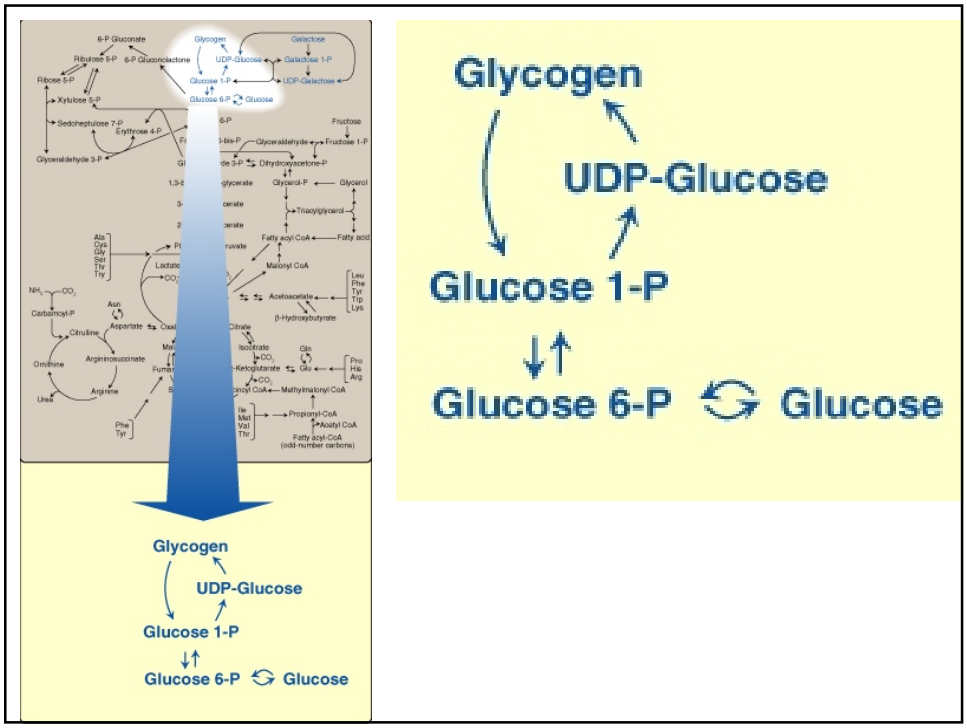
# Glycogen Metabolism

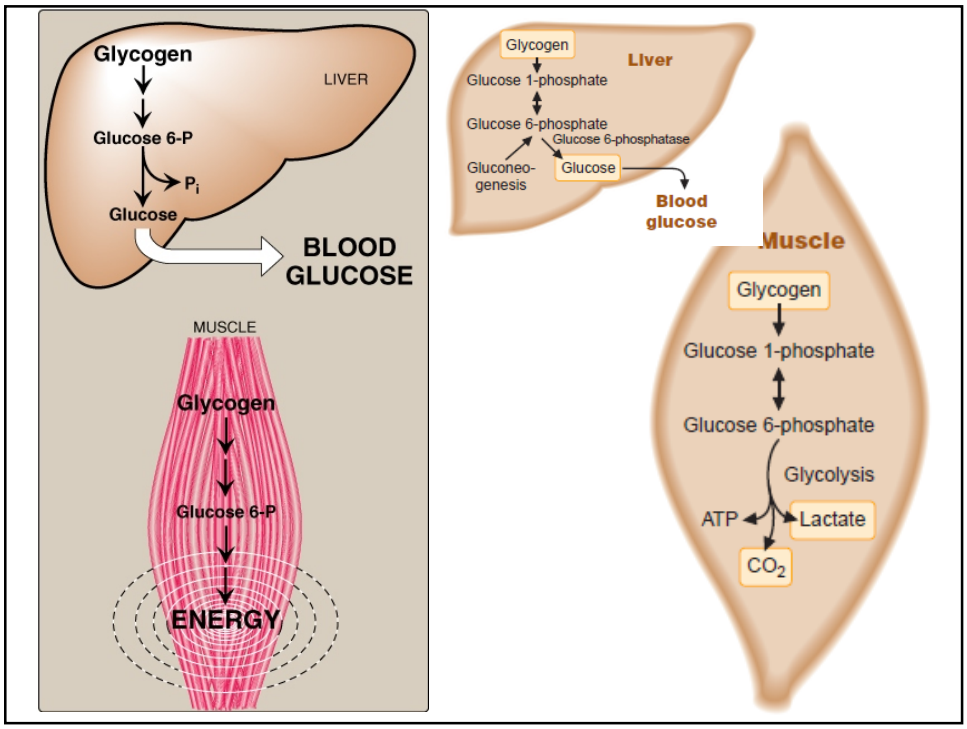
Suggested Reading:

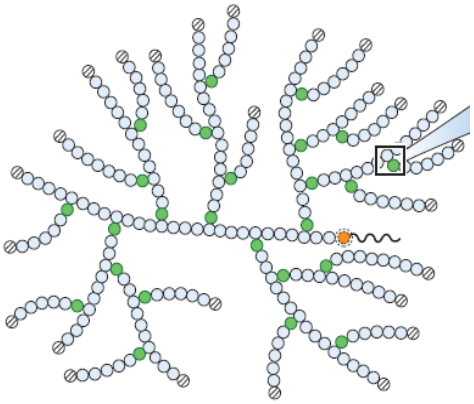
Lippincott's Ilustrated reviews: Biochemistry

## 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.

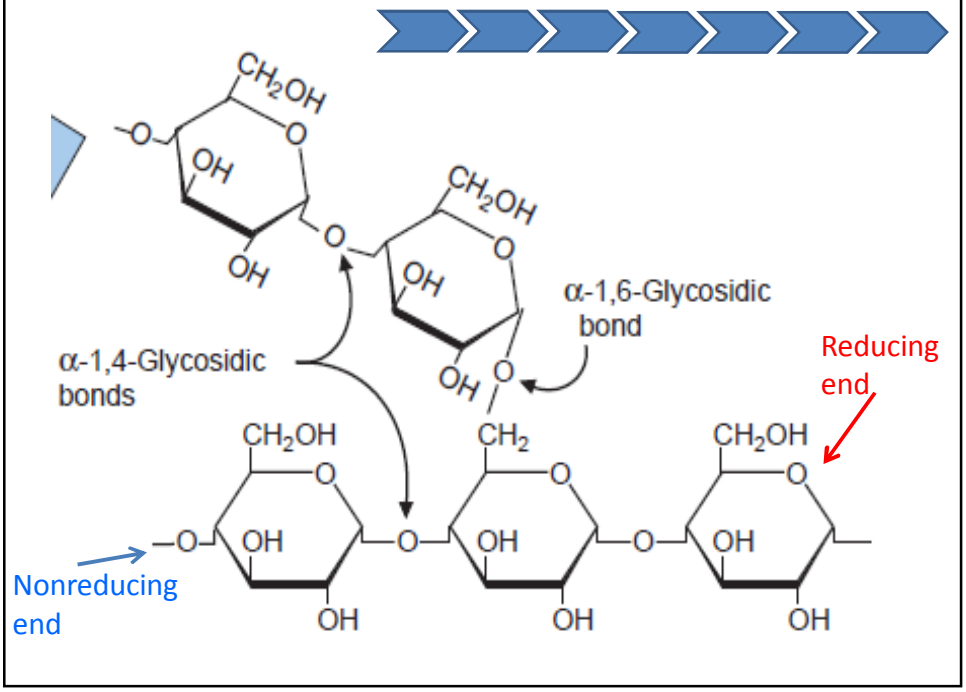

Glycogen
UDP-Glucose
Glucose 1-P
Glucose 6-P
Glucose
Glycogen
UDP-Glucose
Glucose 1-P
Glucose 6-P
Glucose

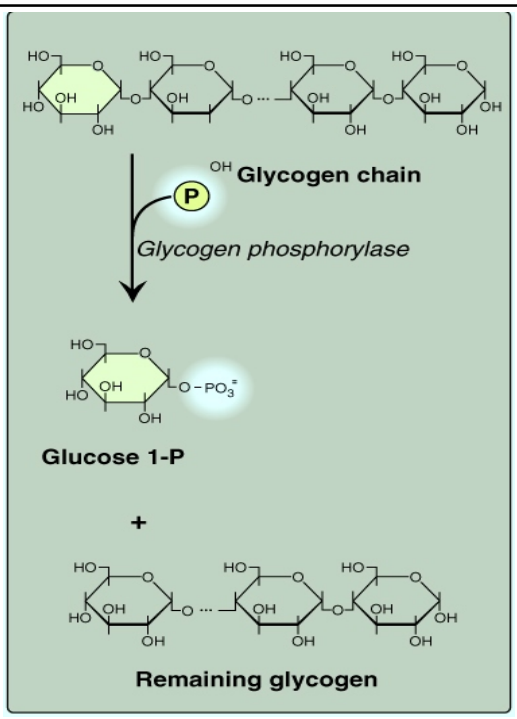

Glycogen
LIVER
Glucose 6-P
Pi
Glucose
BLOOD GLUCOSE
MUSCLE
Glycogen
Glucose 6-P
ENERGY
Glycogen
Liver
Glucose 1-phosphate
Glucose 6-phosphate
Glucose 6-phosphatase
Gluconeo-genesis
Glucose
Blood glucose
Muscle
Glycogen
Glucose 1-phosphate
Glucose 6-phosphate
Glycolysis
ATP
Lactate
CO2



* Extensively branched homopolysaccharide

* One molecule consists of hundreds of thousands of glucose units



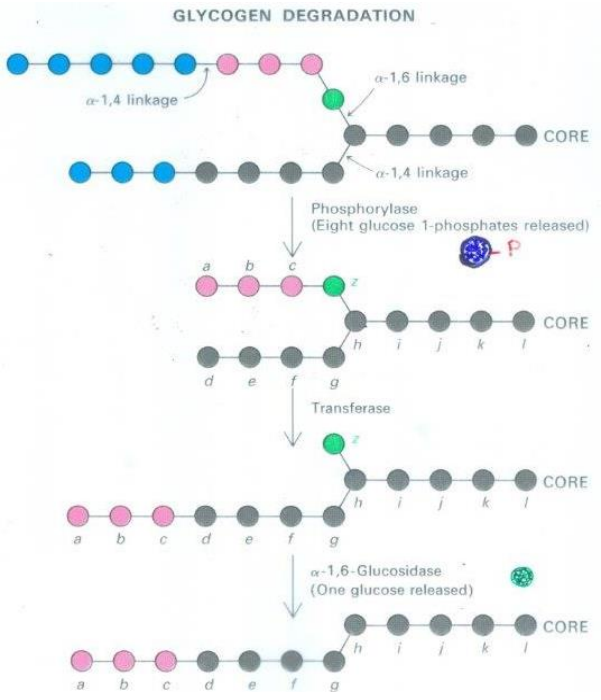



# Degradation of glycogen

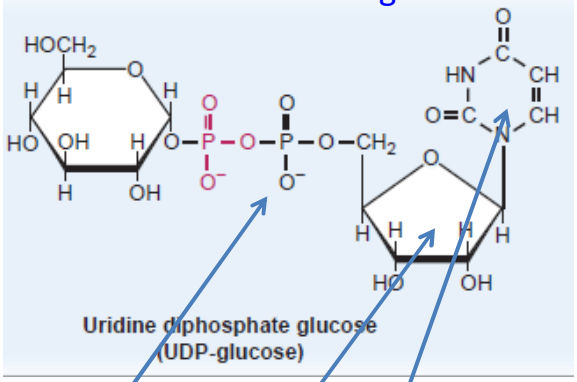
Degradation of glycogen
One glucose unit is removed at a time

From the nonreducing ends

Released in the form of glucose 1-phosphate

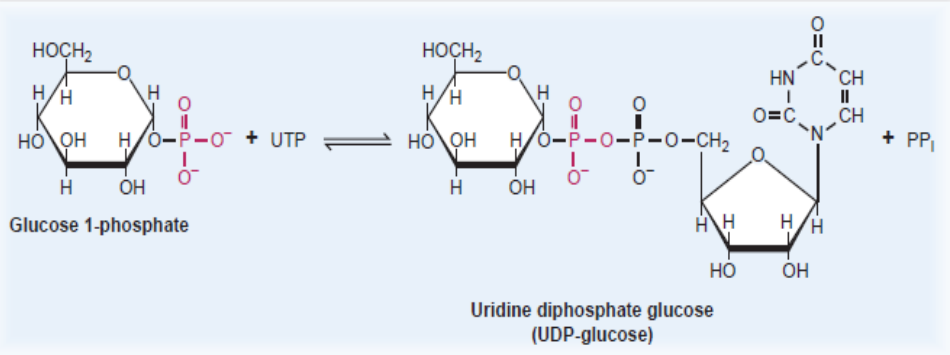


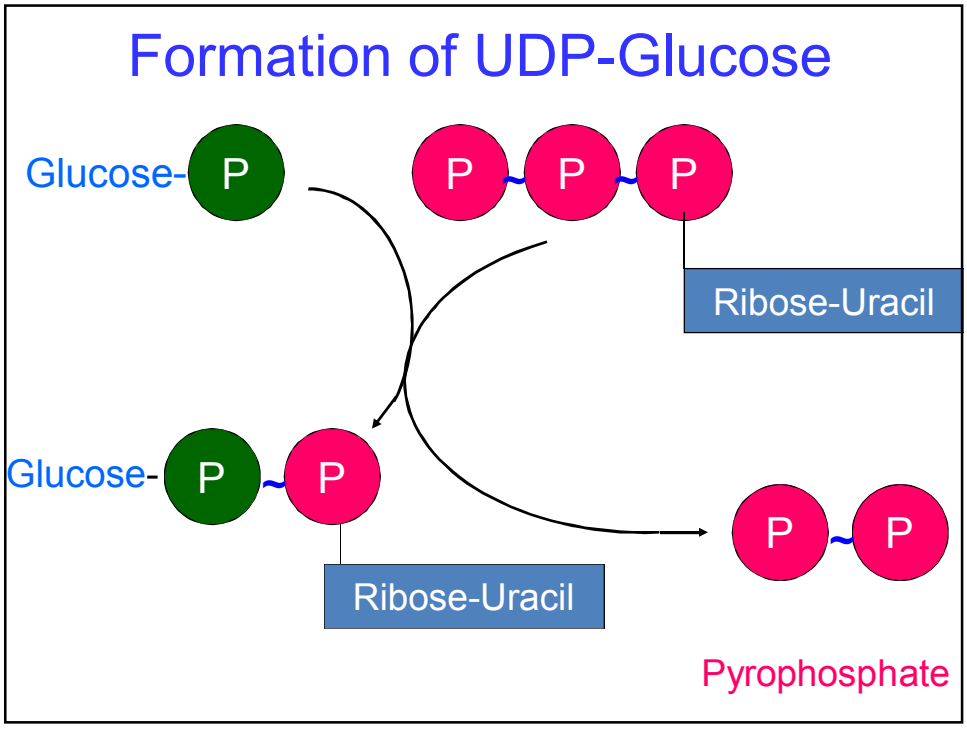
Glycogen is synthesized by adding glucose one by one
UDP-Glucose s the active donor of glucose units

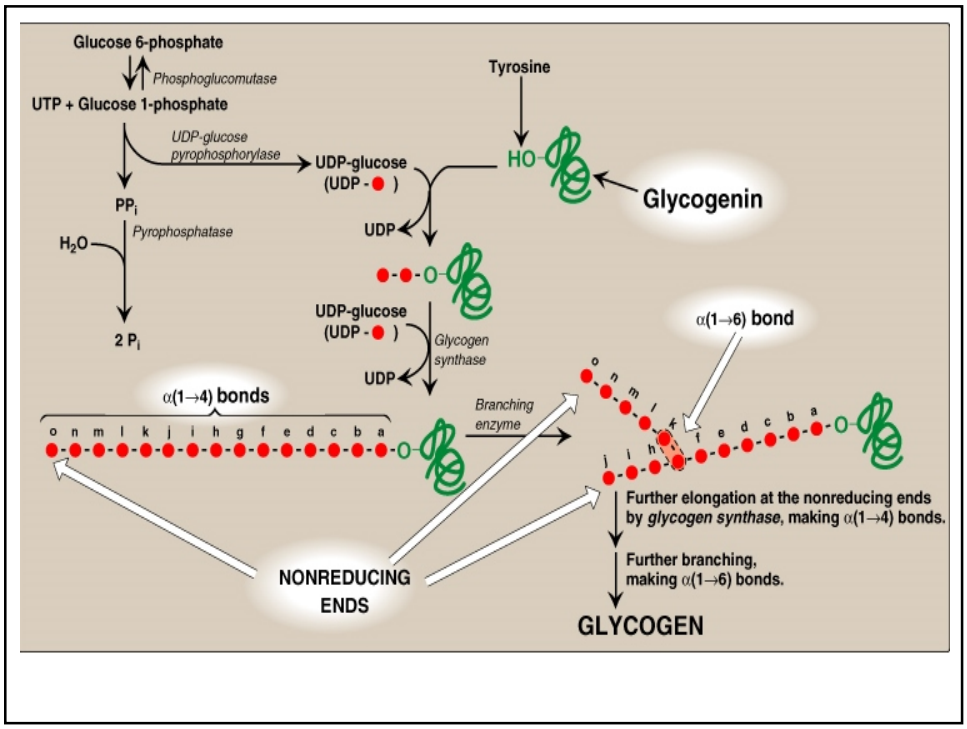


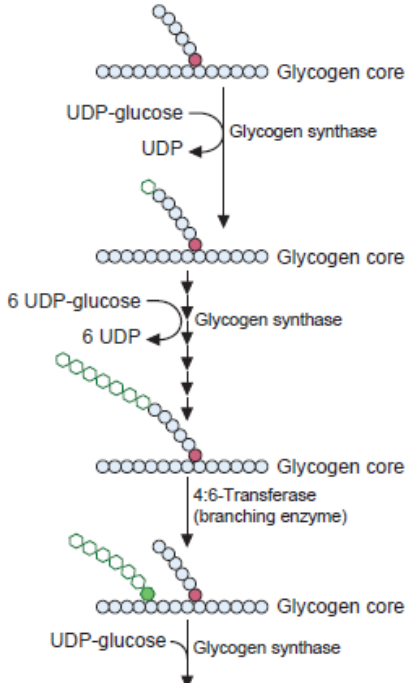

Phosphate Ribose Uracil

# Formation of UDP-Glucose




Formation of UDP-Glucose
Glucose-
P
P
P
P
Ribose-Uracil
Glucose-
P
P
Ribose-Uracil
P
P
Pyrophosphate


Glucose 6-phosphate
Phosphoglucomutase
UTP + Glucose 1-phosphate
UDP-glucose pyrophosphorylase
UDP-glucose (UDP- )
PPi
Pyrophosphatase
H2O
2 Pi
UDP
Tyrosine
HO
Glycogenin
UDP-glucose (UDP- )
Glycogen synthase
UDP
α(1→4) bonds
o n m l k j i h g f e d c b a
Branching enzyme
α(1→6) bond
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 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)

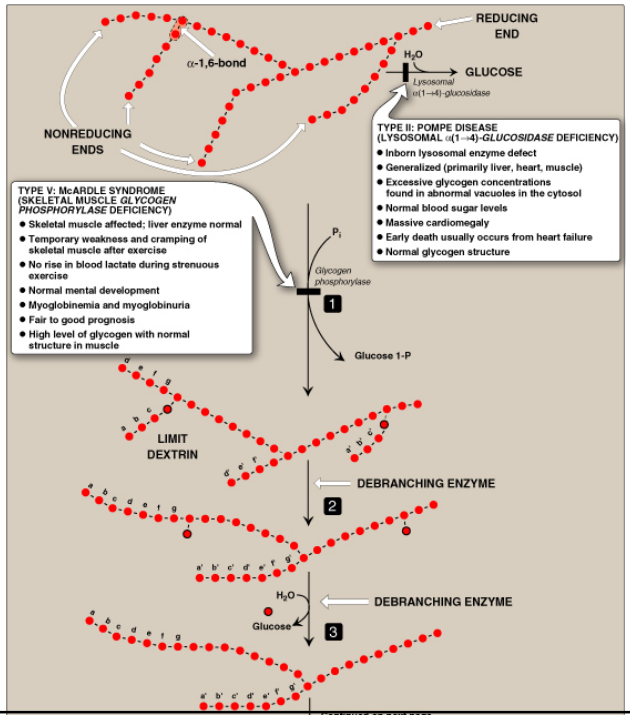
- I Glucose-6-phosphataseon (von Gierk's) disease
  - Liver, kidney and intestine.
  - Severe fasting hypoglycemia
  - Hepatomegaly  fatty liver.
  - Normal glycogen structure.
  - Progressive renal disease.
  - Growth retardation.

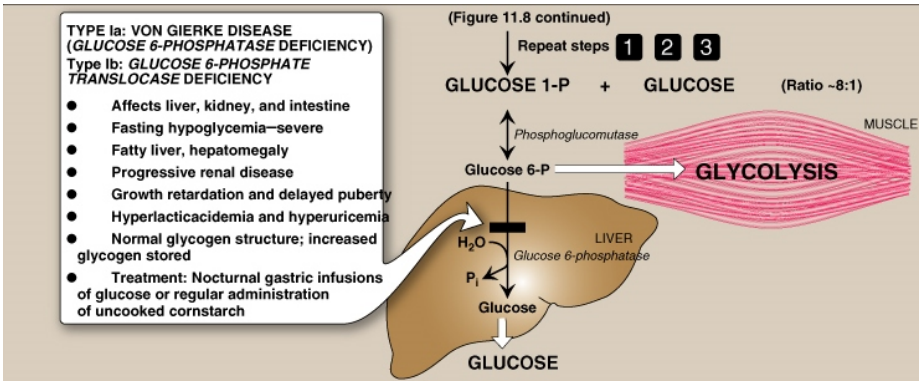
## Glycogen Storage Diseases (examples)

- 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.






## Energy needed for glycogen synthesis

Glucose + ATP ⟶ Glucose 6-phosphate + ADP

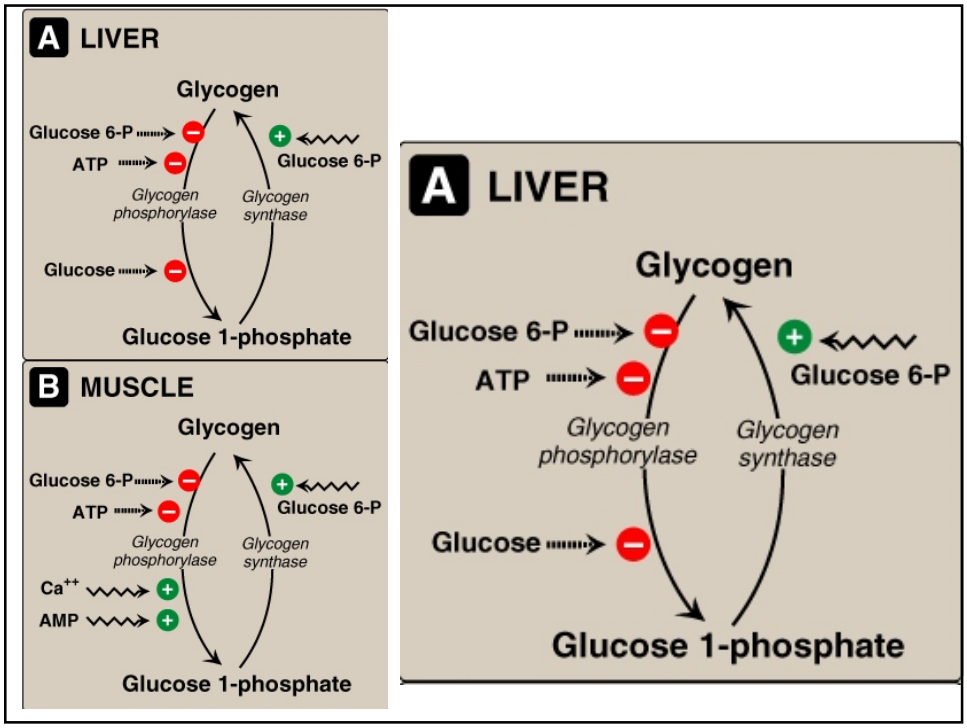
Glucose 6-phosphate ⇌ Glucose 1-phosphate

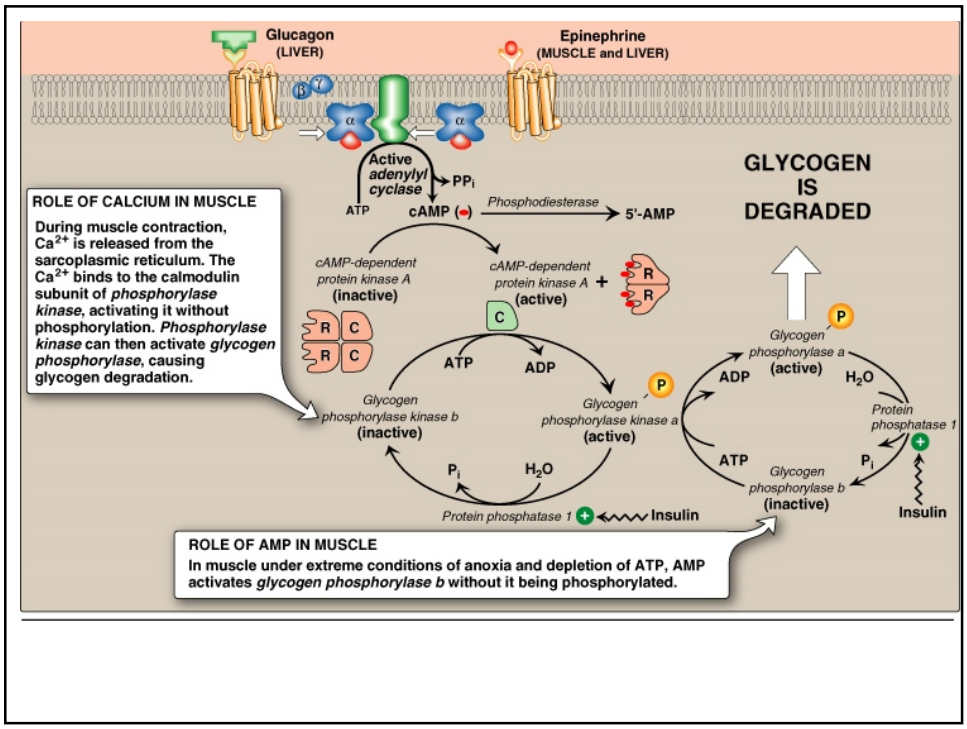
Glucose 1-phosphate UTP ⇌ UDP-Glucose $PP_i$

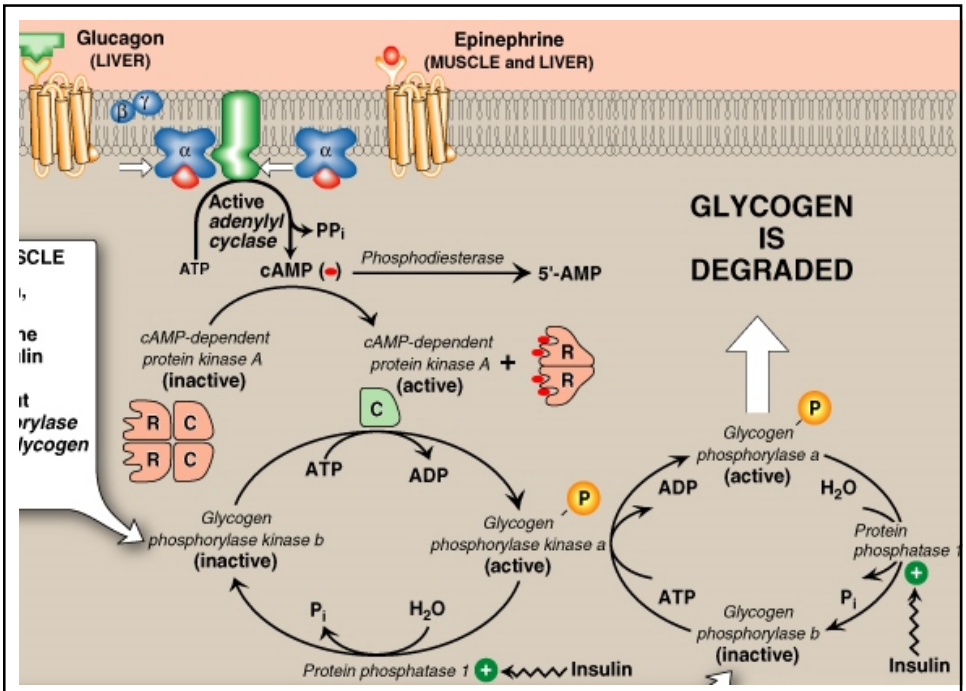
$PP_i$ + $H_2O$ ⟶ $2P_i$

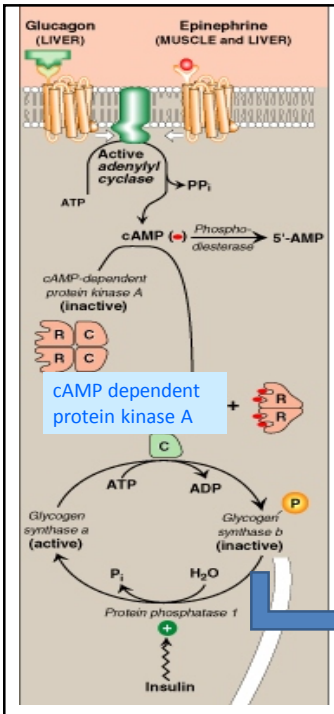
UDP-Glucose + $Glycogen_{(n)}$ ⟶ UDP + $Glycogen_{(n+1)}$

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

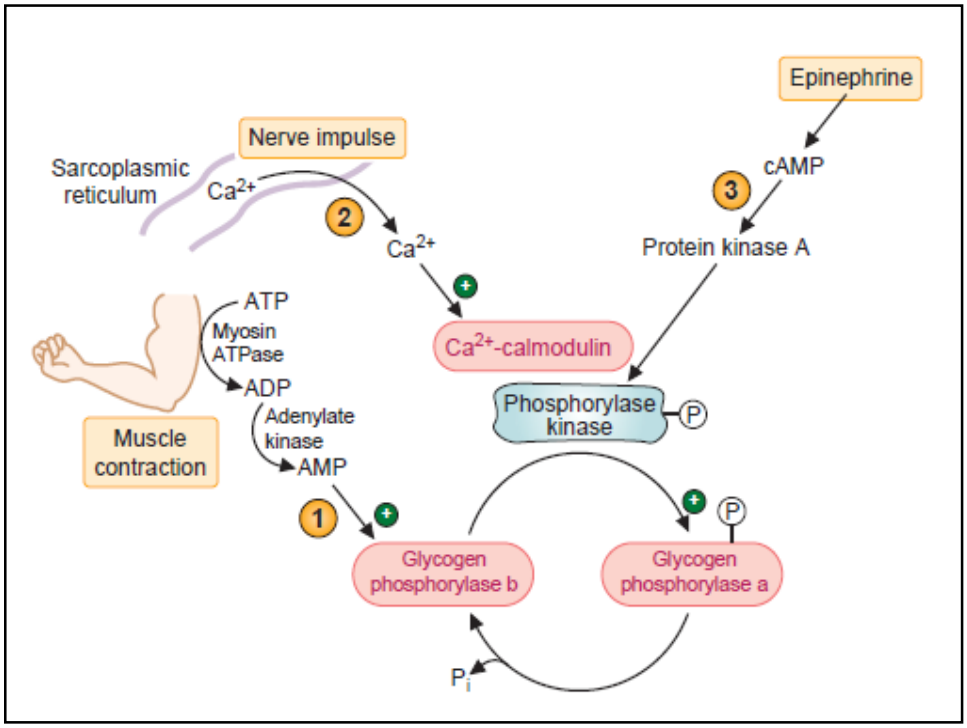

A LIVER
Glycogen
Glucose 6-P
ATP
Glucose 6-P
Glycogen phosphorylase
Glycogen synthase
Glucose
Glucose 1-phosphate
B MUSCLE
Glycogen
Glucose 6-P
ATP
Glucose 6-P
Glycogen phosphorylase
Glycogen synthase
Ca++
AMP
Glucose 1-phosphate
A LIVER
Glycogen
Glucose 6-P
ATP
Glucose 6-P
Glycogen phosphorylase
Glycogen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

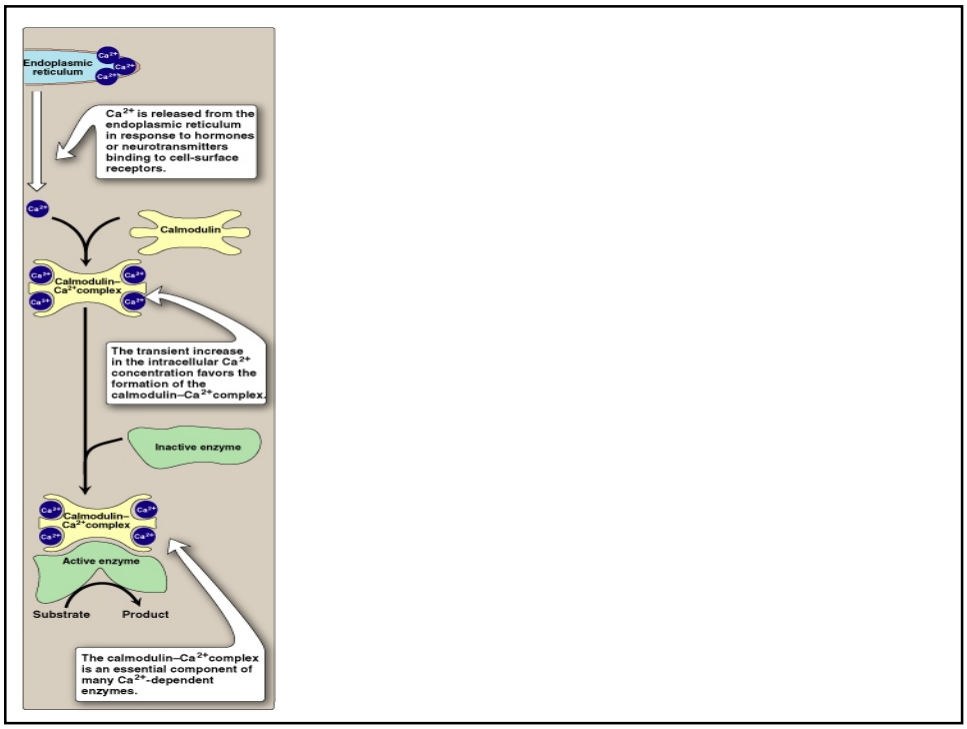

Glucagon (LIVER)
Epinephrine (MUSCLE and LIVER)
Active adenylyl cyclase
PPi
ATP
cAMP
Phosphodiesterase
5'-AMP
GLYCOGEN IS DEGRADED
ROLE OF CALCIUM IN MUSCLE
During muscle contraction, Ca2+ is released from the sarcoplasmic reticulum. The Ca2+ binds to the calmodulin subunit of phosphorylase kinase, activating 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
C
ATP
ADP
Glycogen phosphorylase kinase b (inactive)
Glycogen phosphorylase kinase a (active)
Glycogen phosphorylase a (active)
ADP
H2O
Protein phosphatase 1
ATP
Pi
Glycogen phosphorylase b (inactive)
Insulin
Pi
H2O
Protein phosphatase 1
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.

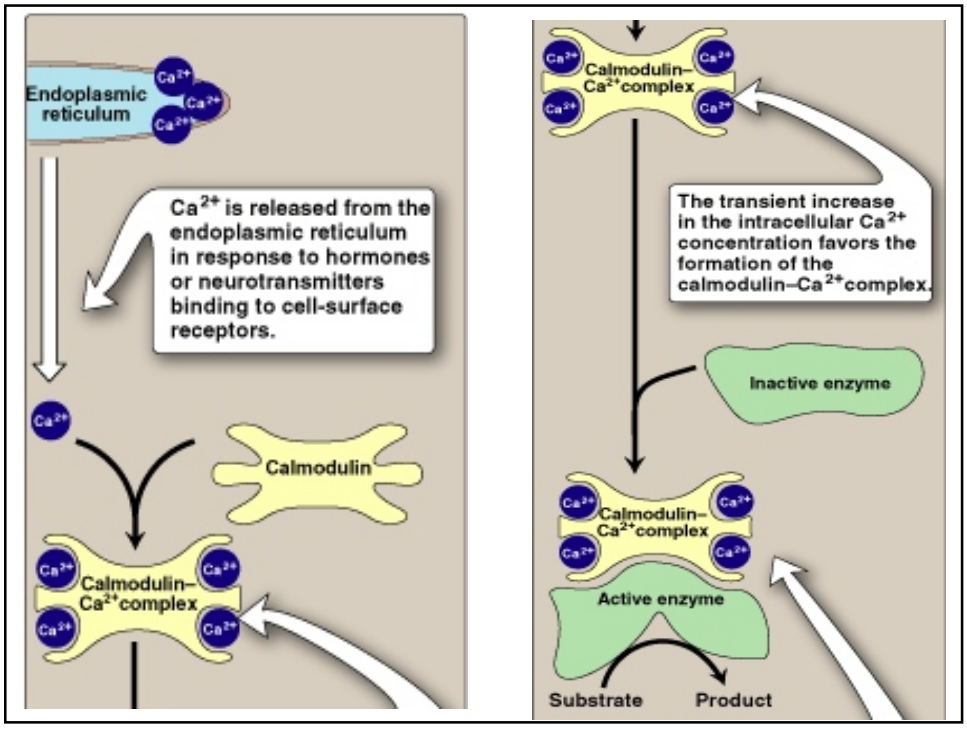


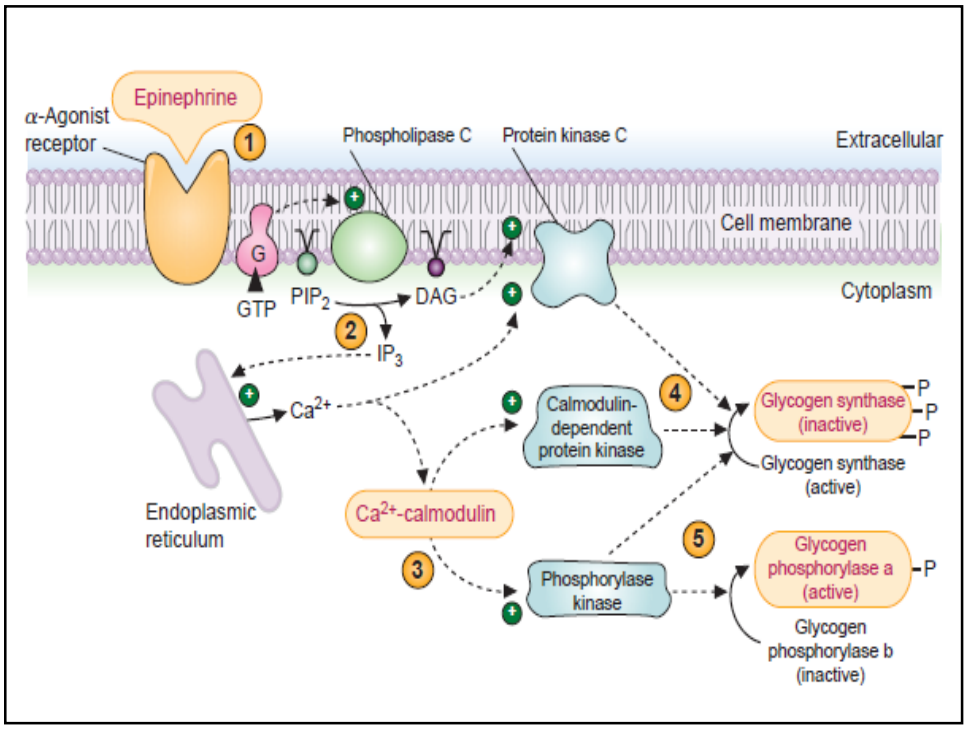




GLYCOGEN SYNTHESIS IS INHIBITED


Epinephrine
Nerve impulse
Sarcoplasmic reticulum
$Ca^{2+}$
cAMP
3
2
$Ca^{2+}$
Protein kinase A
ATP
Myosin ATPase
$Ca^{2+}$-calmodulin
ADP
Phosphorylase kinase
P
Adenylate kinase
Muscle contraction
AMP
1
P
Glycogen phosphorylase b
Glycogen phosphorylase a
$P_i$


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


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


Epinephrine
α-Agonist receptor
1
Phospholipase C
Protein kinase C
Extracellular
Cell membrane
Cytoplasm
G
GTP
$PIP_2$
DAG
2
$IP_3$
$Ca^{2+}$
Endoplasmic reticulum
Calmodulin-dependent protein kinase
4
Glycogen synthase (inactive)
P
P
P
Glycogen synthase (active)
$Ca^{2+}$-calmodulin
3
Phosphorylase kinase
5
Glycogen phosphorylase a (active)
P
Glycogen phosphorylase b (inactive)