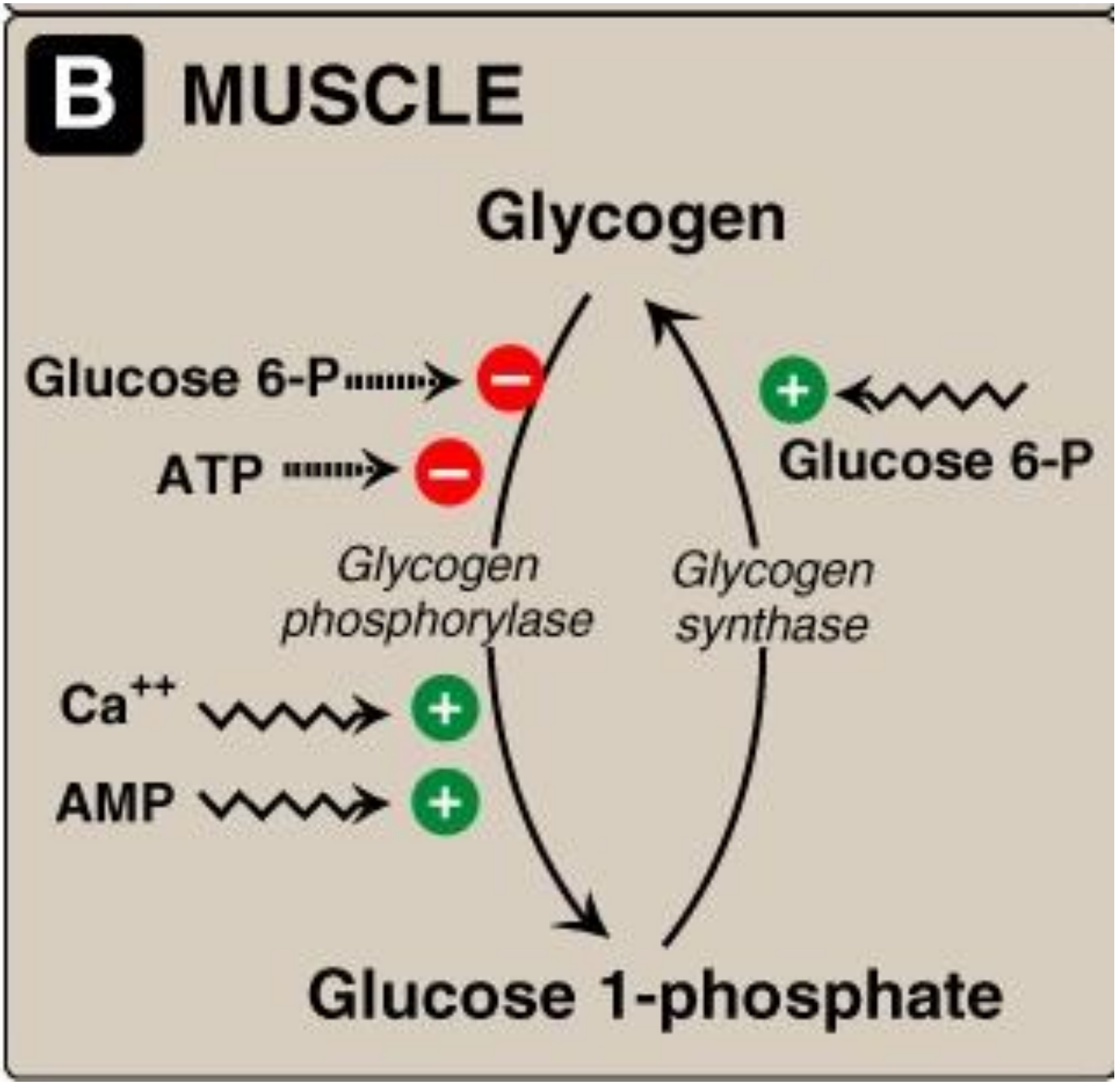
Allosteric Regulation

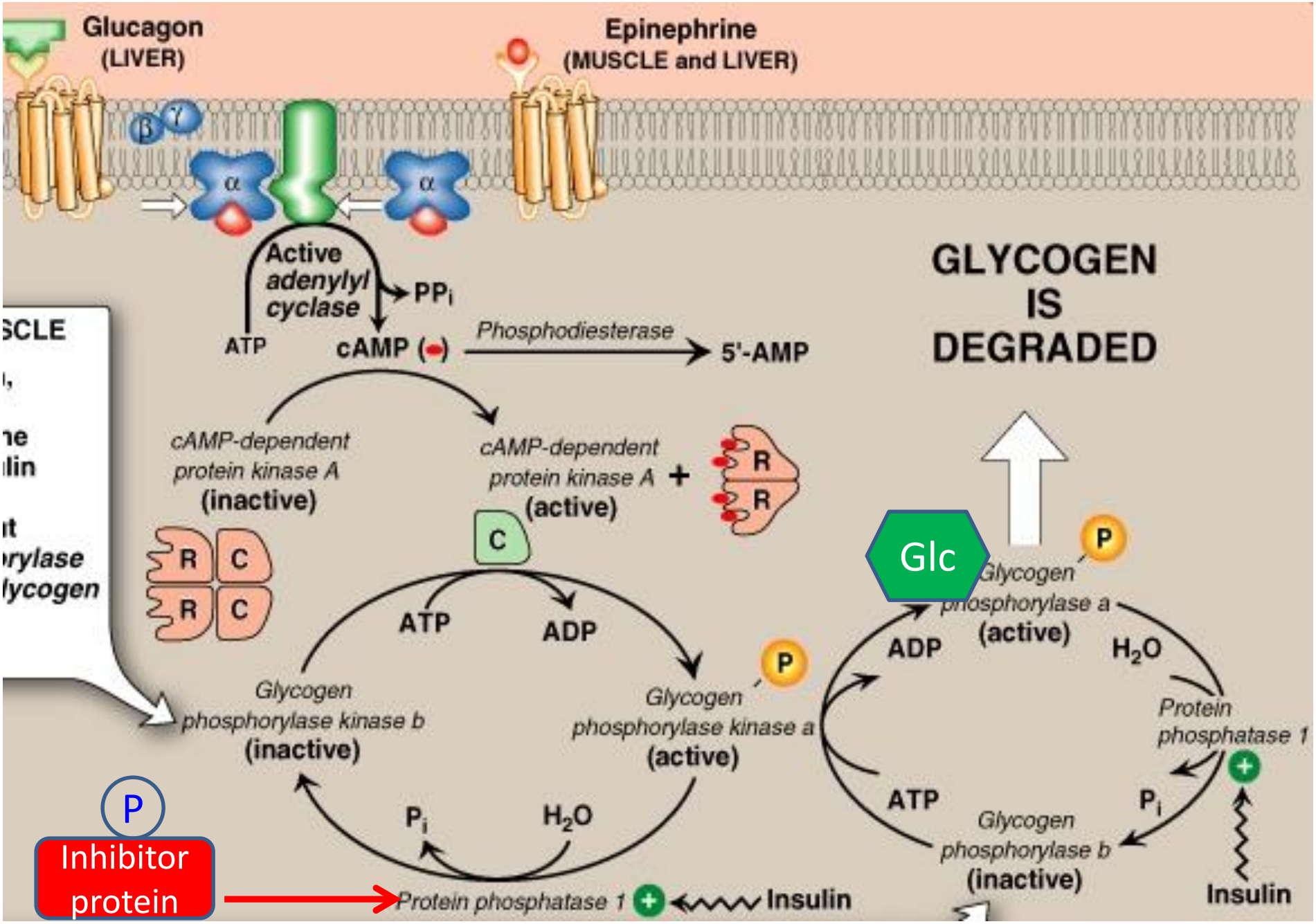
Rapid response to cell's needs

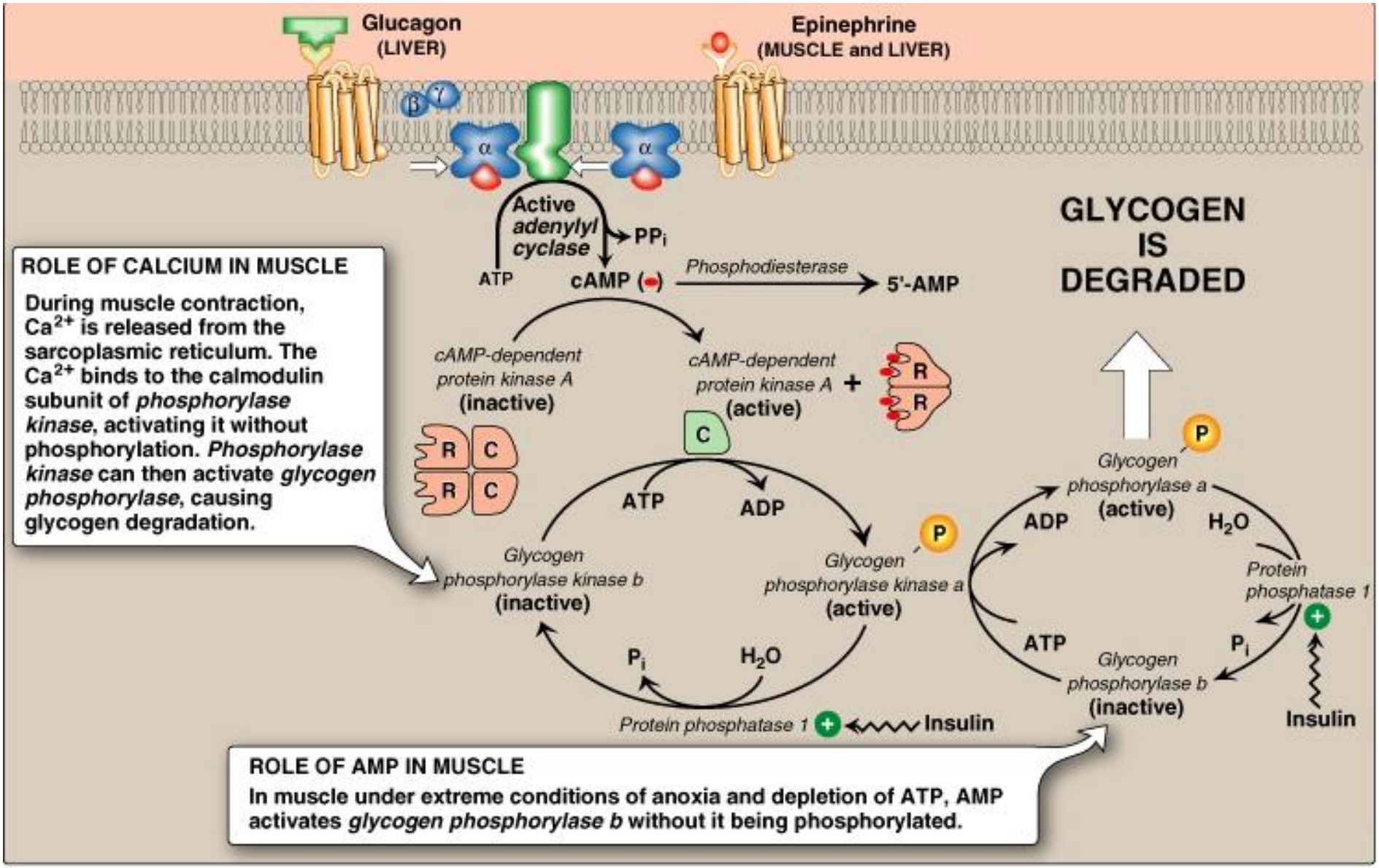
Available substate and ATP➔ synthesis

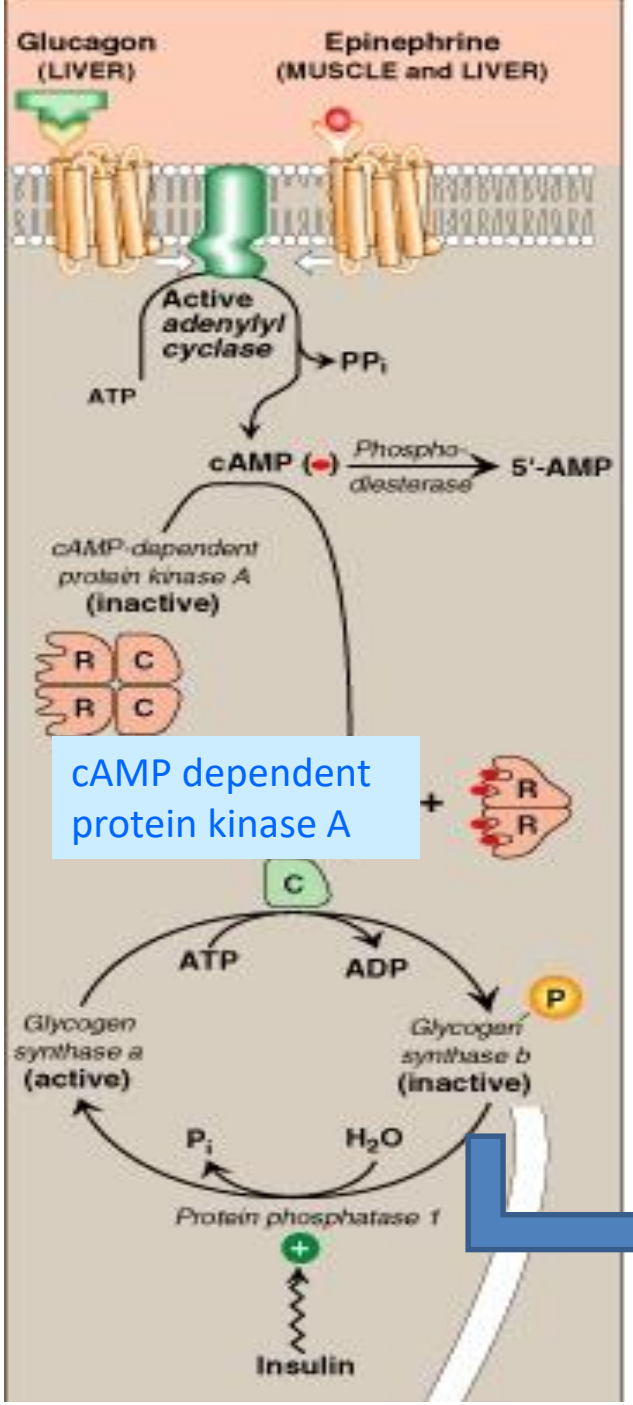
↓↓Glucose and ↓ATP ➔ Glycogenolysis


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


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


Glucagon
(LIVER)
Epinephrine
(MUSCLE and LIVER)
β
γ
α
α
Active
adenylyl
cyclase
PPi
ATP
cAMP (-)
Phosphodiesterase
5'-AMP
GLYCOGEN
IS
DEGRADED
cAMP-dependent
protein kinase A
(inactive)
cAMP-dependent
protein kinase A
(active)
+
R
R
C
R
C
R
C
ATP
ADP
Glycogen
phosphorylase kinase b
(inactive)
Glycogen
phosphorylase kinase a
(active)
P
Glc
P
Glycogen
phosphorylase a
(active)
ADP
H2O
Protein
phosphatase 1
ATP
Pi
Glycogen
phosphorylase b
(inactive)
Pi
H2O
Protein phosphatase 1
Insulin
Insulin
P
Inhibitor
protein

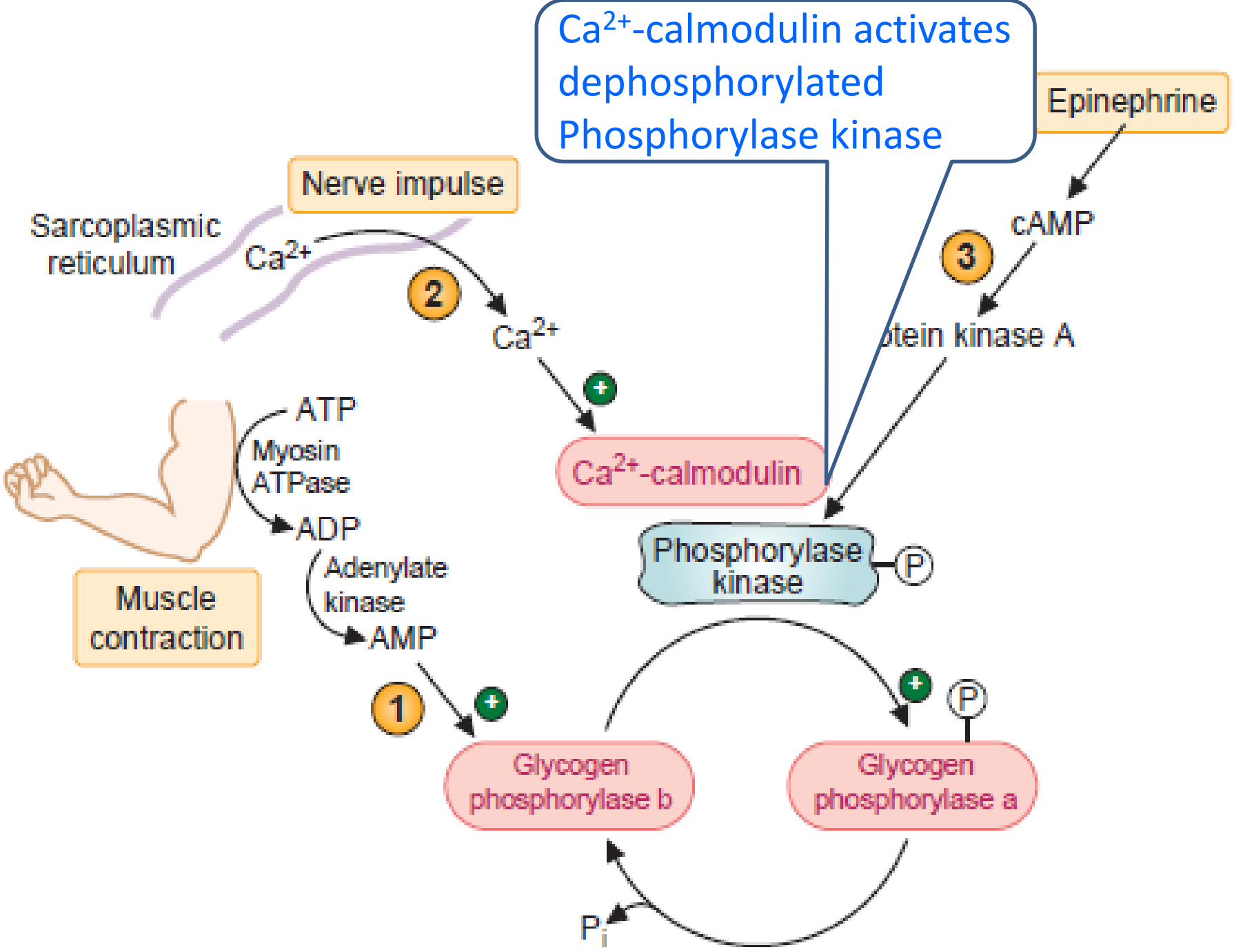

Glucagon
(LIVER)
Epinephrine
(MUSCLE and LIVER)
β
γ
α
α
Active
adenylyl
cyclase
PPi
ATP
cAMP (-)
Phosphodiesterase
5'-AMP
GLYCOGEN
IS
DEGRADED
ROLE OF CALCIUM IN MUSCLE
During muscle contraction, Ca2+ is released from the sarcoplasmic reticulum. The Ca2+ binds to the calmodulin subunit of phosphorylase kinase, activating it without phosphorylation. Phosphorylase kinase can then activate glycogen phosphorylase, causing glycogen degradation.
cAMP-dependent
protein kinase A
(inactive)
cAMP-dependent
protein kinase A
(active)
+
R
R
R
C
R
C
C
ATP
ADP
Glycogen
phosphorylase kinase b
(inactive)
Glycogen
phosphorylase kinase a
(active)
P
Pi
H2O
Protein phosphatase 1
+
Insulin
Glycogen
phosphorylase a
(active)
P
ADP
H2O
Protein
phosphatase 1
+
ATP
Pi
Glycogen
phosphorylase b
(inactive)
Insulin
ROLE OF AMP IN MUSCLE
In muscle under extreme conditions of anoxia and depletion of ATP, AMP activates glycogen phosphorylase b without it being phosphorylated.

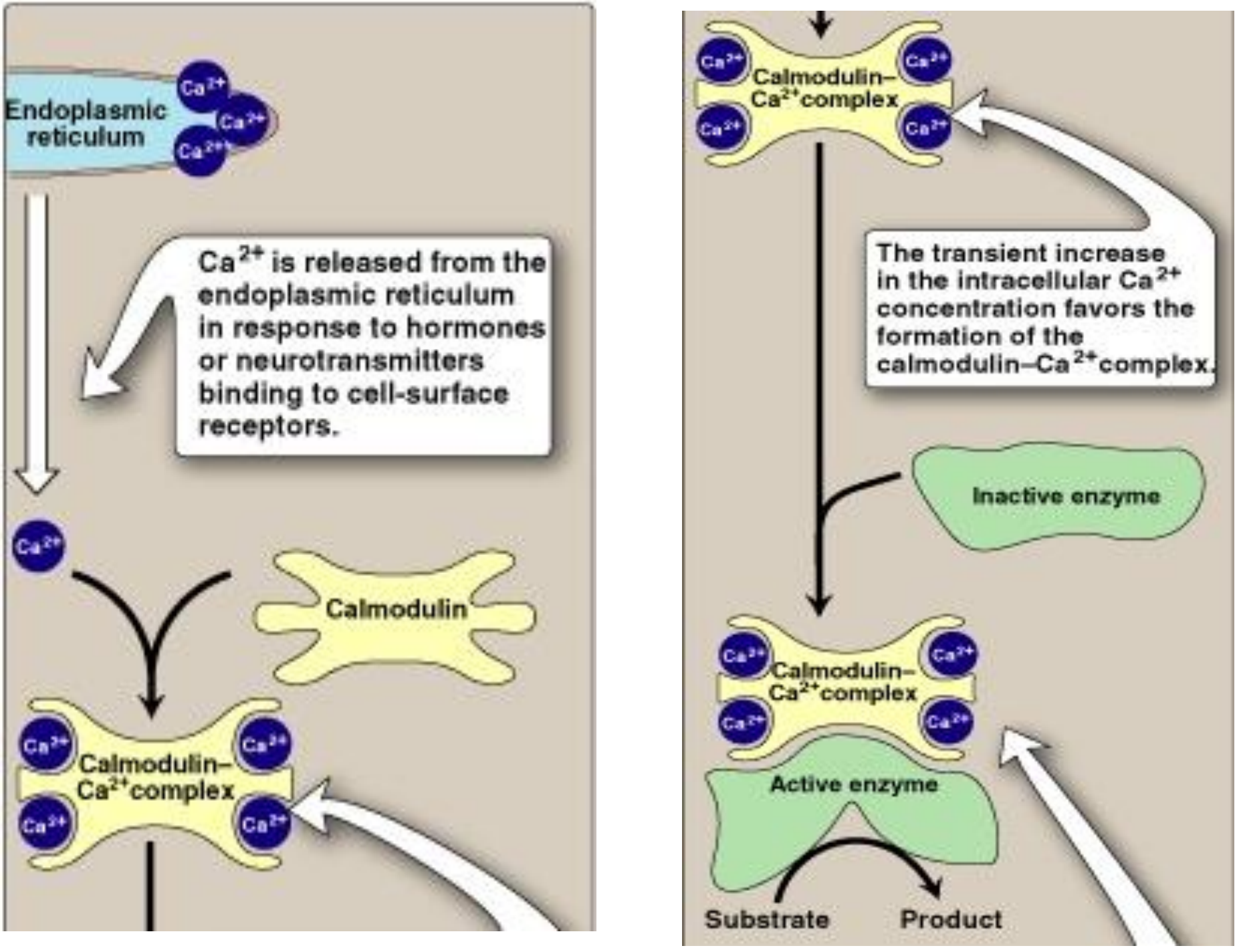


Phosphorylation at several sites

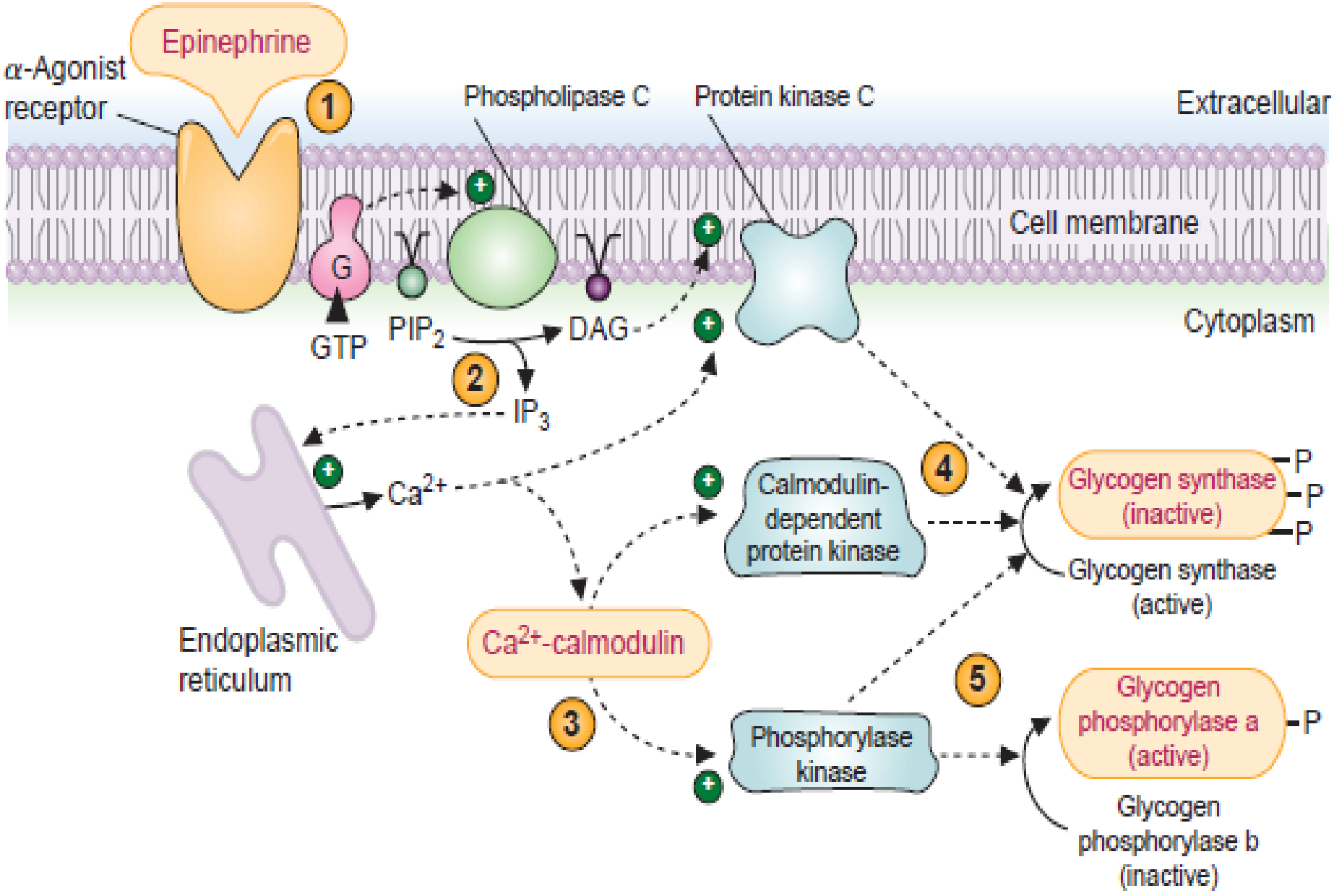
Inhibition is proportional to the degree of phosphorylation

GLYCOGEN SYNTHESIS IS INHIBITED


Ca2+-calmodulin activates dephosphorylated Phosphorylase kinase
Epinephrine
Nerve impulse
Sarcoplasmic reticulum
Ca2+
2
cAMP
3
Ca2+
tein kinase A
ATP
Myosin ATPase
Ca2+-calmodulin
ADP
Phosphorylase kinase
P
Muscle contraction
Adenylate kinase
AMP
1
P
Glycogen phosphorylase b
Glycogen phosphorylase a
Pi

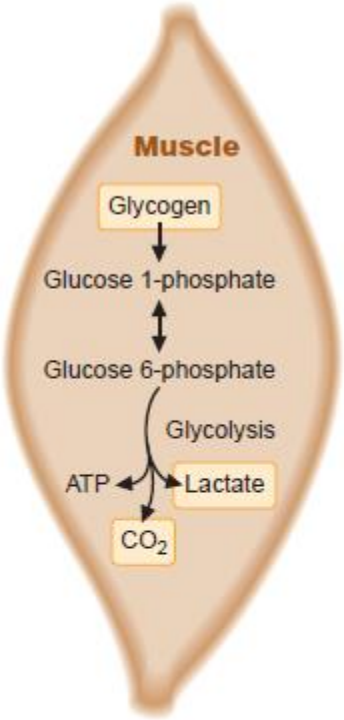

Endoplasmic reticulum
Ca^{2+}
Ca^{2+}
Ca^{2+}
Ca^{2+} is released from the endoplasmic reticulum in response to hormones or neurotransmitters binding to cell-surface receptors.
Ca^{2+}
Calmodulin
Calmodulin–Ca^{2+}complex
Ca^{2+}
Ca^{2+}
Ca^{2+}
Ca^{2+}
Calmodulin–Ca^{2+}complex
Ca^{2+}
Ca^{2+}
Ca^{2+}
Ca^{2+}
The transient increase in the intracellular Ca^{2+} concentration favors the formation of the calmodulin–Ca^{2+}complex.
Inactive enzyme
Calmodulin–Ca^{2+}complex
Ca^{2+}
Ca^{2+}
Ca^{2+}
Ca^{2+}
Active enzyme
Substrate
Product

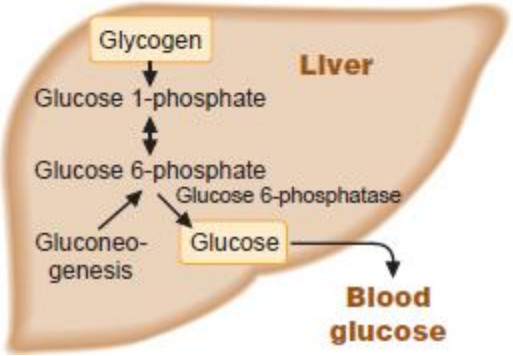
Calcium Activation of liver phosphorylase Kinase

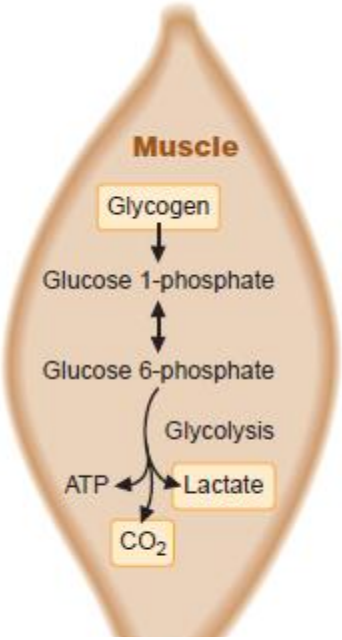


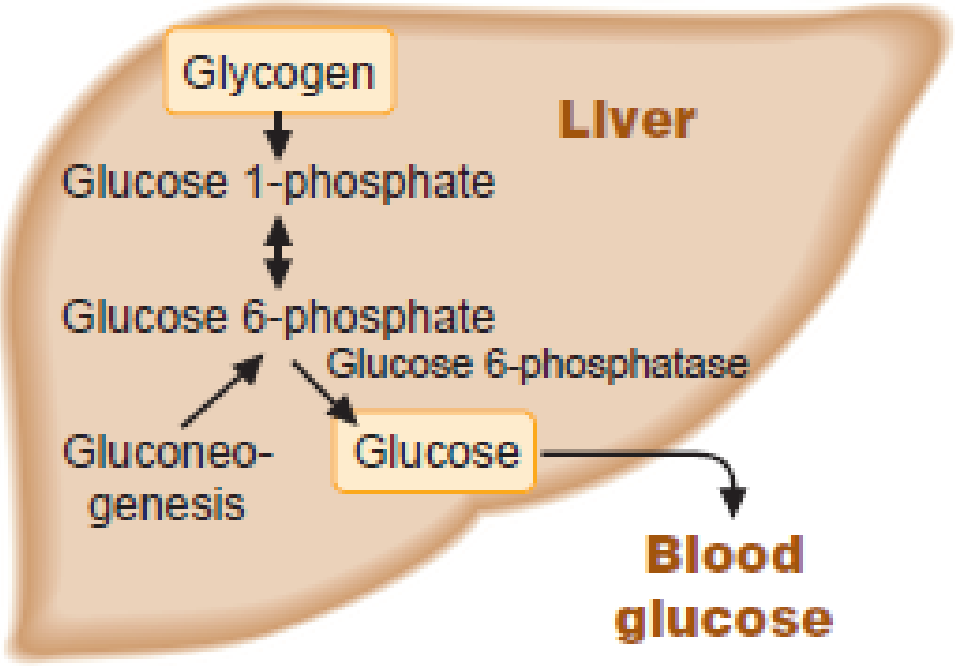
Next Topic

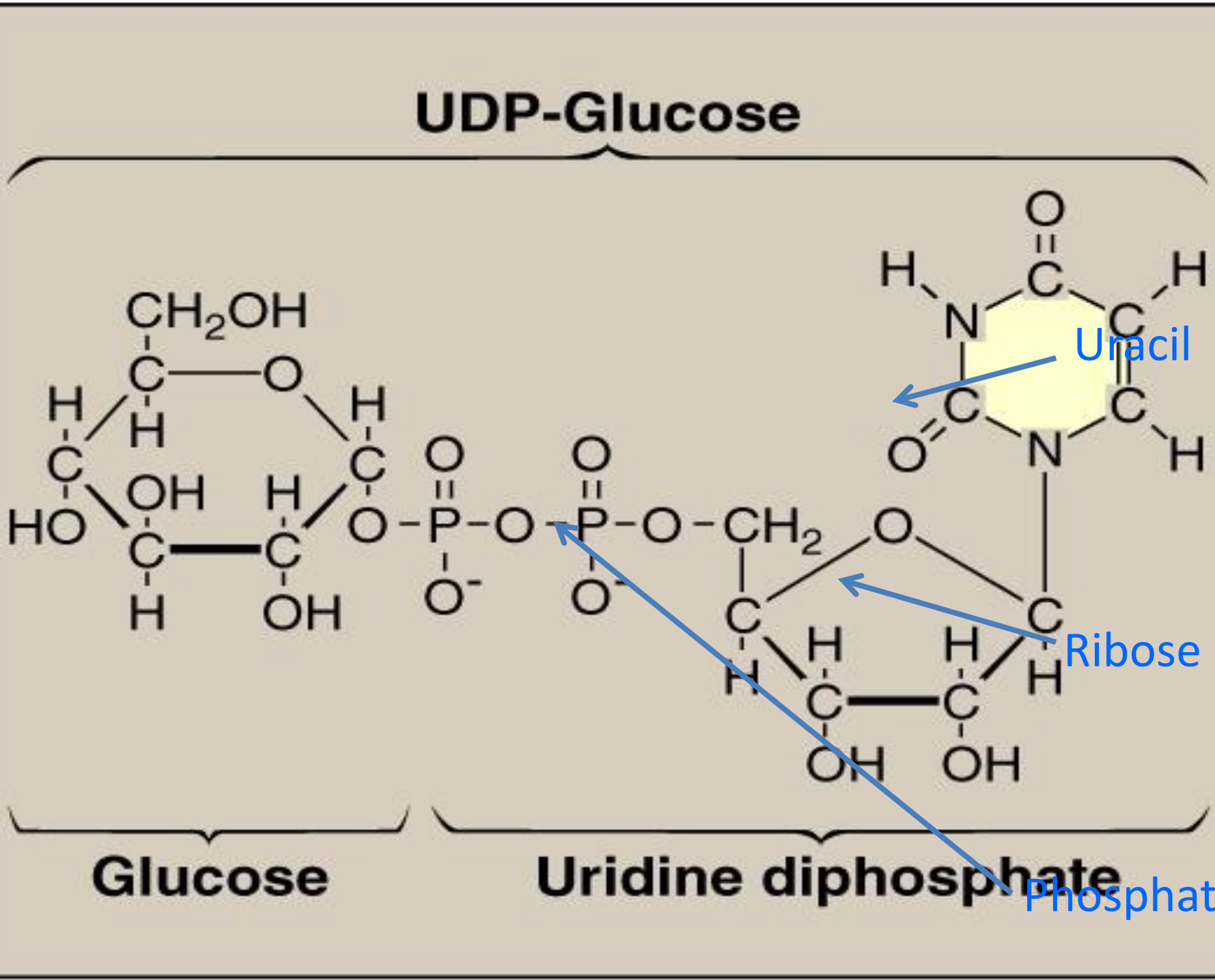
Metabolism of mono and disaccharides

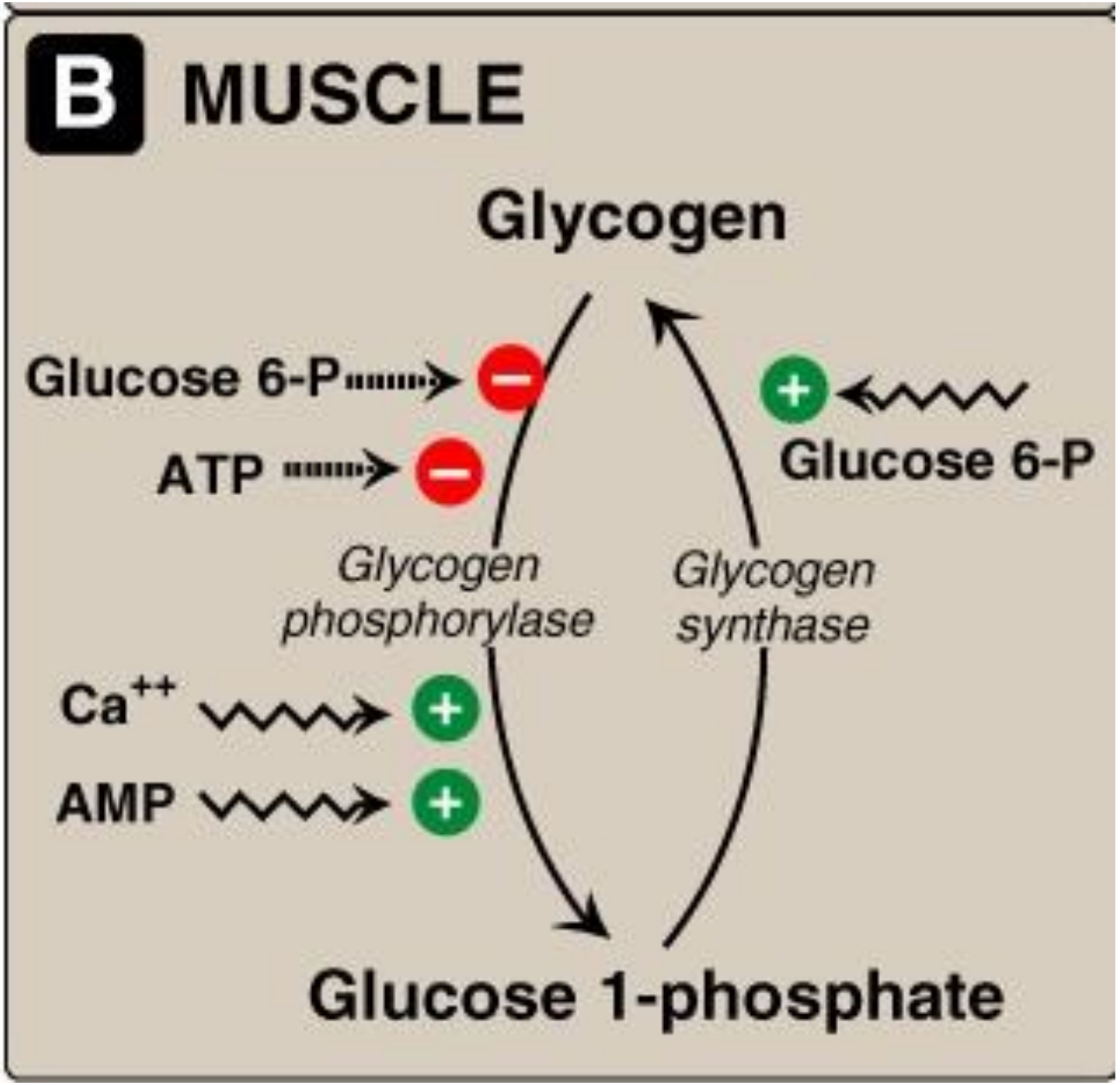

Muscle
Glycogen
Glucose 1-phosphate
Glucose 6-phosphate
Glycolysis
ATP
Lactate
CO_2

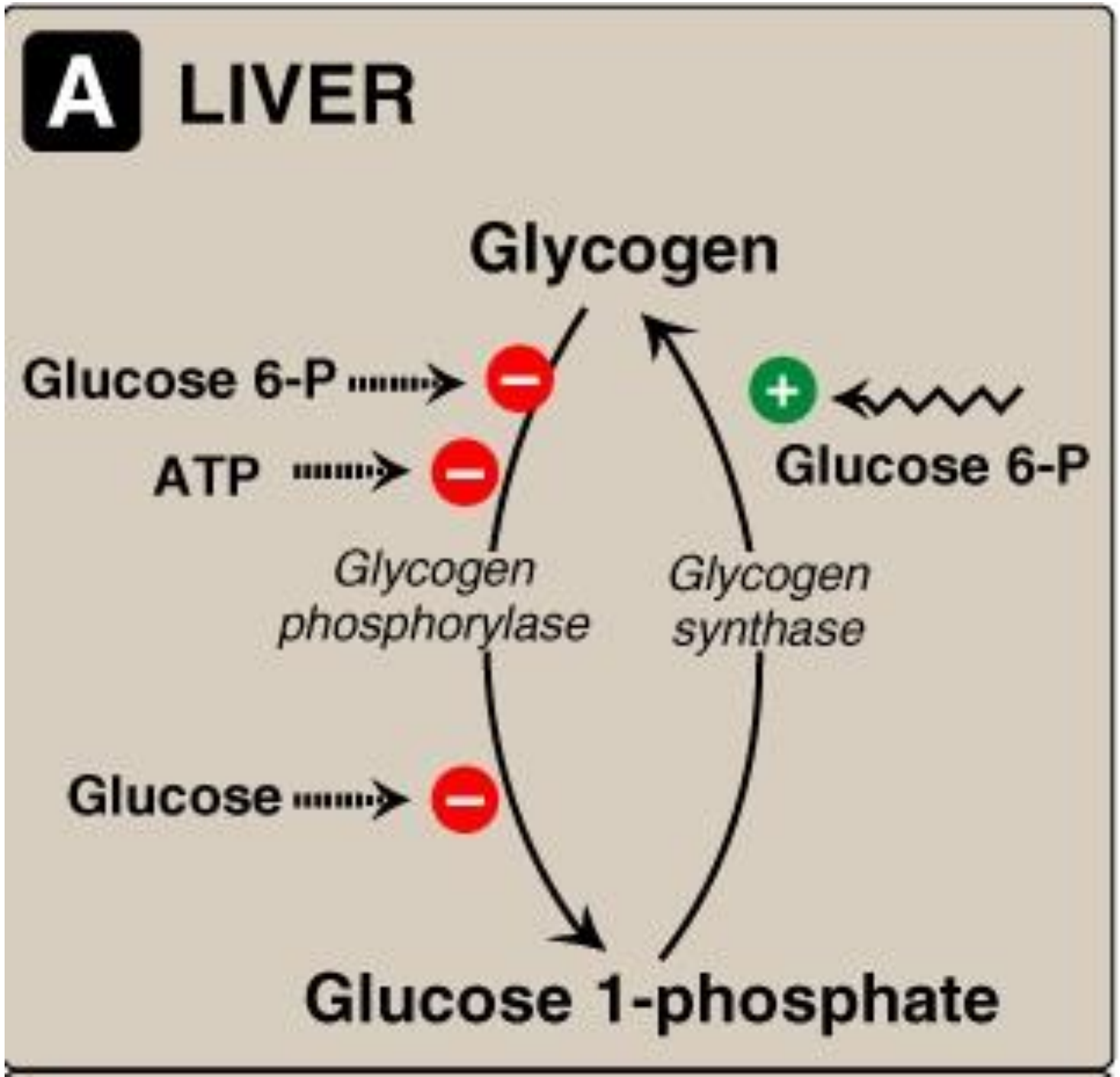

Glycogen
Liver
Glucose 1-phosphate
Glucose 6-phosphate
Glucose 6-phosphatase
Gluconeo-
genesis
Glucose
Blood
glucose


Muscle
Glycogen
Glucose 1-phosphate
Glucose 6-phosphate
Glycolysis
ATP
Lactate
CO_2


Glycogen
Liver
Glucose 1-phosphate
Glucose 6-phosphate
Glucose 6-phosphatase
Gluconeo-
genesis
Glucose
Blood
glucose


UDP-Glucose
Uracil
Ribose
Phosphate
Glucose
Uridine diphosphate


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


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