liver
Kidneys
يفنوا نقسم للكل

glut 2
Bidirictional

muscles
آناني
glut 4
بس يخزن لحاله

Liver glycogen	Muscle glycogen
Maintains blood glucose	Used for muscle energy
Has glucose-6-phosphatase	No glucose-6-phosphatase
Can release free glucose to blood	Cannot release glucose to blood

Very common MCQ:

> Muscle cannot release free glucose because it lacks glucose-6-phosphatase.

organs :

liver 100 g

muscles 300 - 400 g

Glycogen metabolism

anabolism + catabolism

glycogensis ← high glucose levels ← hyperglycemia

Fed state insulin

glycogenlysis → Fasting state (glucagon) → low glucose level → hypoglycemia

https://youtu.be/zVGbd-df7Y8?si=tW7Xt3Pxys2xEazk

https://youtu.be/YQV_ODVCzQQ?si=7_uZwfrYFfXQY3eO

Glycogen

- Blood glucose can be obtained from three sources: diet, degradation of glycogen and gluconeogenesis.
  glycogenlysis
- Glycogen is a rapidly mobilized form of glucose which is stored in both liver and kidney to raise blood glucose during early stages of fast.
- When glycogen stores are depleted, glucose is produced from amino acids in specific tissues.
- Glycogen works as fuel for synthesis of ATP during muscle contraction

The organ that stores glycogen for its own use is:

1. Liver
2. Brain
3. Kidney
4. Adipose tissue
5. Skeletal muscle

5

Structure and function of glycogen

- 400 g make up 1-2% of muscle weight but 100 g make up 10% of liver
- Glycogen is a branched chain homopolysaccharides made of α-D-glucose linked together by α (1-4) glycosidic bond in the linear chain and α-(1-6) glycosidic bond in the branches.
- Fluctuation in glycogen stores: liver glycogen is not affected by short fast (days) but decreased in prolonged fasting.

1) Which of the following is false about glycogen molecules?

a) Glycogen is polysaccharide

b) Glycogen is a polymer of beta-D-Glucose

c) Glycogen consists of α(1-4) and α (1-6) glycosidic linkage

b

Glycogenesis

liver Kidneys muscles

- Occurs in the cytosol and requires energy supplied by ATP and UTP

- Active form -

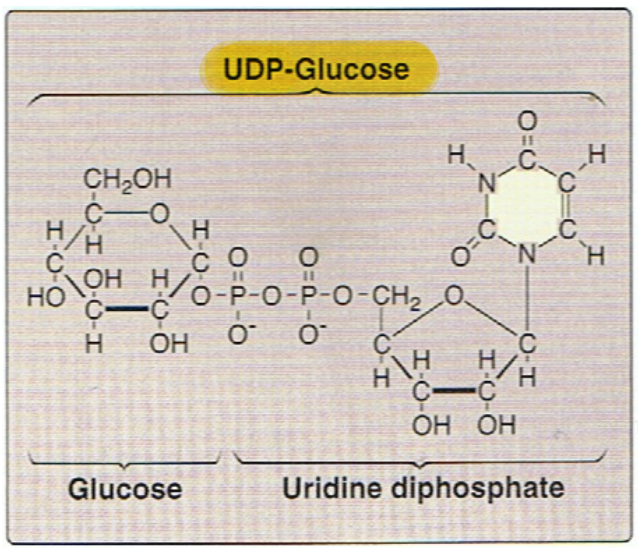
- Synthesis of UDP-glucose: from glucose 1-phosphate and UTP by **UDP-glucose pyrophosphorylase**

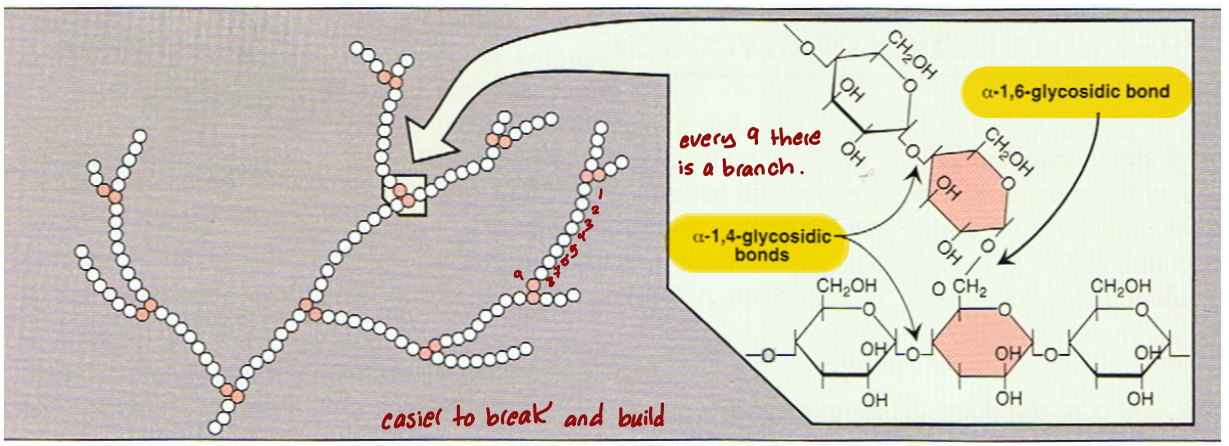
Focus

- Synthesis of a primer to initiate glycogen synthesis: **Glycogen synthase** is responsible for making the α(1- 4) linkages in glycogen. This enzyme cannot initiate chain synthesis using free glucose as an acceptor of a molecule of glucose from UDP-glucose (only elongation).

α-(1,4) just elongation not initiation

no branches just linear α(1,4)





Glycogenesis

rate limiting enzyme

C. Elongation of glycogen chains by glycogen synthase

D. Formation of branches in glycogen: branches are present almost every glycosyl residues which has more solubility than unbranched and increase the number of non-reducing ends where Glu-UDP can be added and this will accelerate the rate of glycogenesis.

Branching occurs by branching enzyme (**amylo α(1-4) □ α(1-6) transglucosidase**) followed by elongation using glycogen synthase

- Branching increases:
  - solubility
  - number of non-reducing ends
  - speed of glycogen synthesis/breakdown

الجواب الغير صحيح بال glycogen
كان : glycogen synthase is branching
enzyme

Glycogenesis

1. Glucose → G6P

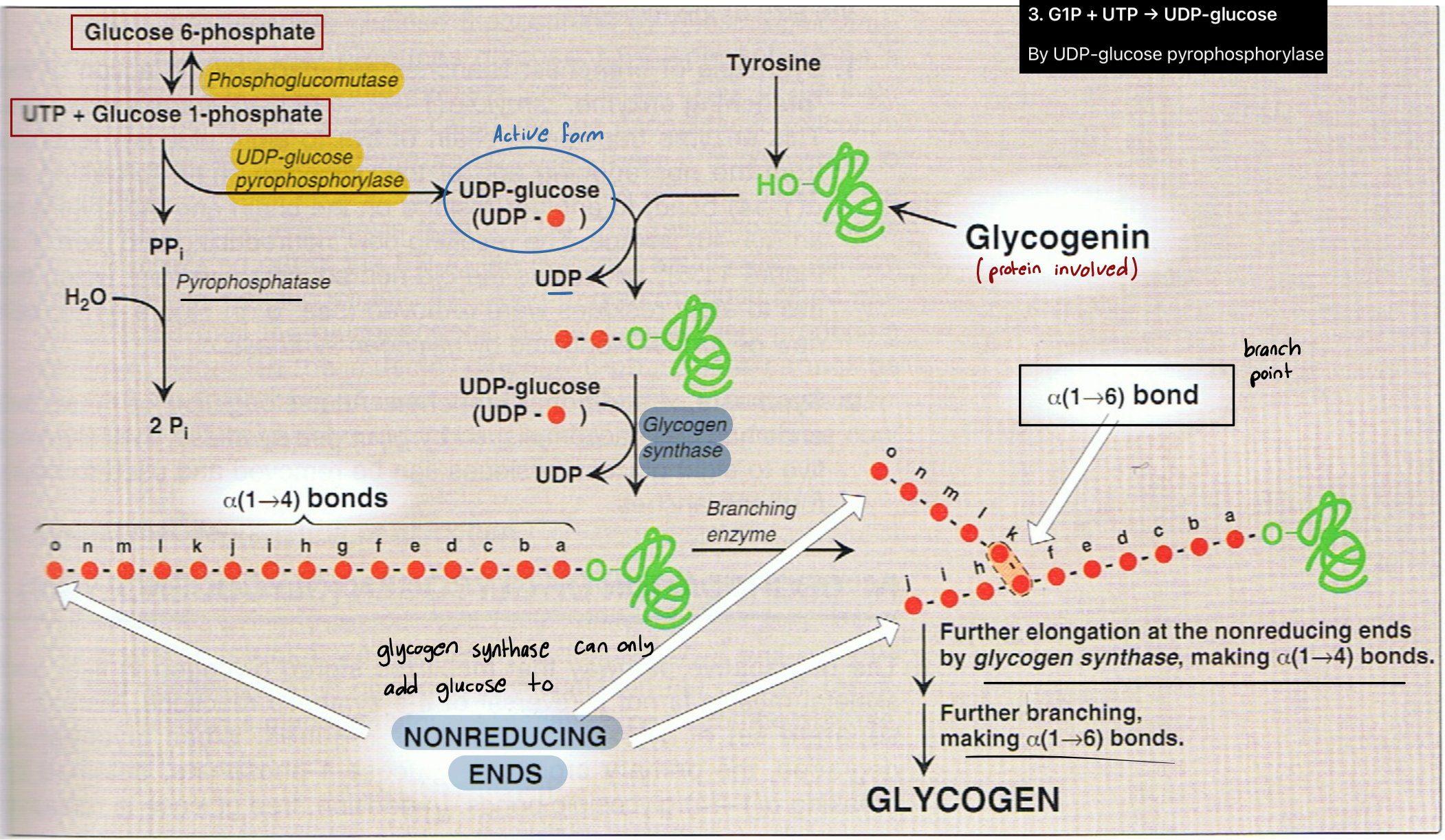
Uses ATP

2. G6P → G1P

By phosphoglucomutase

3. G1P + UTP → UDP-glucose

By UDP-glucose pyrophosphorylase



14) Which of the following statement is false regarding glycogenesis?

a) Glycogen synthase is activated in the phosphorylated state.

b) Glycogen synthase enzyme is inhibited by glucagon and epinephrine action.

c) Protein phosphatase removes the phosphate group and activates the enzyme

d) Insulin promotes glycogen synthesis in liver and skeletal muscles

ANS=A

α(1-4) → G-1-P

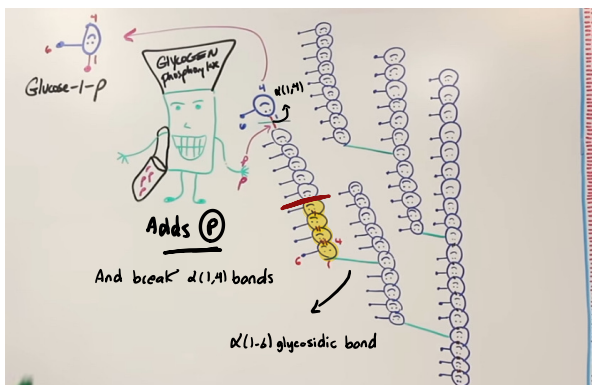
α(1,6) → glucose

glycogenolysis

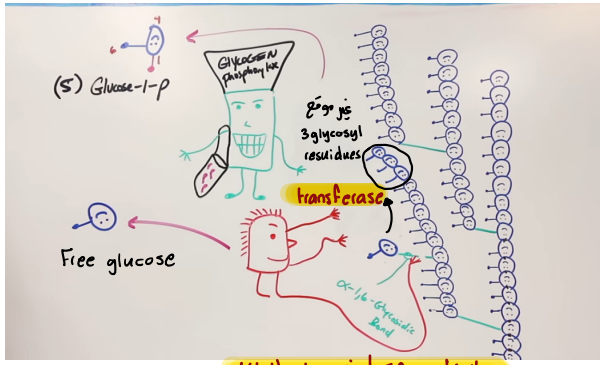
- From breaking of α(1-4) produce glucose 1-phosphate
- Breaking of α(1-6) release free glucose

Shortening of the chains: rate limiting enzyme

- α(1-4) is cleaved by **glycogen phosphorylase** until four glycosyl units remain on each chain before branch point
- The enzyme utilize pyridoxal phosphate which is required as coenzyme (vitamin B6)
- The resulting structure is called limit dextrin



glycogenolysis



debranching

B. Removal of branches: it involves two enzymes:

- oligo α(1-4)-> (α(1-4) glucan transferase: removes the three of the four glycosyl residues at a branch. Then it transfers them to the nonreducing end of another chain.
- The remaining α(1-6) single glucose residue is removed by amylo- α(1-6) glucosidase activity

Both enzymes are called debranching enzyme.

C. Conversion of glucose 1-phosphate to G6P:

Occurs in cytosol by phosphoglucomutase. G-1-P —> G-6-P

phospho-gluco-mutase

In liver, G6P is translocated in ER by G6P translocase and then converted to glucose by G6phosphatase.

G-6-P —> Free glucose

No G6 phosphatase in muscle so G6P enter glycolysis

4) Liver glycogen contributes to the maintenance of glucose but not muscle glycogen. Which of the following enzyme is absent in muscle?

a) Glycogen phosphorylase

b) Hexokinase

c) Glucose-6-phosphatase

d) Debranching enzyme

ANS=C

glycogenolysis

D. Lysosomal degradation of glycogen

small amount of glycogen is continuously degraded by the lysosomal enzyme α(1-4) glucosidase.

deficiency in this enzyme causes accumulation of glycogen in vaccuole in cytosol (glycogen storage disease type II (pompe disease))

prompe disease (glycogen storage disease type II)

↳ deficiency in The lysosomal enzyme (α(1-4) glucosidase)

↳ glycogen accumulation

https://youtu.be/NL6ETs9k3Wk?si=KGZ64N_EsSdxzCu2

Regulation of Glycogen metabolism

- cAMP Integrates the Regulation of Glycogenolysis & Glycogenesis
- The principal enzymes controlling glycogen metabolism- glycogen phosphorylase and glycogen synthase are regulated by allosteric mechanisms and covalent modifications due to reversible phosphorylation and dephosphorylation of enzyme protein kinase in response to hormone action

ATP → cyclic AMP

- cAMP is formed from ATP by **adenylyl cyclase** at the inner surface of cell membranes and acts as an intracellular **second messenger** in response to hormones such as **epinephrine**, **norepinephrine**, and **glucagon**

released in fasting state

break down cAMP so we stop glycogen breakdown into glucose.

- cAMP is hydrolyzed by **phosphodiesterase**, so terminating hormone action, in liver, insulin increases the activity of phosphodiesterase

(fed state)

Meaning:

If glucose is already present/bound, the enzyme becomes less responsive to AMP.

So even if AMP tries to activate it:

- activation is blocked
- glycogen breakdown decreases

Regulation

- when muscle glycogen phosphorylase b is bound to glucose, it cannot be allosterically activated by AMP

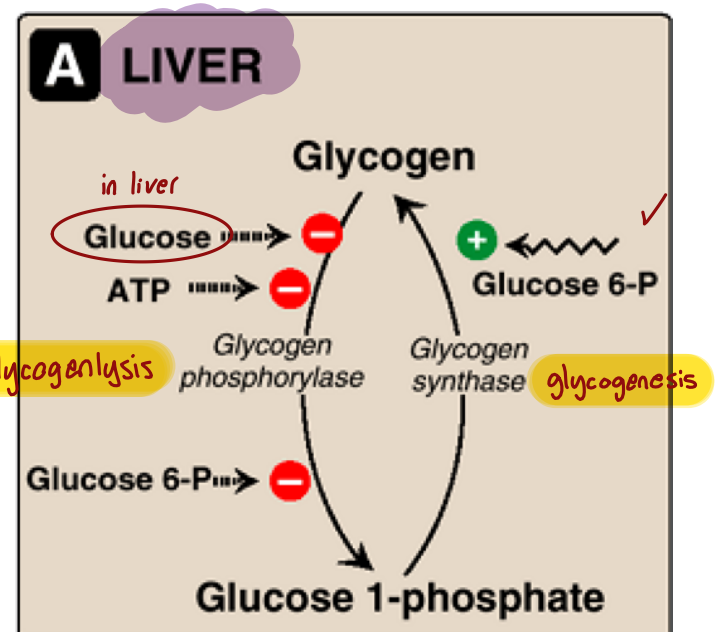
glycogen → glucose

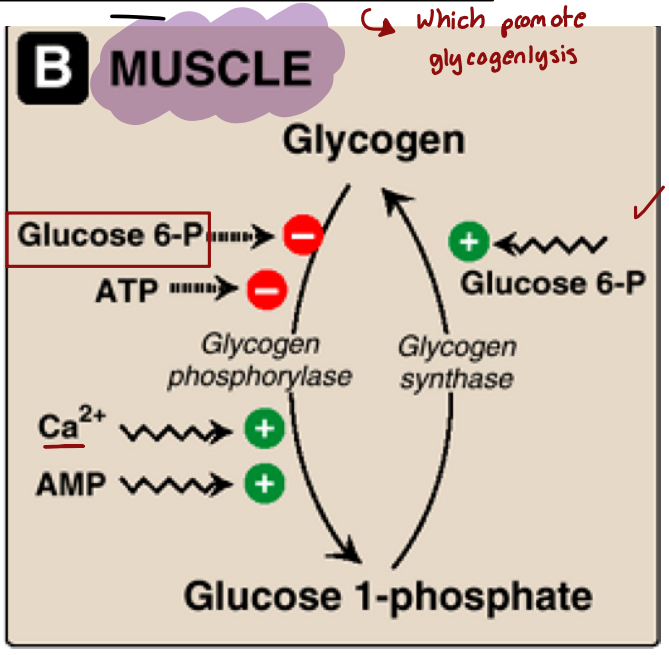
inactive form (dephosphorylated)

- In the muscle, insulin indirectly inhibits the enzyme by increasing the uptake of glucose, leading to an increased level of glucose 6-phosphate-a potent allosteric inhibitor of glycogen phosphorylase

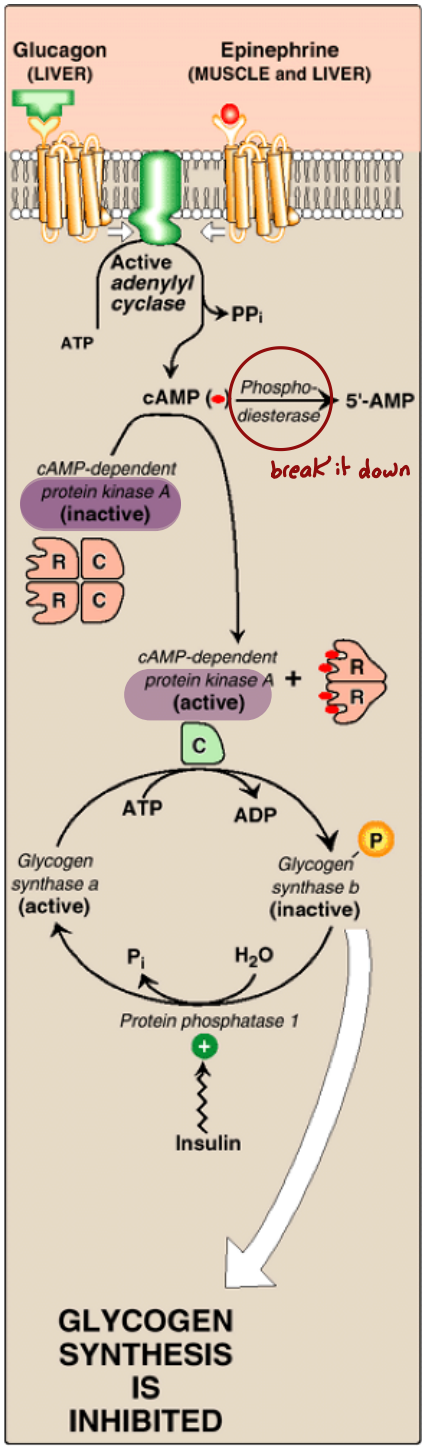
(glycogen phosphorylase)

Allosteric inhibitor





which promote glycogenlysis



10) Which of the following is not the direct/ indirect activator of glycogen phosphorylase in muscle?

a) AMP

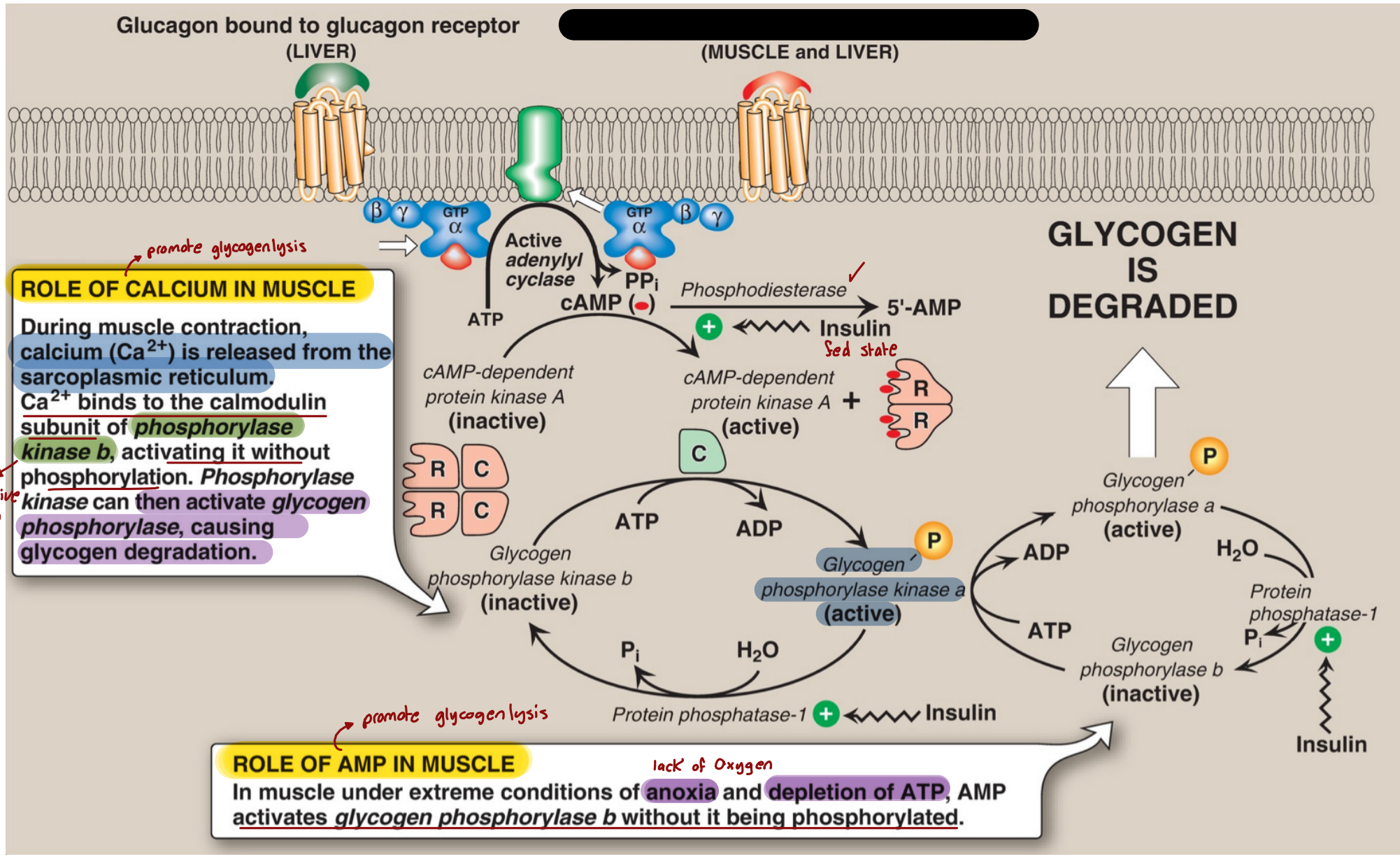
b) Ca++

c) Epinephrine

d) Insulin inhibit it

ANS=D

Regulation

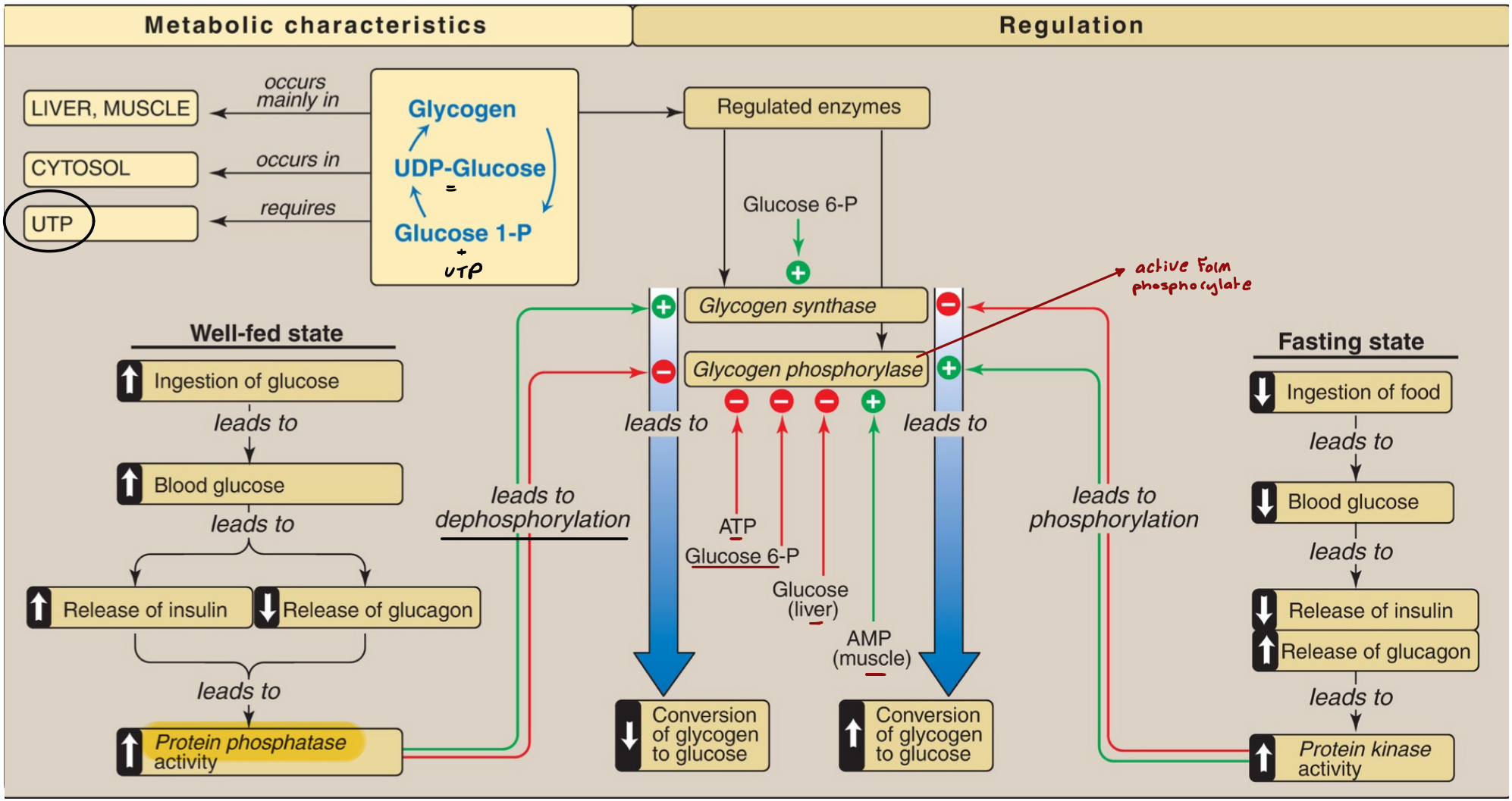

Glucagon bound to glucagon receptor
(LIVER)
(MUSCLE and LIVER)
GTP
Active adenylyl cyclase
ATP
cAMP (-)
PPi
Phosphodiesterase
5'-AMP
Insulin
fed state
promote glycogenlysis
ROLE OF CALCIUM IN MUSCLE
During muscle contraction, calcium (Ca^{2+}) is released from the sarcoplasmic reticulum. Ca^{2+} binds to the calmodulin subunit of phosphorylase kinase b, activating it without phosphorylation. Phosphorylase kinase can then activate glycogen phosphorylase, causing glycogen degradation.
inactive form
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)
P
Pi
H2O
Protein phosphatase-1
Glycogen phosphorylase a (active)
Glycogen phosphorylase b (inactive)
GLYCOGEN IS DEGRADED
promote glycogenlysis
ROLE OF AMP IN MUSCLE
lack of Oxygen
In muscle under extreme conditions of anoxia and depletion of ATP, AMP activates glycogen phosphorylase b without it being phosphorylated.

6. The active form of glycogen ___ is phosphorylated; the active form of glycogen ___ is dephosphorylated.

- a) hydrolase; dehydrogenase
- b) dehydrogenase; hydrolase
- c) hydrolase; semisynthase
- d) phosphorylase; synthase
- e) synthase; phosphorylase

d

Regulation


Metabolic characteristics
Regulation
LIVER, MUSCLE
occurs mainly in
CYTOSOL
occurs in
UTP
requires
Glycogen
UDP-Glucose
=
Glucose 1-P
+
UTP
Regulated enzymes
Glucose 6-P
Glycogen synthase
Glycogen phosphorylase
active form phosphorylate
Well-fed state
Ingestion of glucose
leads to
Blood glucose
leads to
Release of insulin
Release of glucagon
leads to
Protein phosphatase activity
leads to dephosphorylation
leads to
ATP
Glucose 6-P
Glucose (liver)
AMP (muscle)
leads to
Conversion of glycogen to glucose
Conversion of glycogen to glucose
leads to phosphorylation
Fasting state
Ingestion of food
leads to
Blood glucose
leads to
Release of insulin
Release of glucagon
leads to
Protein kinase activity

Glycogen storage diseases GSDs

- They result either in formation of glycogen that has an abnormal structure, or in the accumulation of excessive amounts of normal glycogen in specific tissues as a result of impaired degradation.
- A particular enzyme may be defective in a single tissue, such as the liver, or the defect may be more generalized, affecting liver, muscle, kidney, intestine, and myocardium.
- The severity of the glycogen storage diseases (GSDs) ranges from fatal in infancy to mild disorders that are not life-threatening

Glycogen storage diseases happen because of a defect in an enzyme involved in:

- **glycogen synthesis** → abnormal glycogen structure

  OR
- **glycogen breakdown** → excess glycogen accumulation