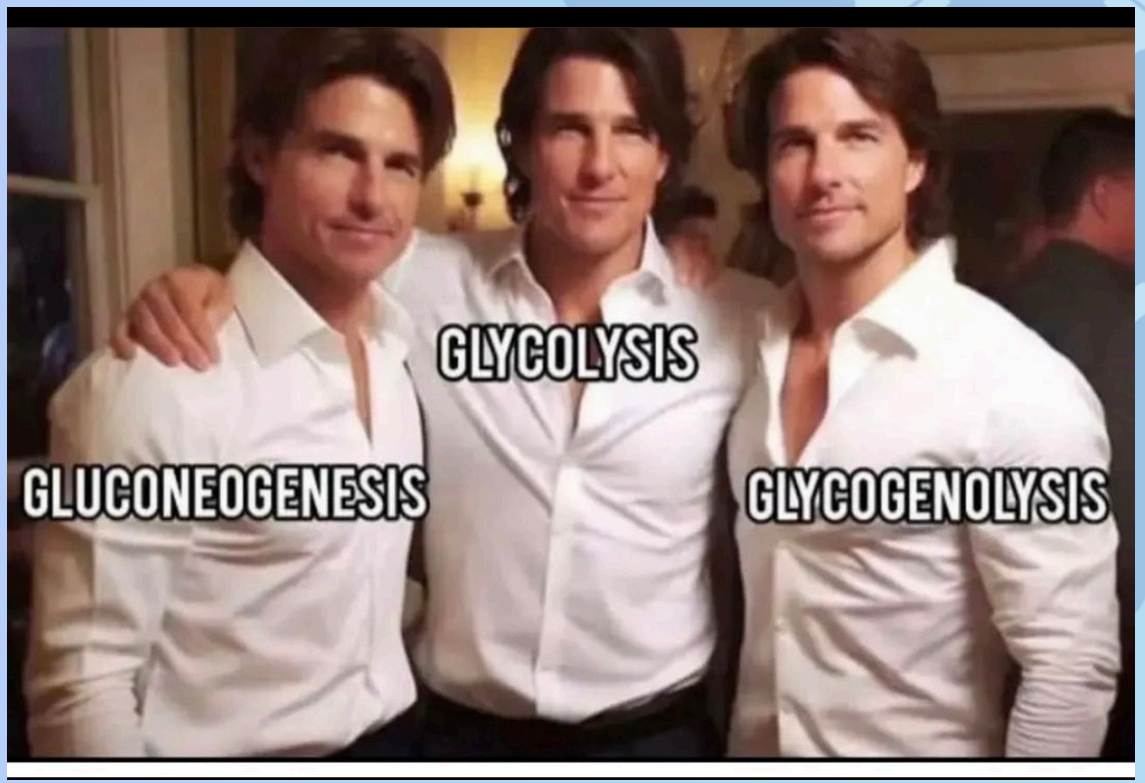
Gluconeogenesis & Cori cycle
Glycogen: the making the breaking

By Niki Brzezinski



SCAN ME

BIOCHEMISTRY

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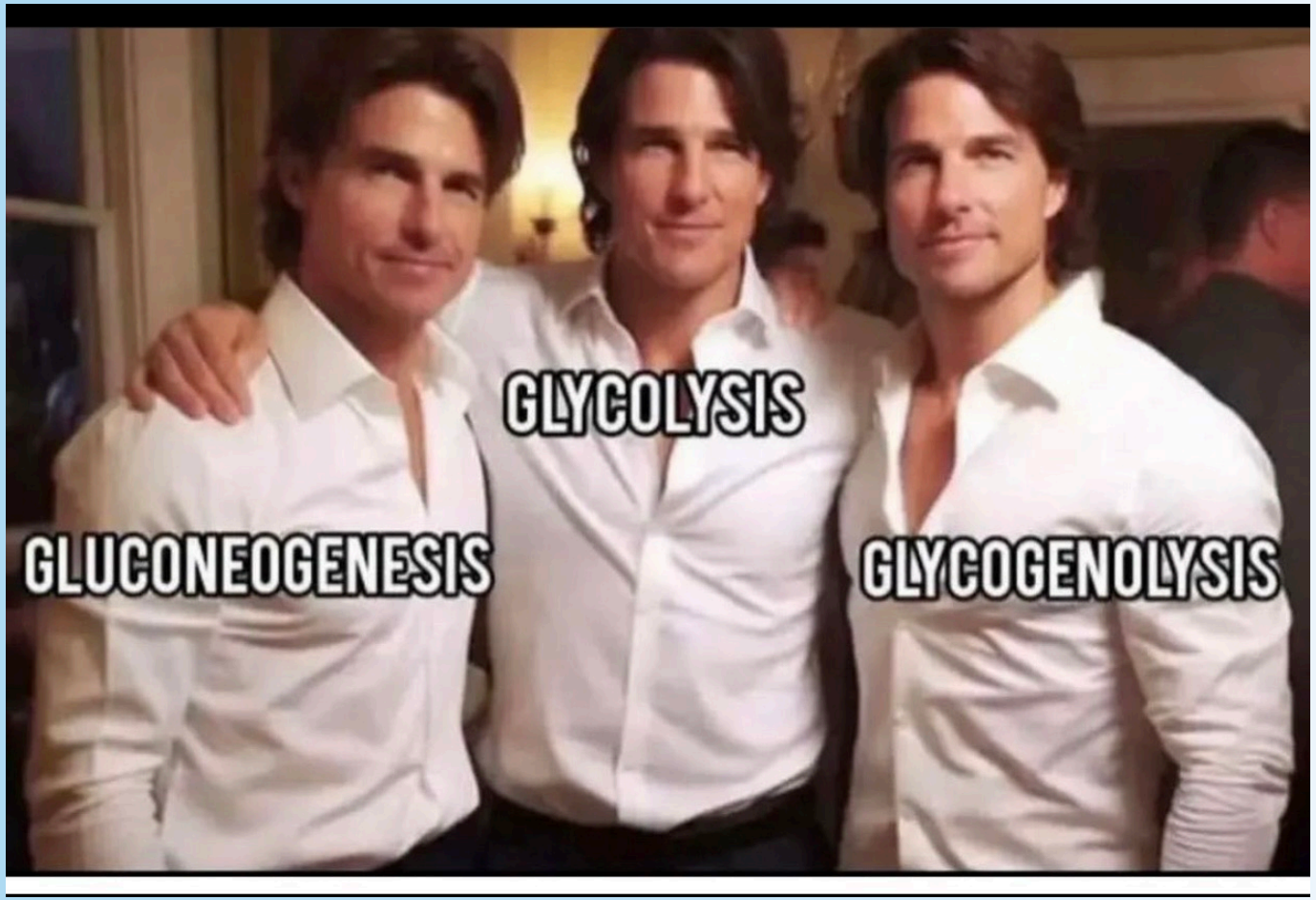
The agenda

~ 1 hour

Overview
Gluconeogenesis

BREAK

Glycogenolysis
Glycogenesis
Deficiencies



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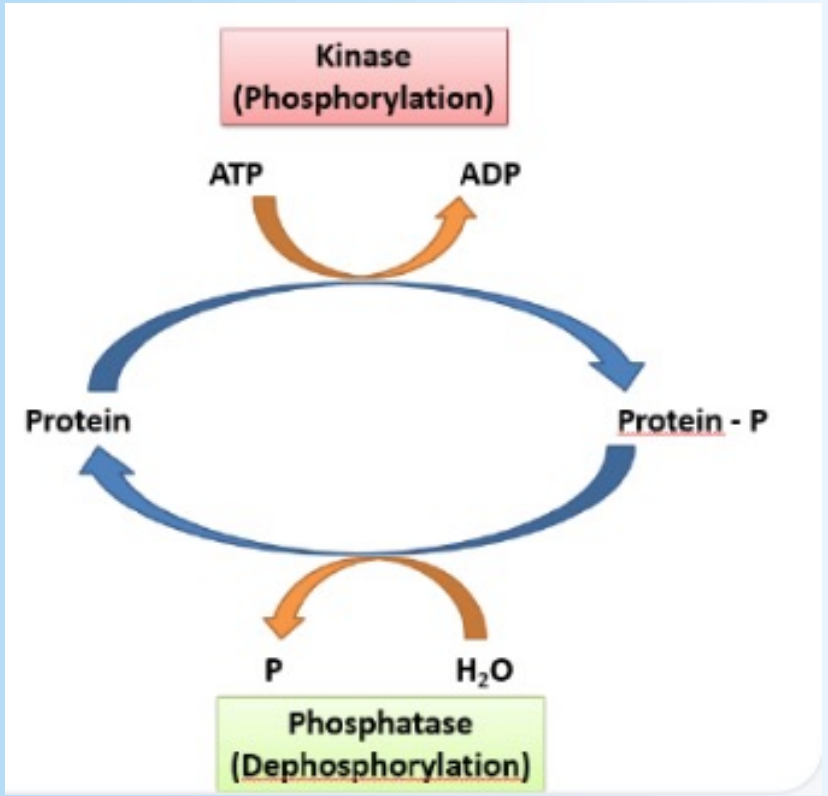
Terminology



Kinase: Add phosphate from ATP +(P)

Phosphorylase: phosphate (P) between compounds

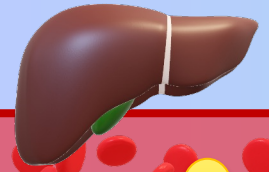
Phosphatase: Use water to remove phosphate -(P)

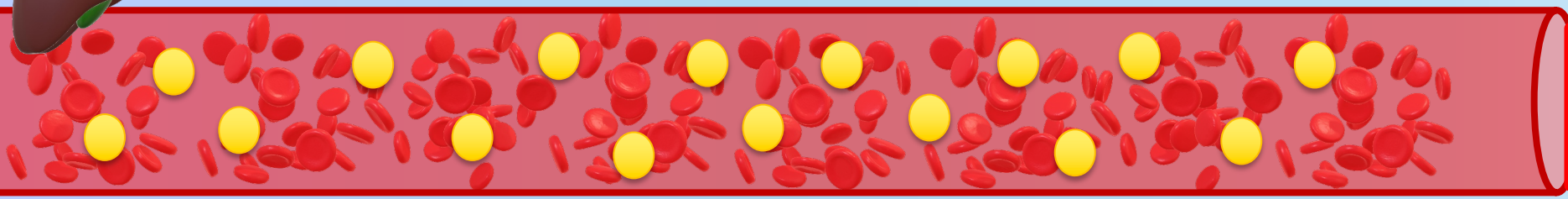
Homeostasis

Take

- Glycolysis
- Glycogenesis

↑ Insulin
↓ Glucagon
↓ Epinephrin





Blood Glucose Range
70-100 mg/dL

Glucose

↓ Insulin
↑ Glucagon
↑ Epinephrin

Make

- Gluconeogenesis
- Glycogenolysis

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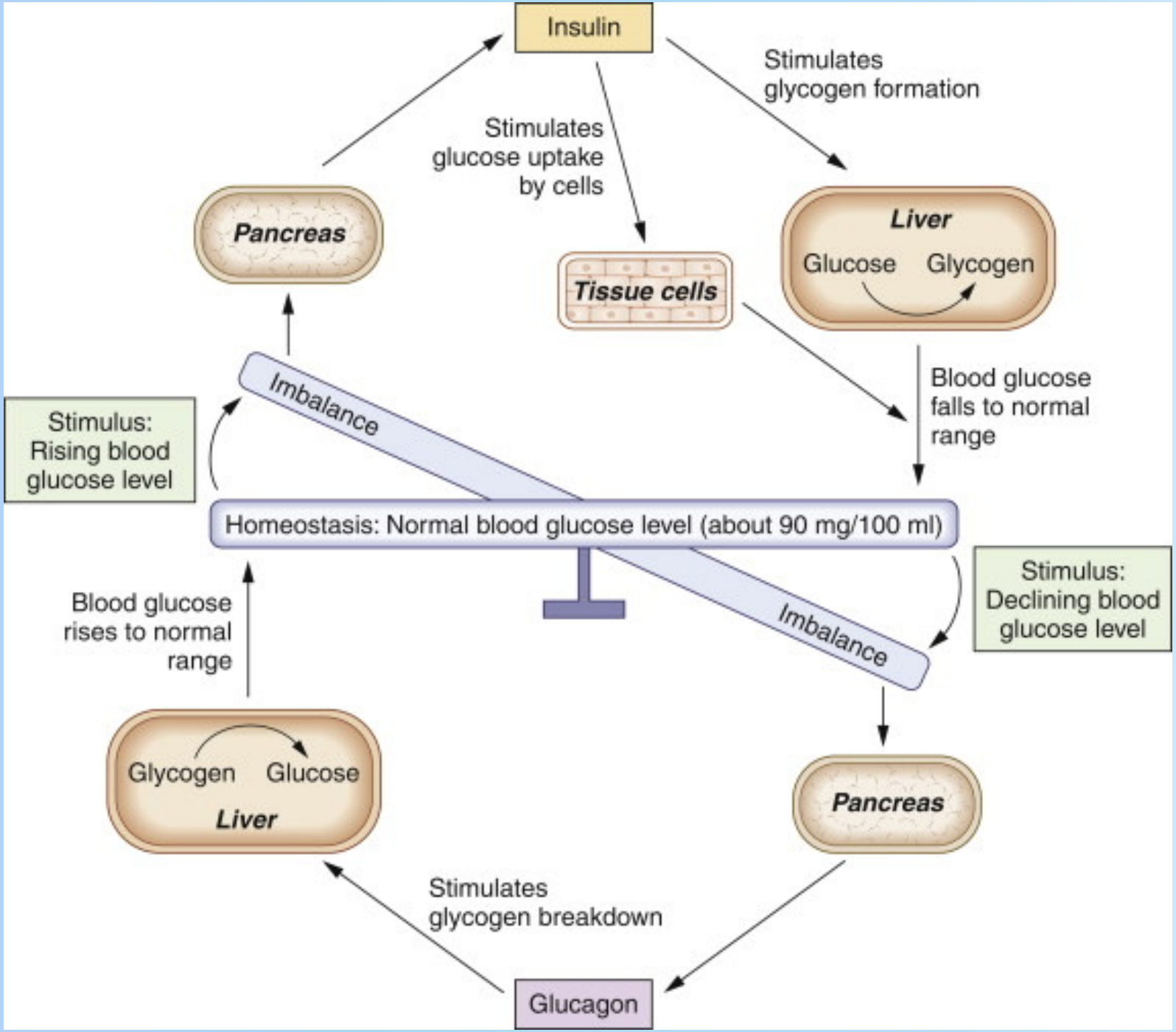
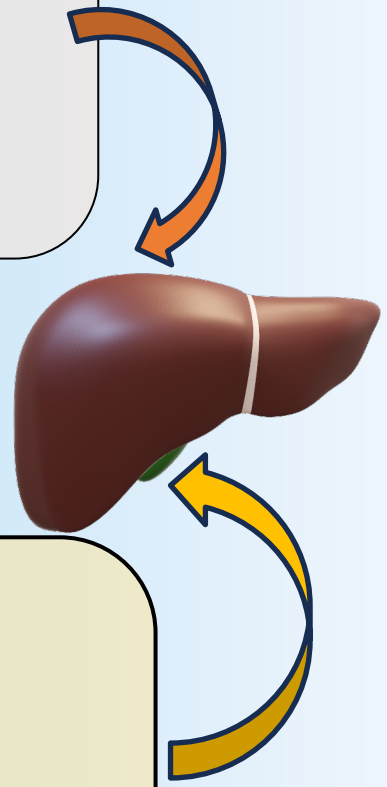

Insulin
Stimulates glycogen formation
Stimulates glucose uptake by cells
Pancreas
Tissue cells
Liver
Glucose
Glycogen
Stimulus: Rising blood glucose level
Imbalance
Blood glucose falls to normal range
Homeostasis: Normal blood glucose level (about 90 mg/100 ml)
Imbalance
Stimulus: Declining blood glucose level
Blood glucose rises to normal range
Glycogen
Glucose
Liver
Pancreas
Stimulates glycogen breakdown
Glucagon

Glycogenosis + Glycolysis



Glycogenolysis + Gluconeogenesis

Blood Glucose Range
70-100 mg/dL

As you eat, ↑ glucose which releases ↑ insulin

Insulin helps cells grab glucose from the blood as it travels through your body.

Your body breaks down glucose into energy – glycolysis.

While your glucose is ↑ your liver will store some away 'just in case' - glycogen (leftovers).

As time goes by, more and more glucose leaves the blood and glucose levels drop.

When glucose ↓ then *glucagon* ↑ which signals the body to make glucose to maintain the balance range.

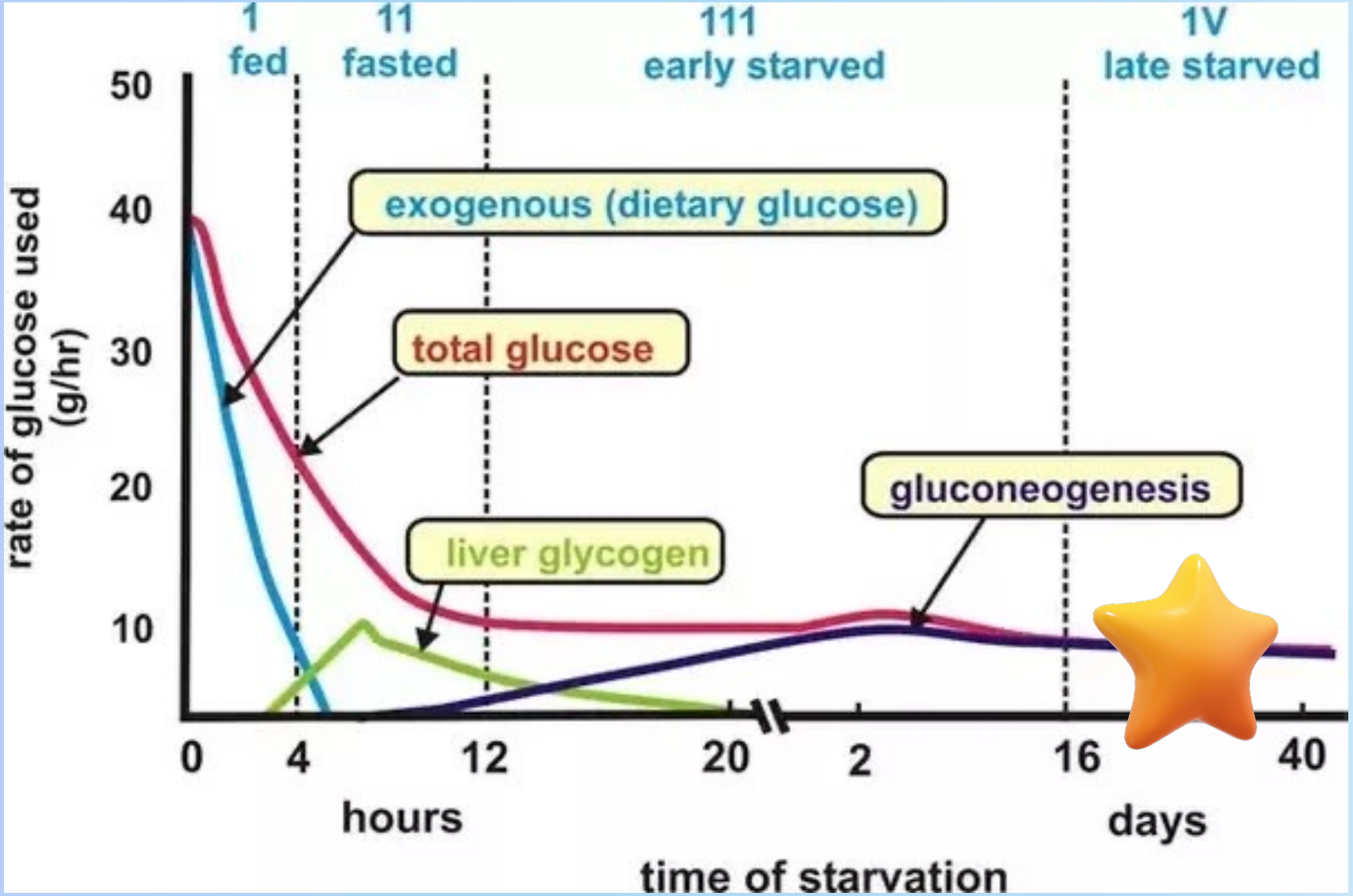
Your body makes glucose in 2 ways:

- Gluconeogenesis (from 3 precursors)
- Glycogenolysis

Gluconeogenesis

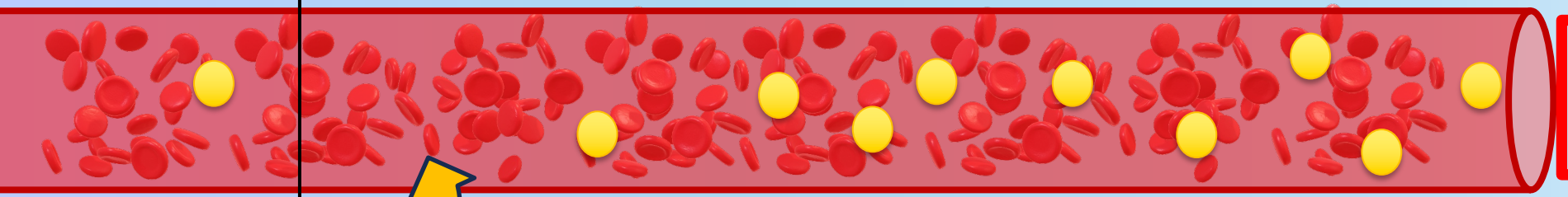
precursor → Glucose

Glucose: ↓
Glucagon: ↑



Fasting/Starved

Make



Blood Glucose Range
70-100 mg/dL

Gluconeogenesis

Majority occurs in liver; little bit in kidney

Making Glucose from 3 precursors
1. Lactate
2. Amino Acids
3. Glycerol

Must override 3 enzymes

Need 2 pyruvate per glucose

↓ Insulin
↑ Glucagon
↑ Epinephrin

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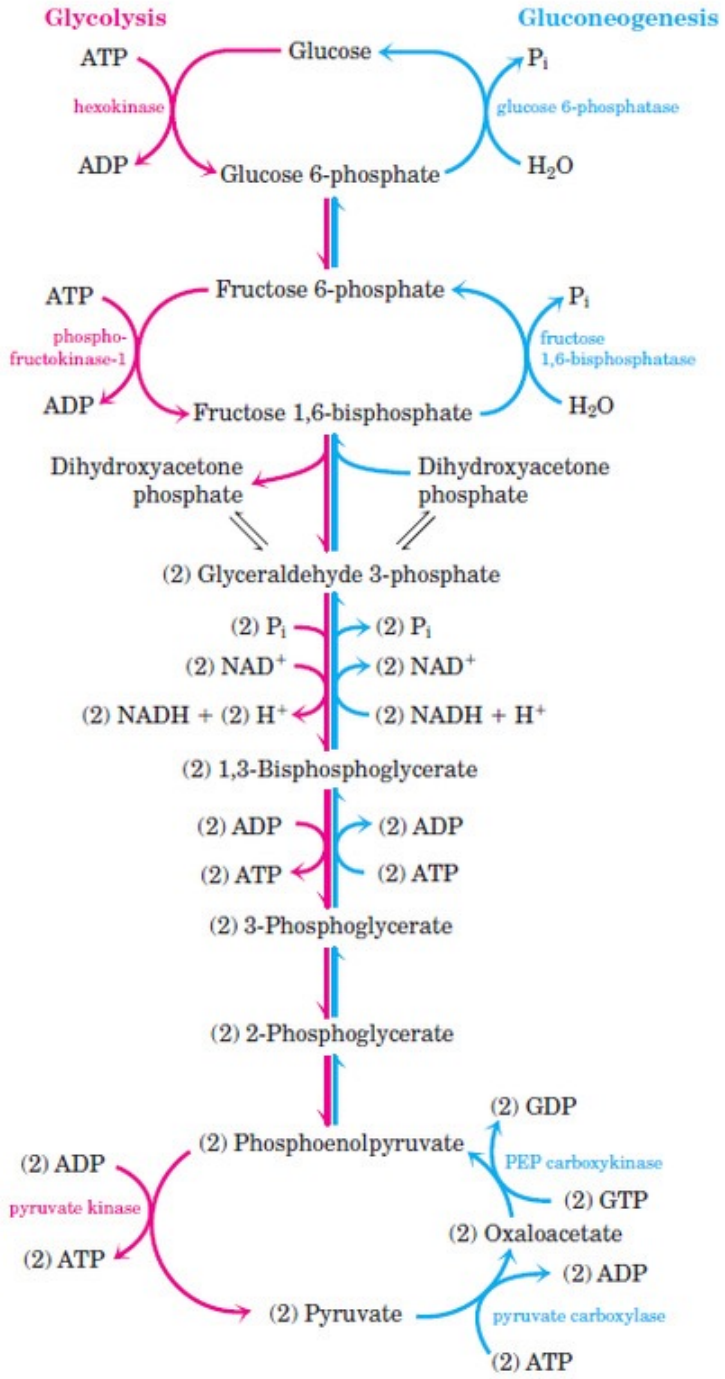
3 Enzyme bypass



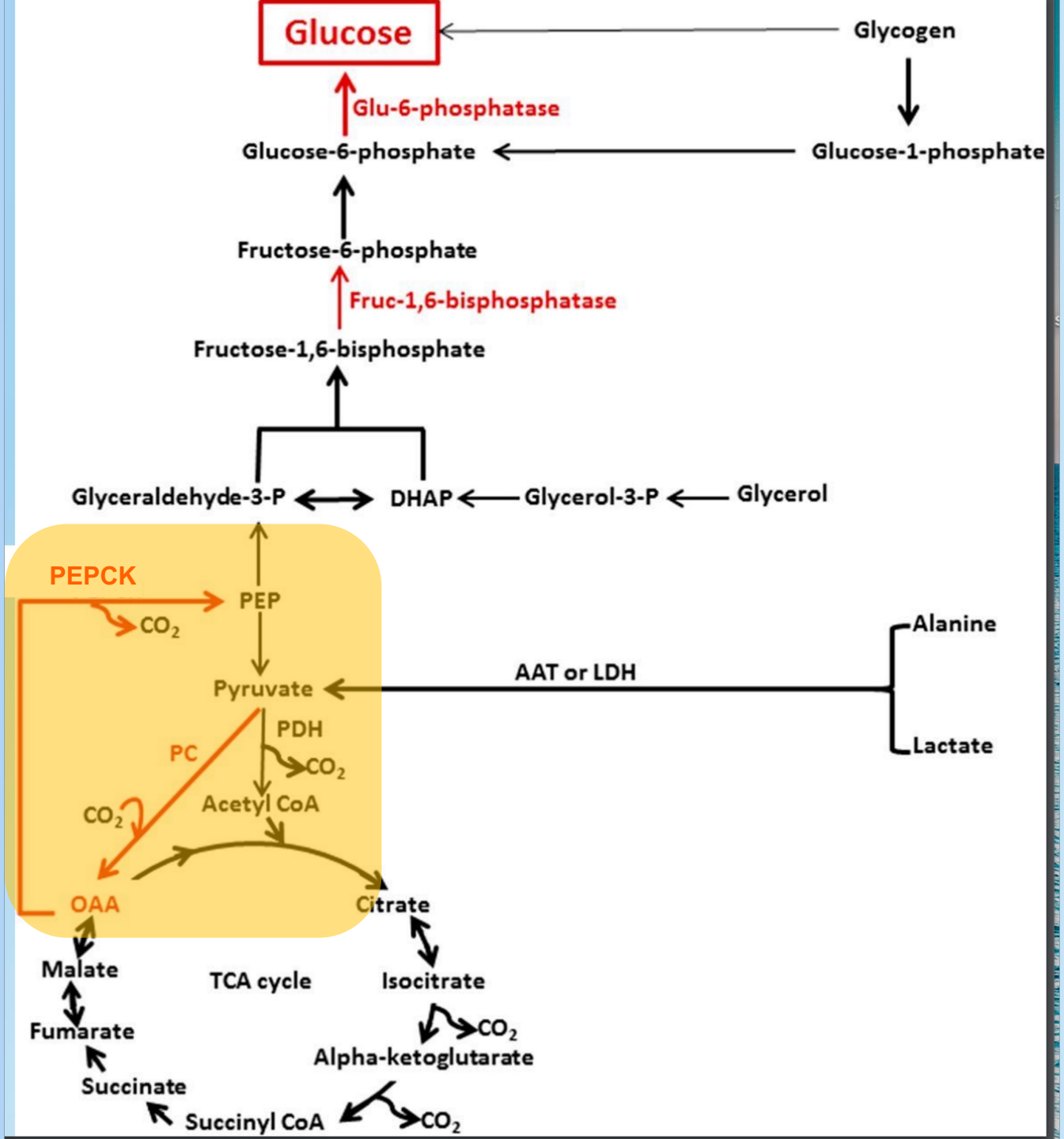
3 Glucokinase* → **glucose-6-phosphatase**
Hexokinase is in muscle and muscles do not contain glucose-6-phosphatase

2 Phosphofructokinase → **Fructose 1,6-biphosphatase**

The 3 irreversible rxn enzymes that need to be bypassed

1 Pyruvate Kinase → **(a) Pyruvate carboxylase +**
(b) Phosphoenolpyruvate carboxyl kinase
(PEP Carboxyl Kinase)

3 Enzyme bypass



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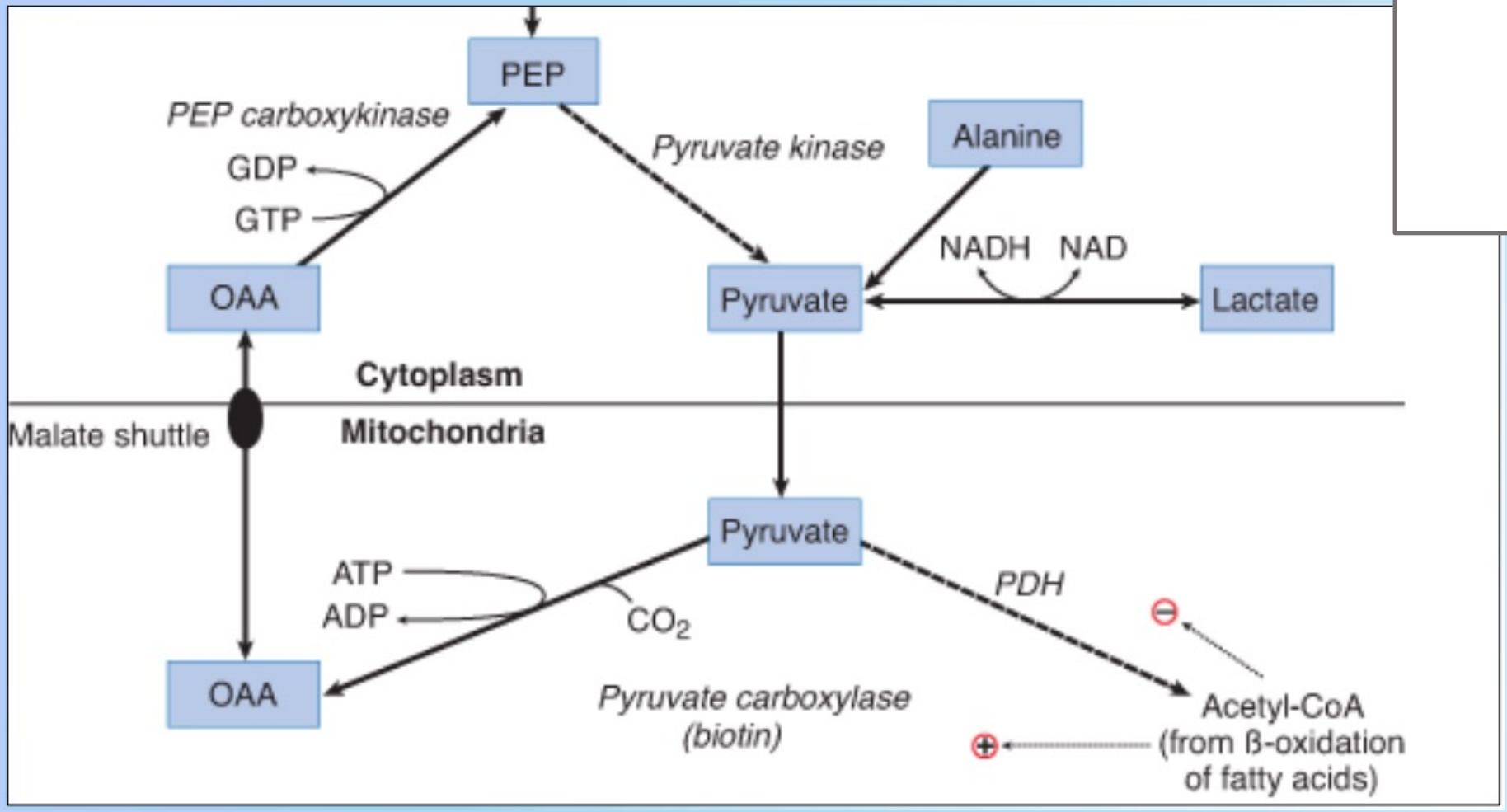
1st Bypass:

3 Enzyme bypass



Energy: ATP, GTP
PC needs Biotin
High CoA: GO
Low CoA: STOP

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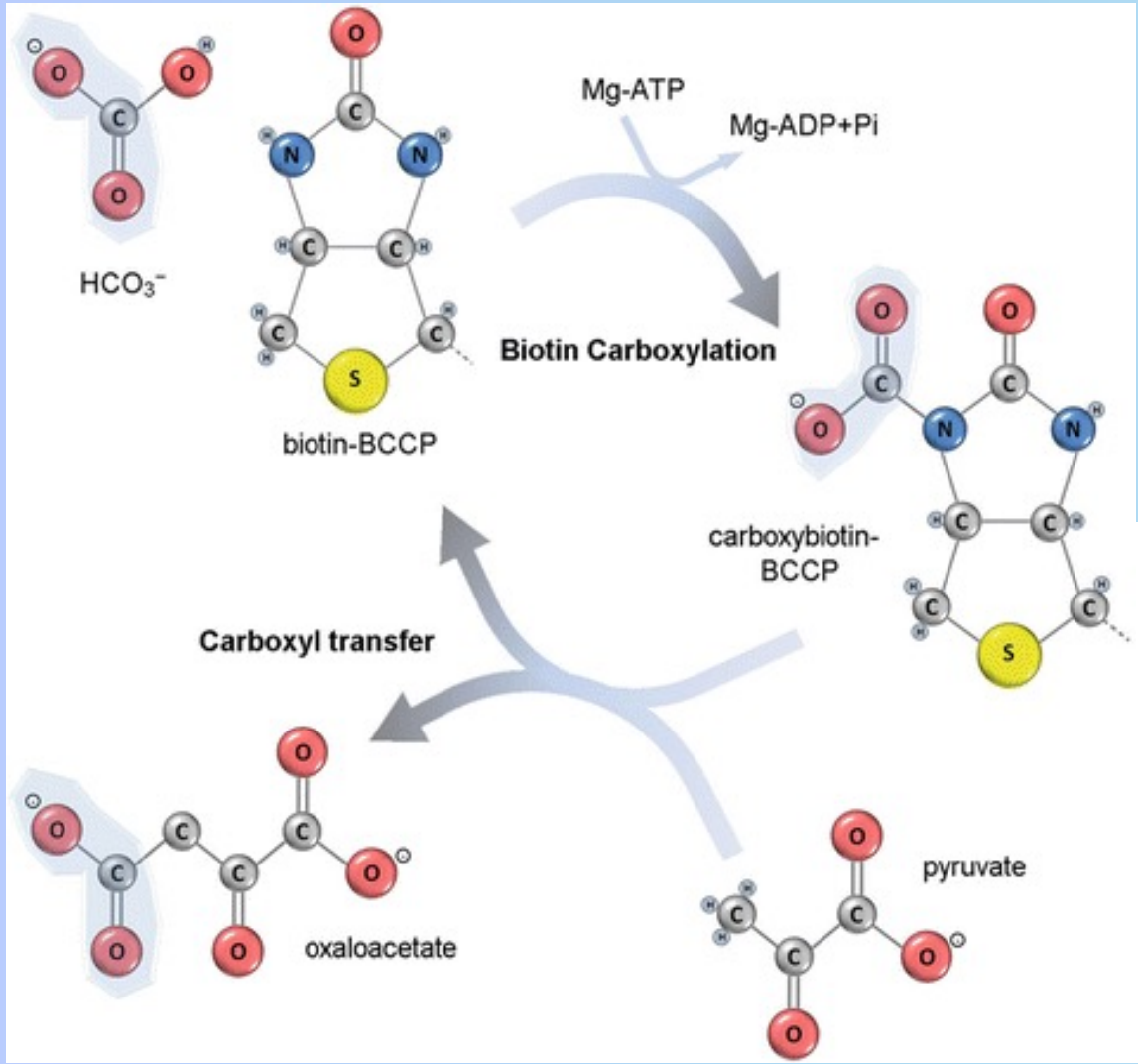
Why is biotin important?

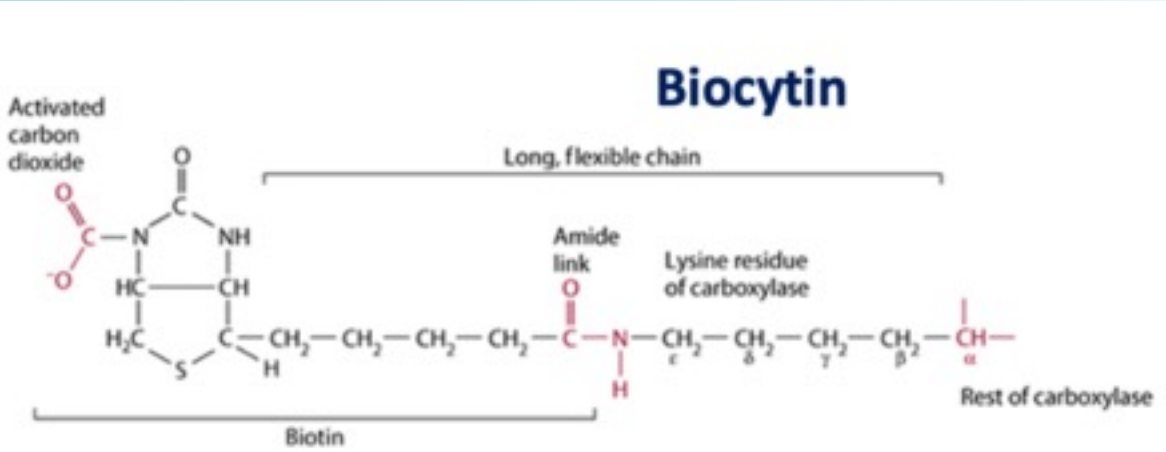


Biotin + bicarbonate (uses ATP) → carboxybiotin

”loads the enzyme with carboxyl”

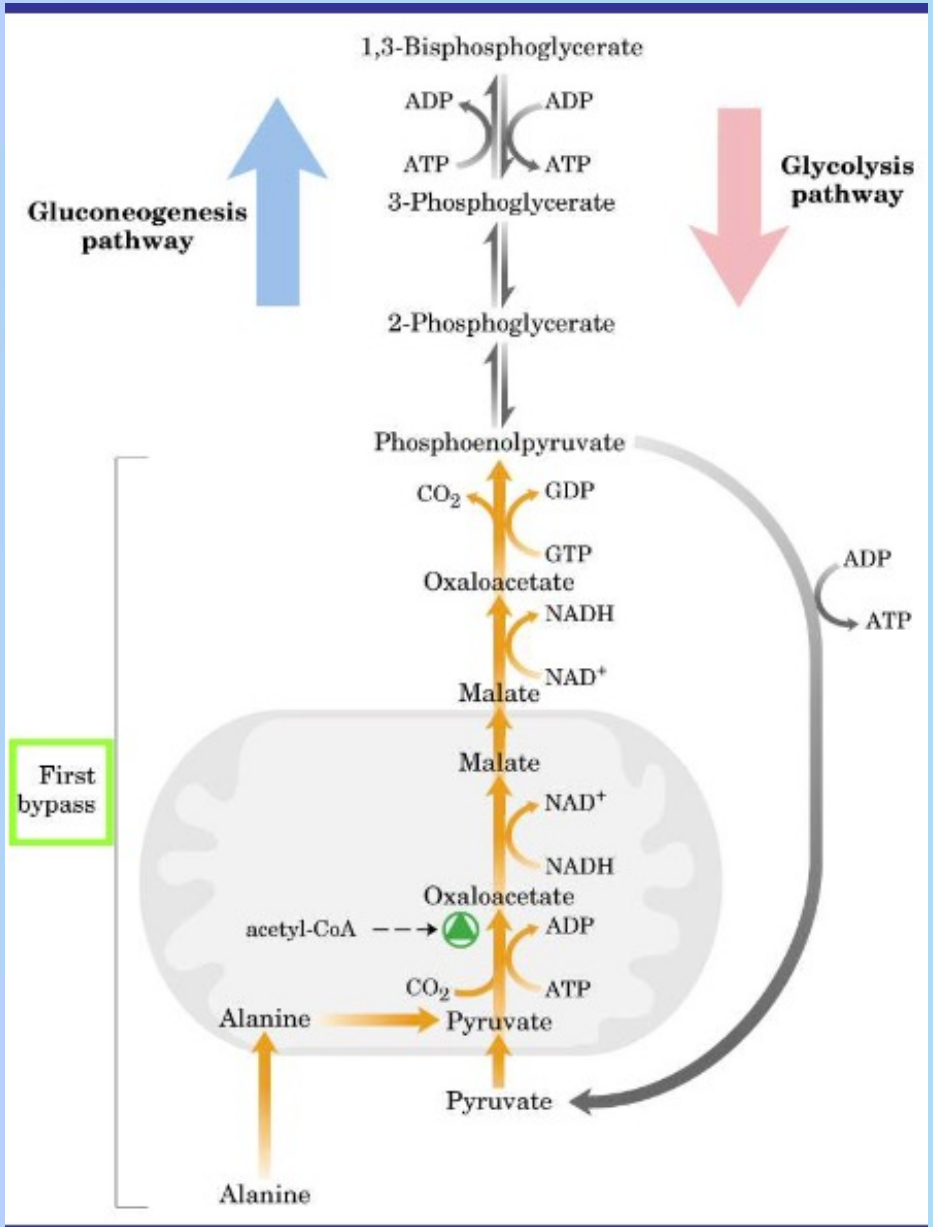
Pyruvate carboxylase then adds carboxyl to pyruvate → OAA

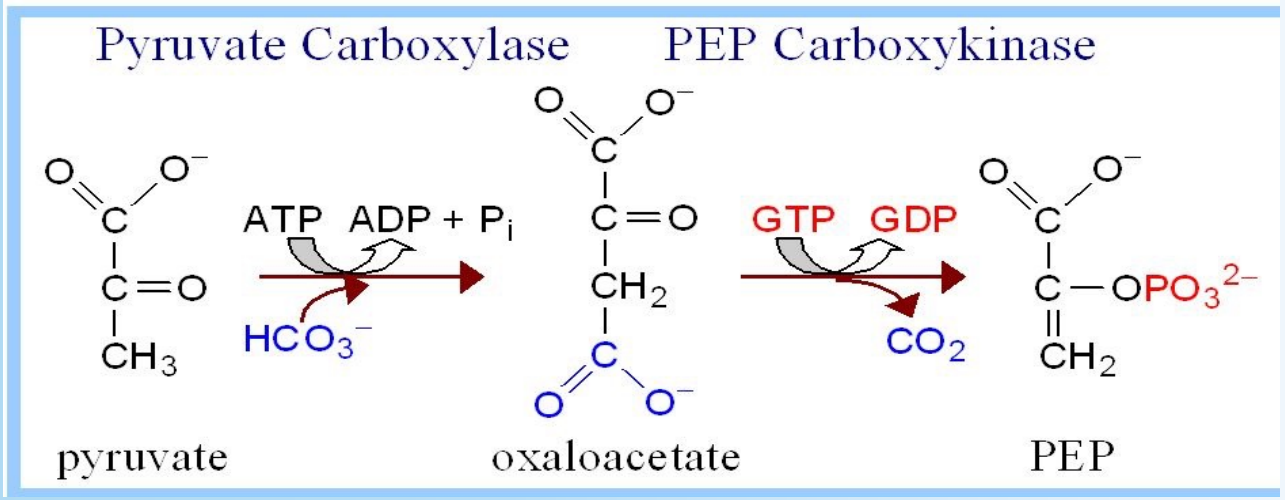
Occurs in mitochondria



3 Enzyme bypass

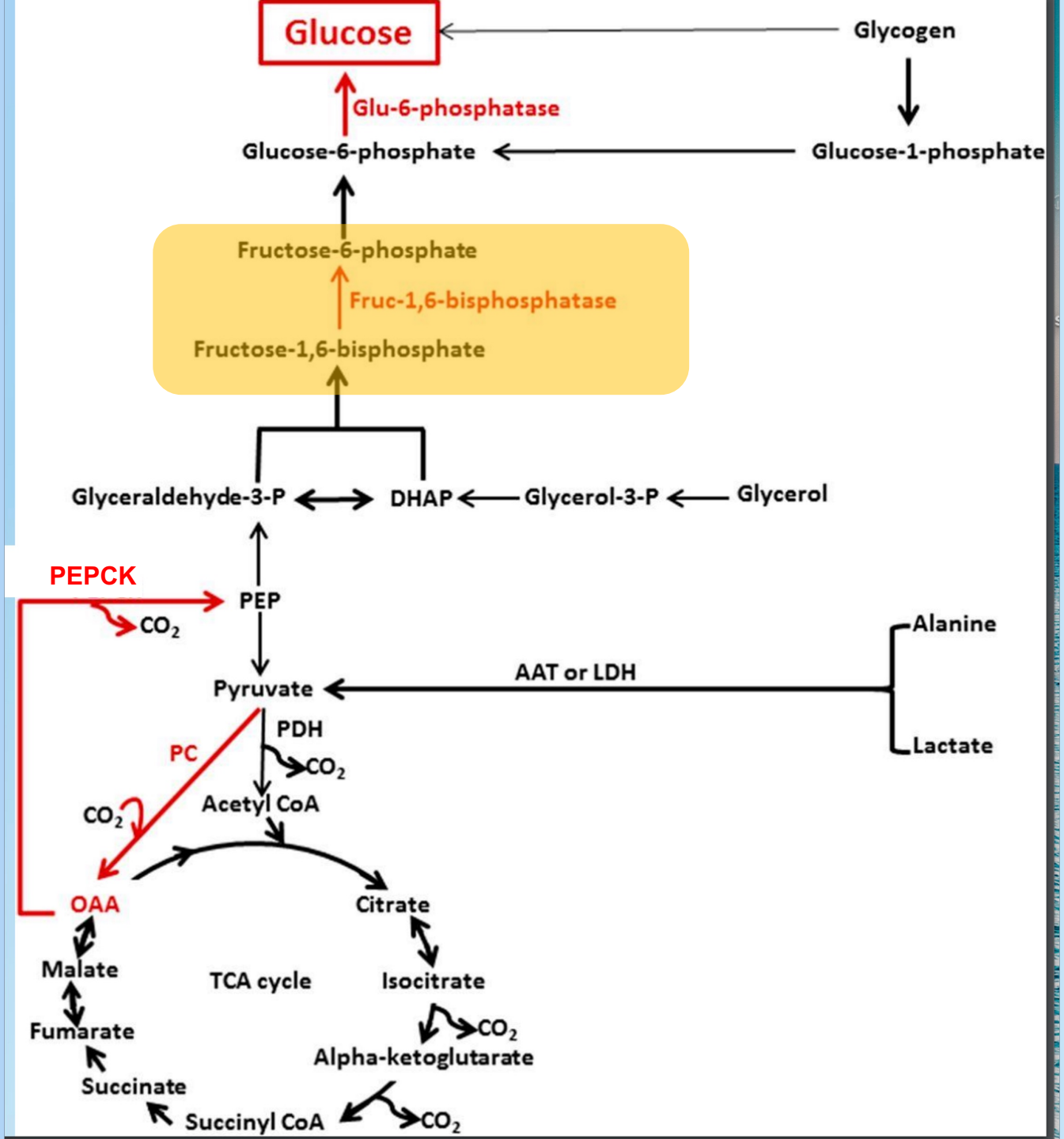
1st Bypass





Pyruvate Carboxylase	Malate shuttle →	PEP carboxykinase
Occurs in mitochondria		Occurs in cytosol
Pyruvate → Oxaloacetate		Oxaloacetate → Phosphoenolpyruvate (PEP)
Adds Carbon Requires ATP		Removes the added carbon Requires GTP
Cofactor: Biotin **Acetyl CoA regulates this enzyme**		

3 Enzyme bypass



3 Enzyme bypass

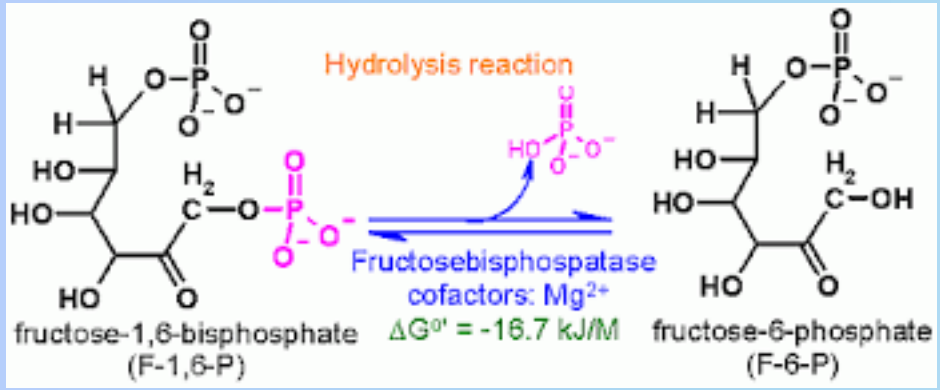
2nd Bypass: Fructose 1,6 biphosphatASE

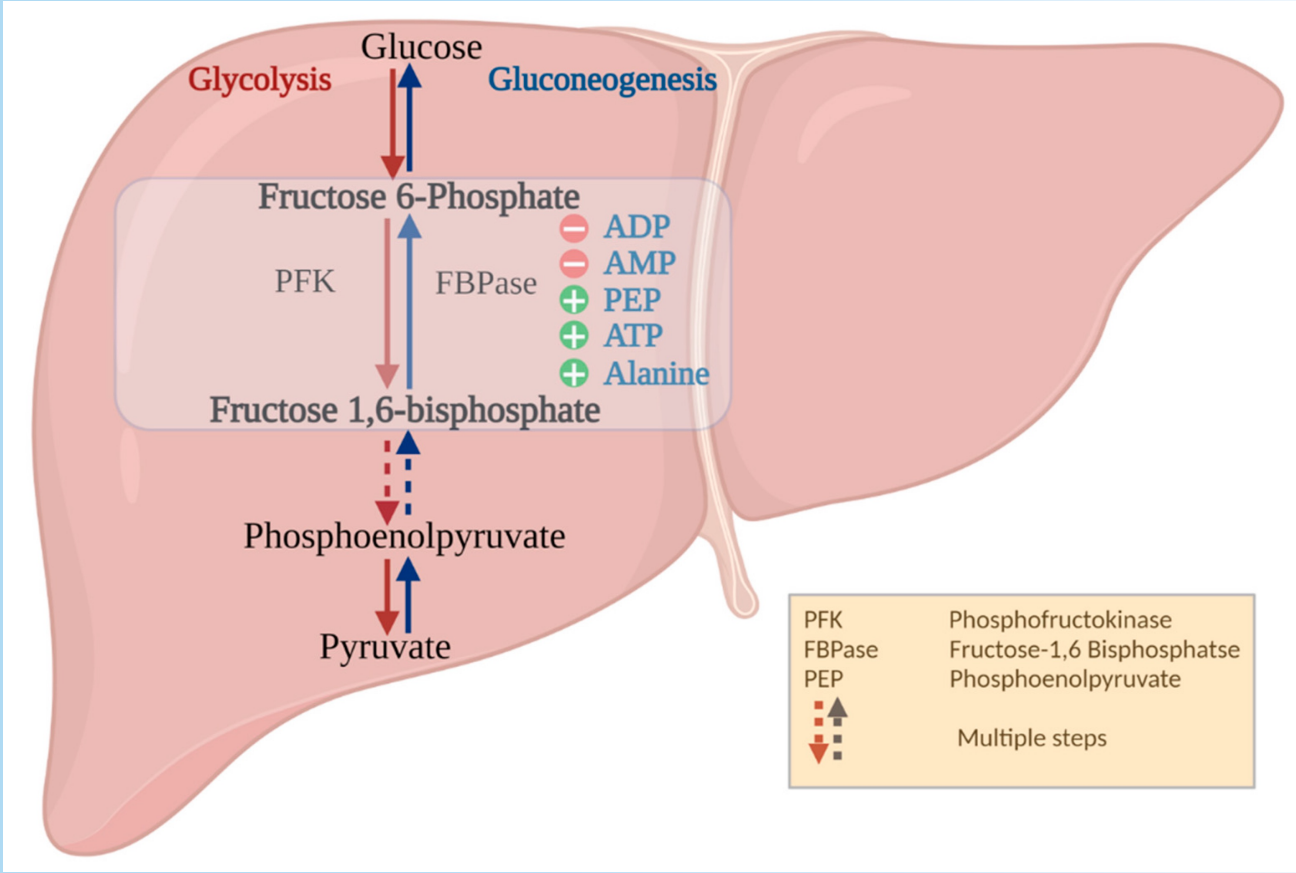
Bypasses phosphofructokinase-1

RATE LIMITING ENZYME

Inhibited by AMP & F2,6BP

Cytosol





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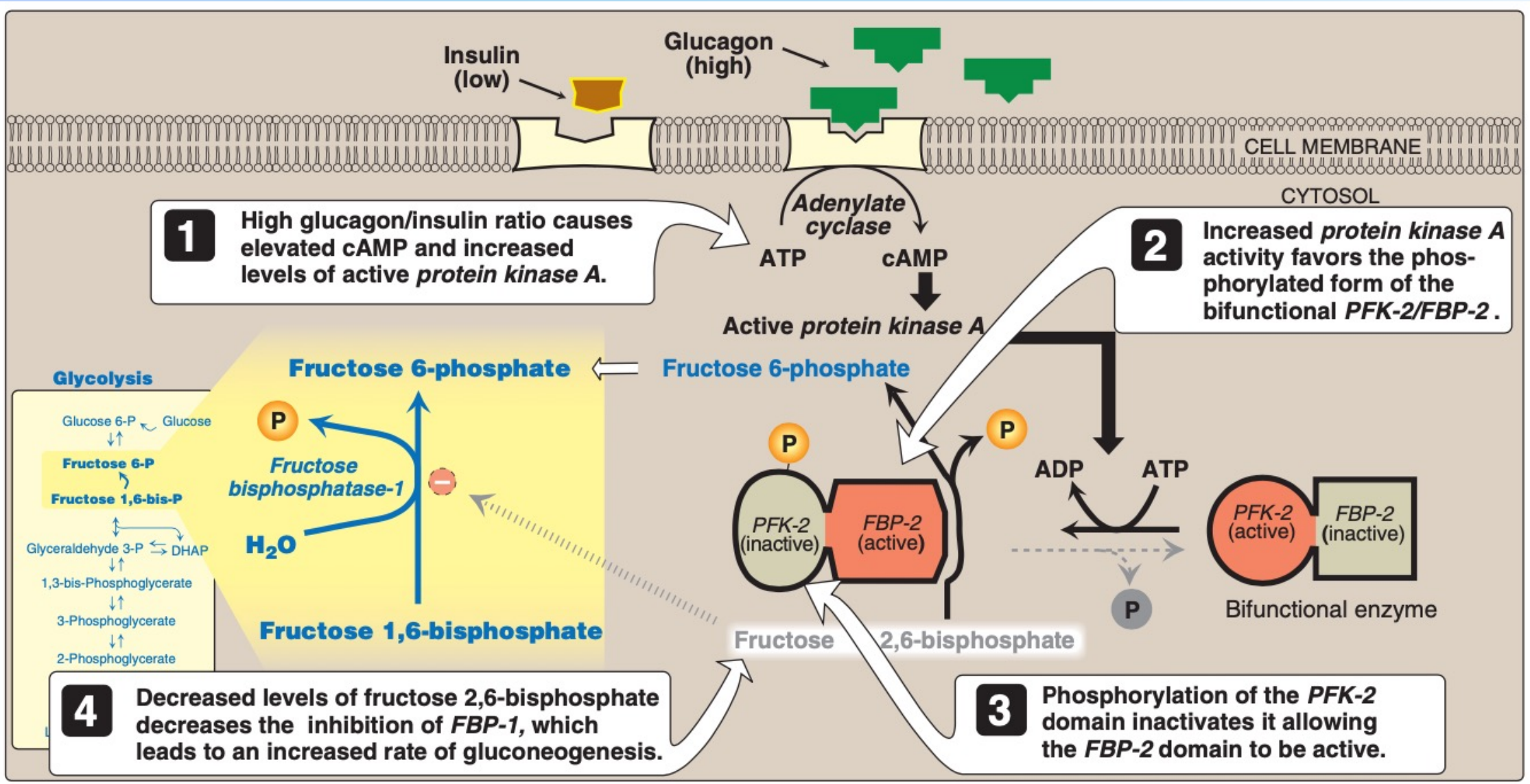
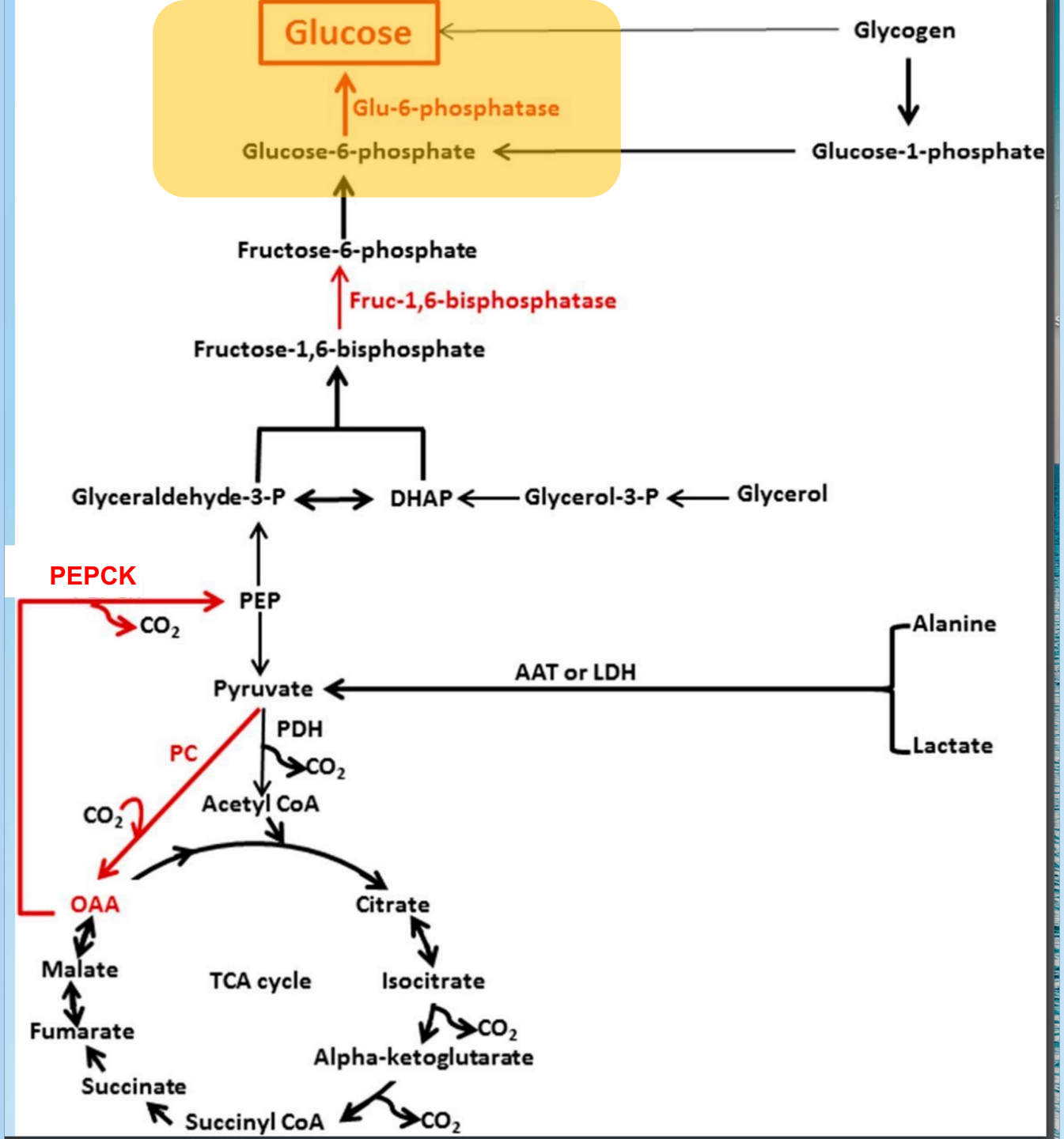


Figure 10.5
Effect of elevated glucagon on the intracellular concentration of fructose 2,6-bisphosphate in the liver. *PFK-2 = phosphofructokinase-2; FBP-2 = fructose bisphosphatase-2.*

3 Enzyme bypass



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3 Enzyme bypass

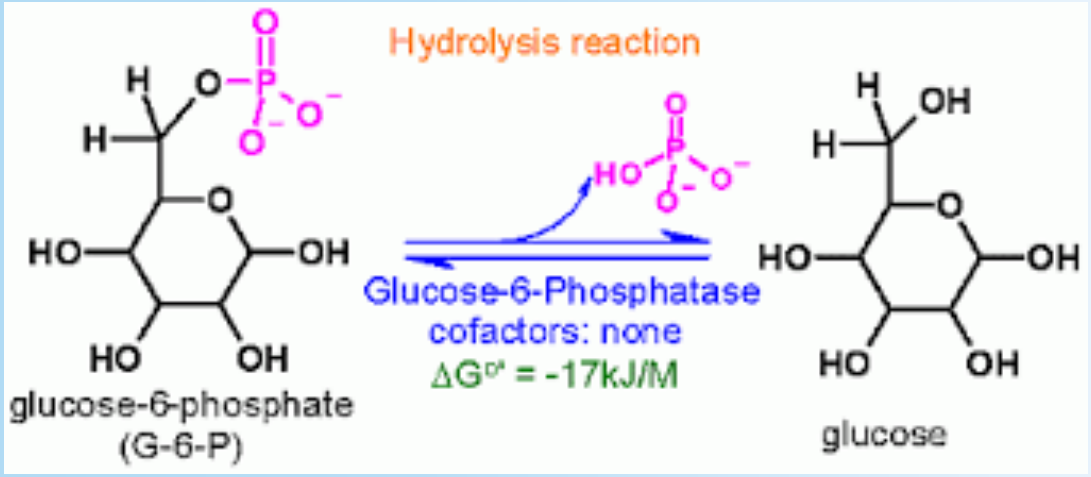
3rd Bypass: Glucose-6-phosphatASE

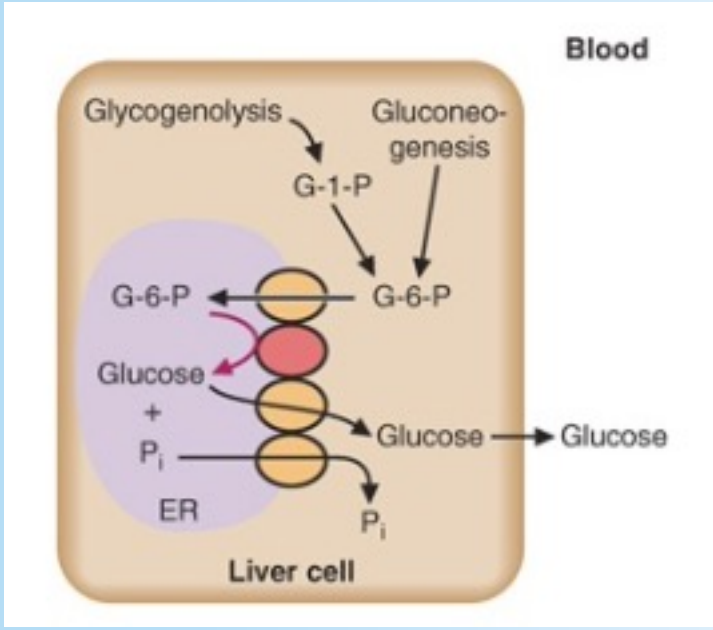
Bypasses Glucokinase

Only present in <u>liver and kidney</u>

Makes glucose

Occurs in the endoplasmic reticulum then transported back to cytosol.





Gluconeogenesis: summary

Pyruvate → PEP (repeated 2x/glucose):

- Pyruvate → oxaloacetate in mitochondria
- Oxaloacetate → malate for export to cytoplasm
- Malate → oxaloacetate in cytoplasm
- Oxaloacetate → PEP
- Hydrolysis of 1 ATP & 1GTP
- Irreversible pyruvate kinase reaction bypassed by PC & PEPCK
- Lactate & glucogenic aminoacids enter at this stage

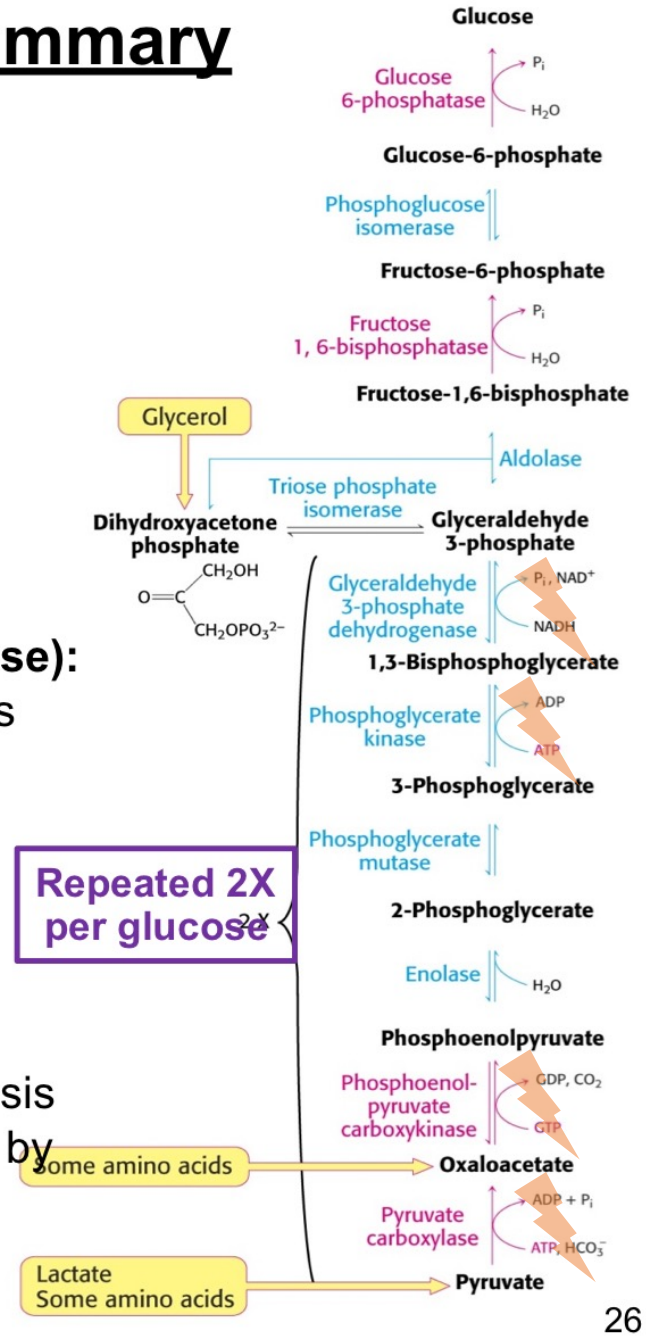
PEP → Fructose-6P (PEP→Glyc-3P repeated 2x/glucose):

- PEP → Fructose-1,6-BP reactions shared with glycolysis
- Hydrolysis of 1 ATP & oxidation of 1 NADH
- Irreversible PFK-1 reaction bypassed by Fructose-1,6-Biphosphatase
- Glycerol enters at this step

Fructose-6-P → Glucose:

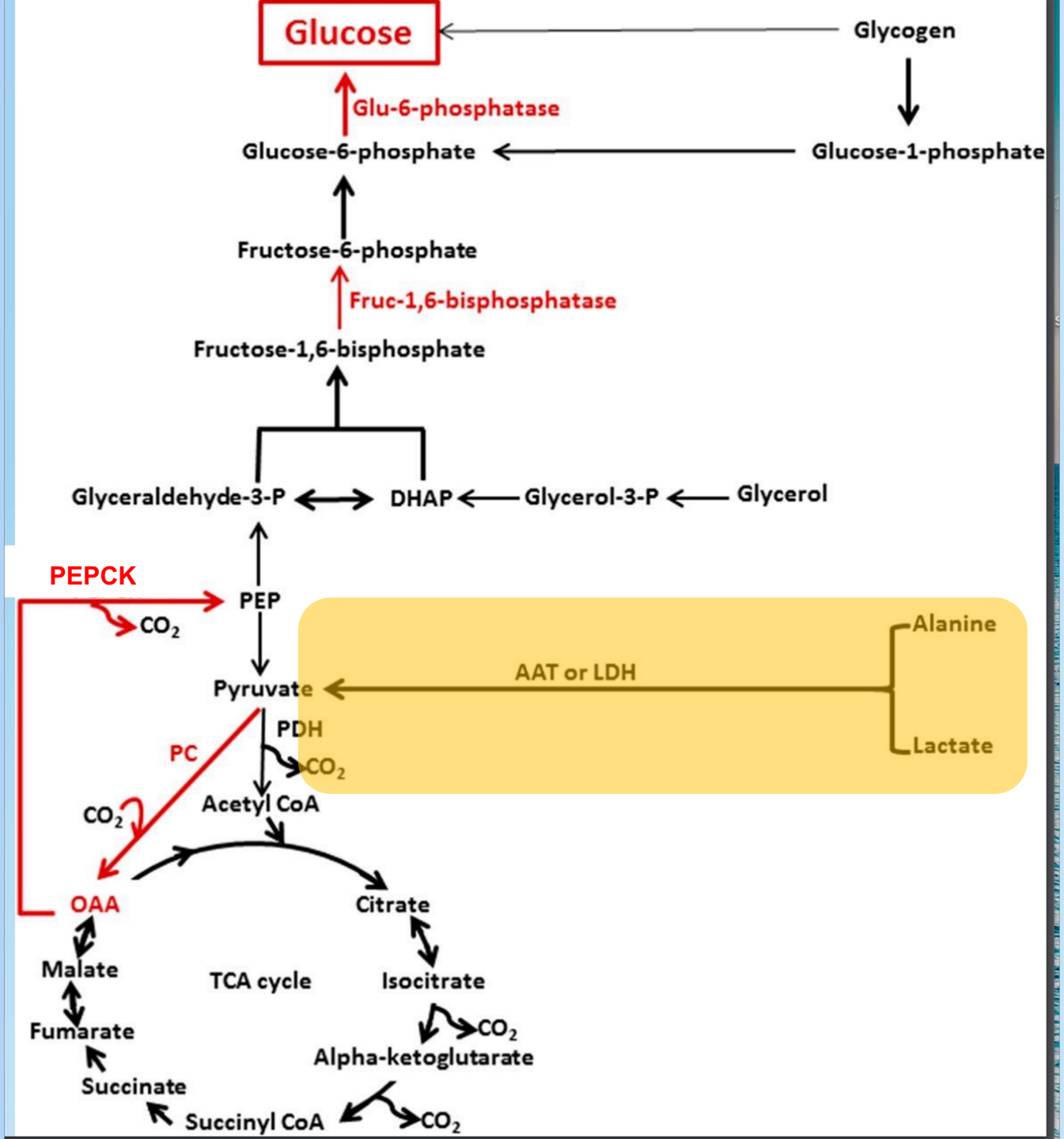
- Fructose-6P → Glucose-6P reaction shared with glycolysis
- Irreversible glucokinase reaction of glycolysis bypassed by glucose-6-phosphatase

**Reactions shared with glycolysis
**Reactions unique to gluconeogenesis



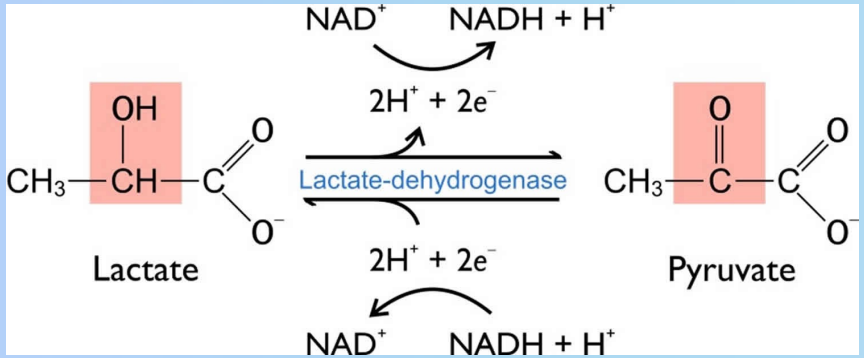
TOTAL ENERGY USED
4 ATPs
2 GTPs
2 NADHs

Precursor



Lactate → Pyruvate

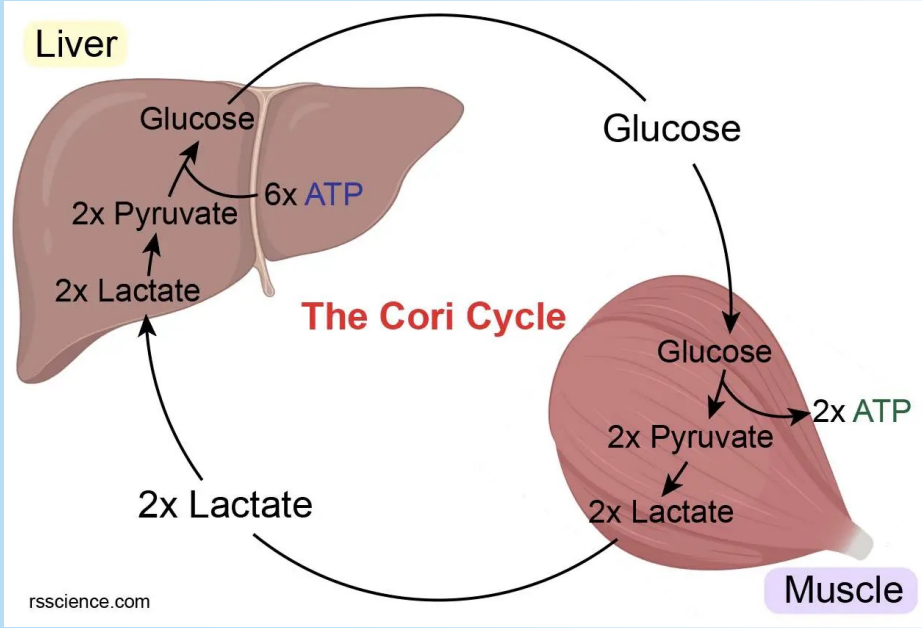
Lactate dehydrogenase



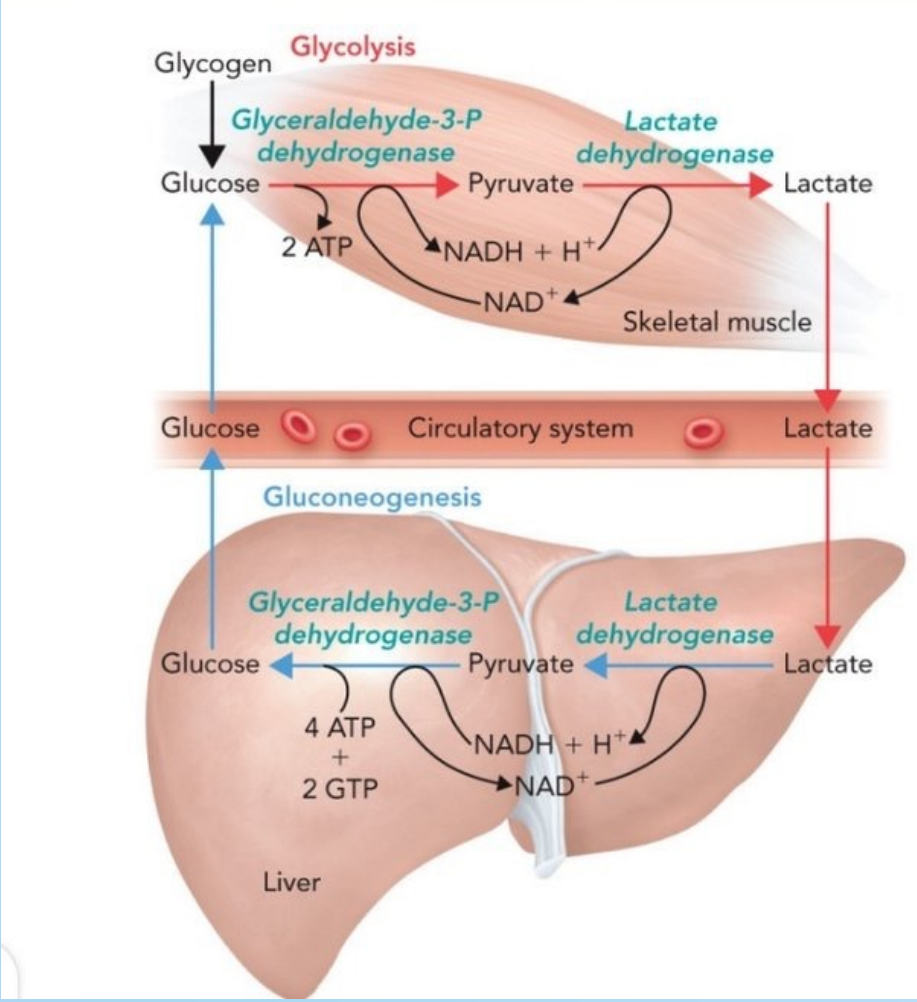
Muscles and RBC (lack of mitochondria) make lactate when body needs glucose during hypoxia, ischemia, tumors, high-intensity exercise or rapid energy needs, like fight-or-flight.

Want to avoid ↑ lactate build up because leads to ↓ drop in pH (acidosis).

Take the lactate and turn it into pyruvate.



Cori cycle

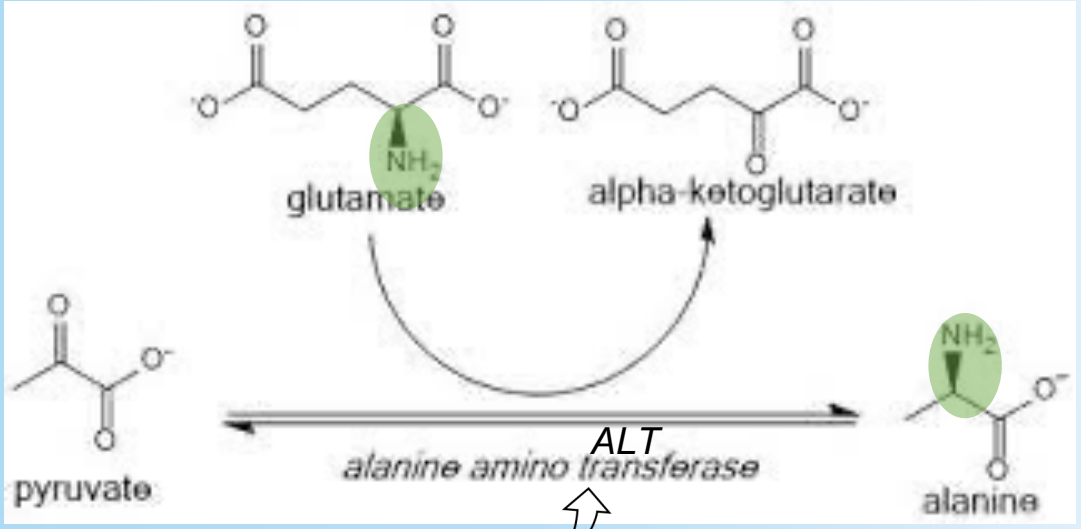

Glycogen
Glycolysis
Glyceraldehyde-3-P dehydrogenase
Lactate dehydrogenase
Glucose
Pyruvate
Lactate
2 ATP
NADH + H+
NAD+
Skeletal muscle
Glucose
Circulatory system
Lactate
Gluconeogenesis
Glyceraldehyde-3-P dehydrogenase
Lactate dehydrogenase
Glucose
Pyruvate
Lactate
4 ATP
+
2 GTP
NADH + H+
NAD+
Liver

Amino Acid precursor: Alanine

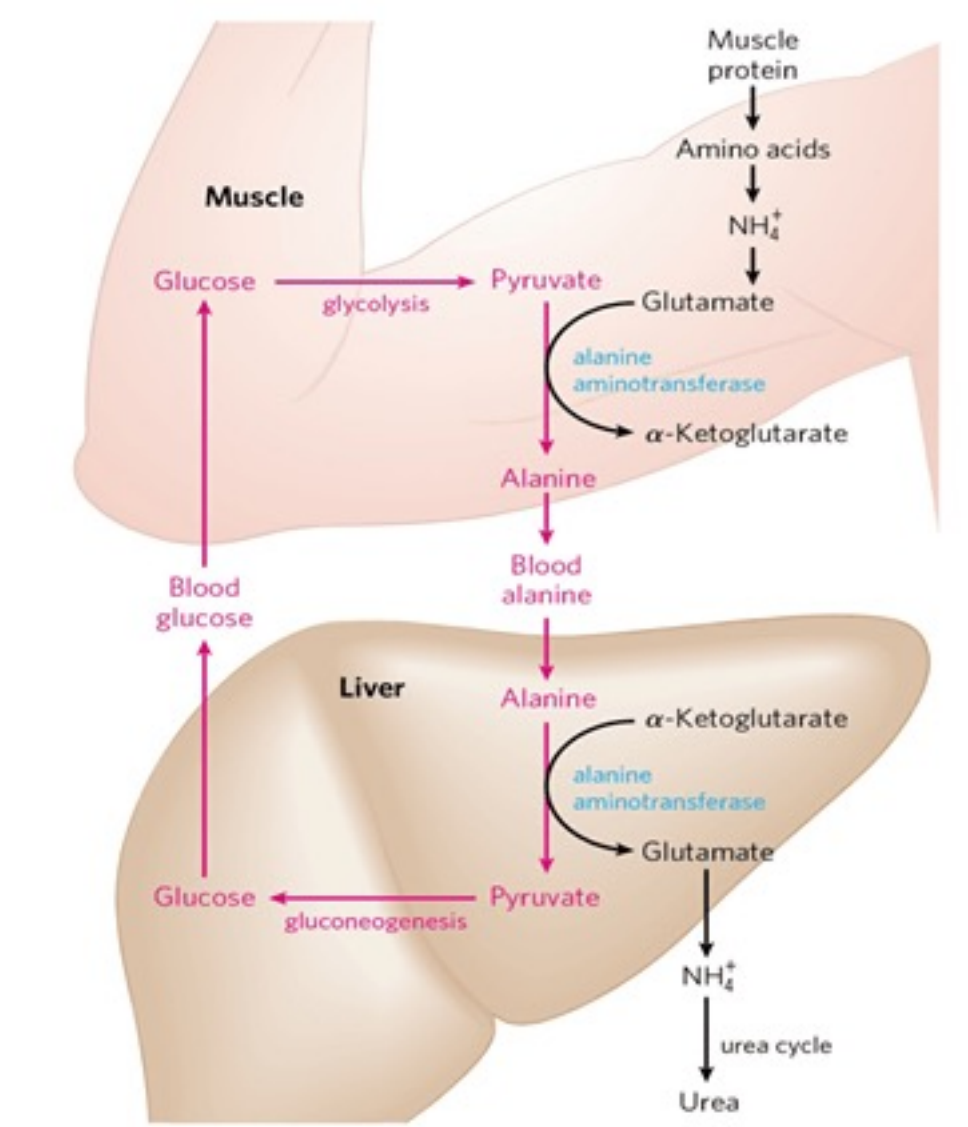
↑ Acetyl-CoA (from fatty acid oxidation) ⊘ pyruvate dehydrogenase
Which leads to ↑ build up of pyruvate

Excess pyruvate → alanine
Alanine amino transferase (ALT)
To be transported to liver and transaminases back to pyruvate

Aids in NH4+ out of the body through urea cycle

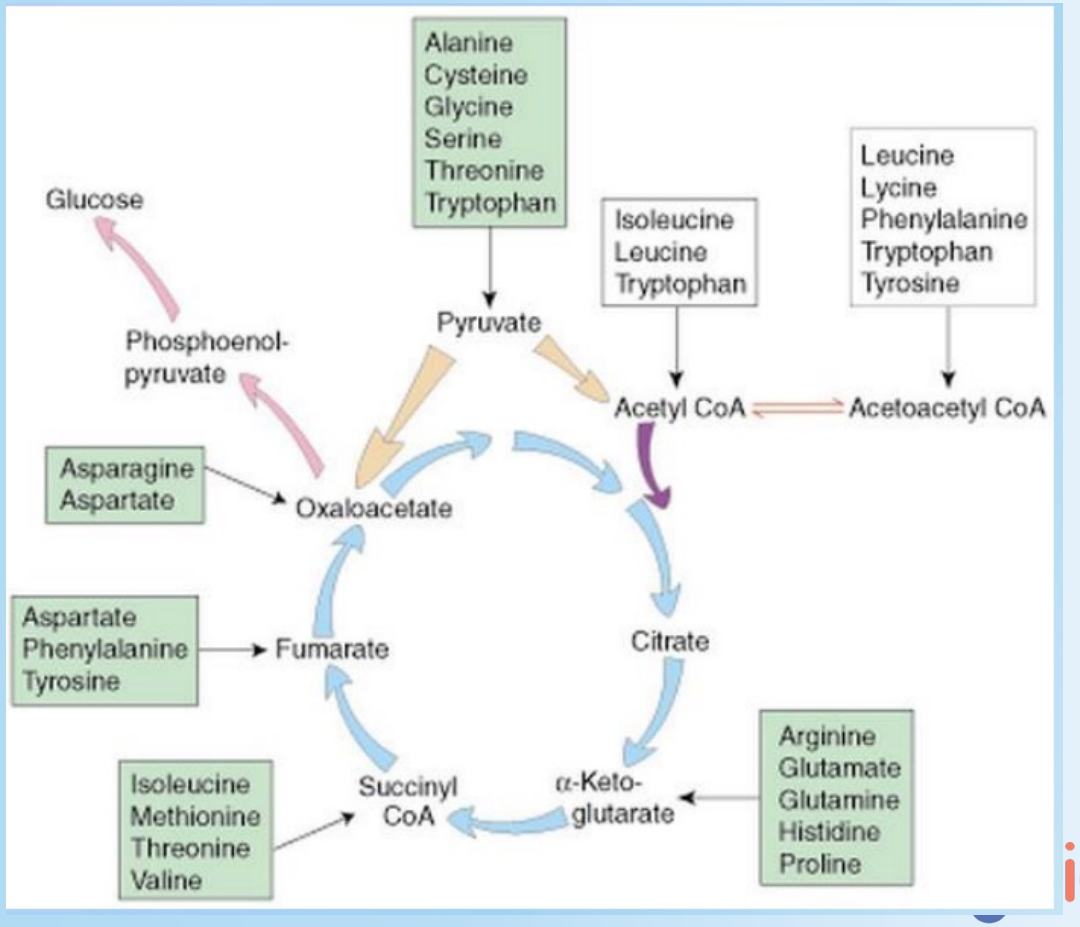


IRL: Marker of liver damage; as hepatocytes are damaged, enzymes get released into blood

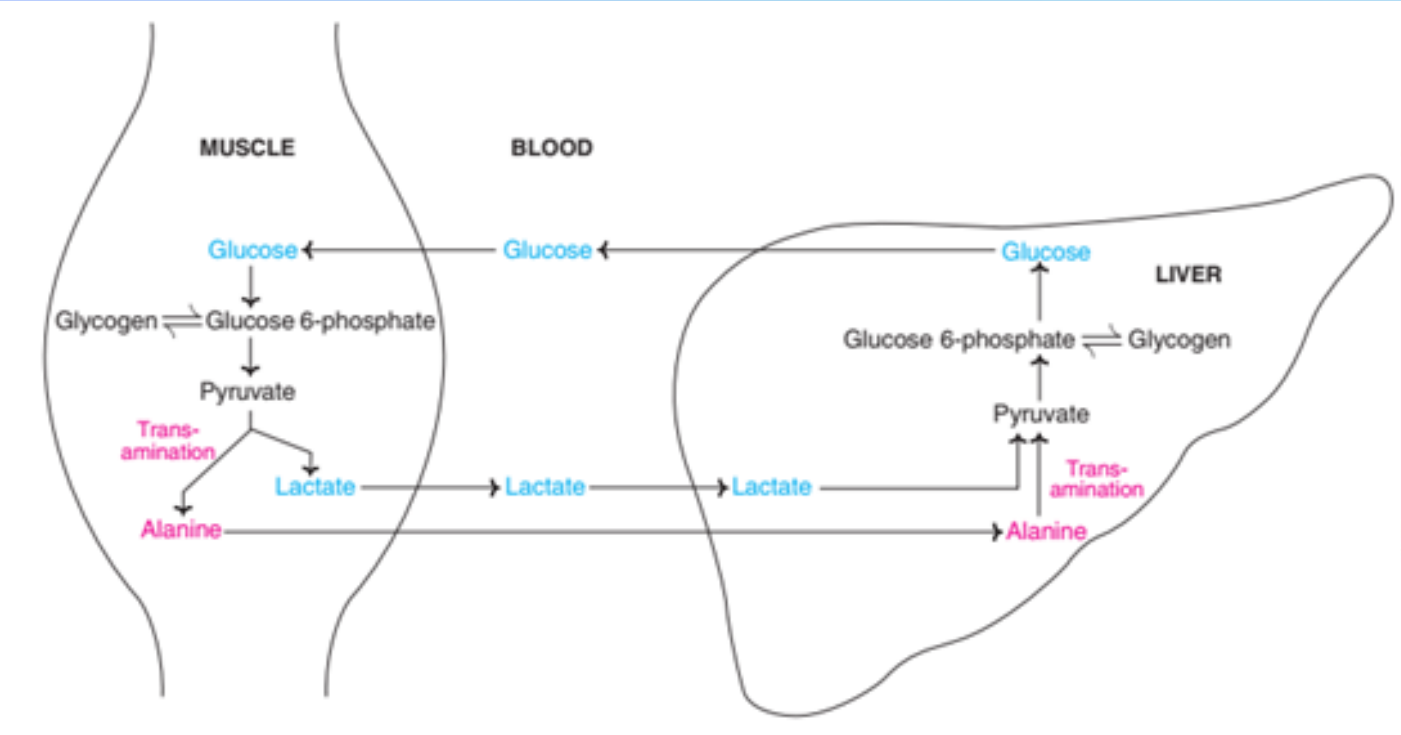


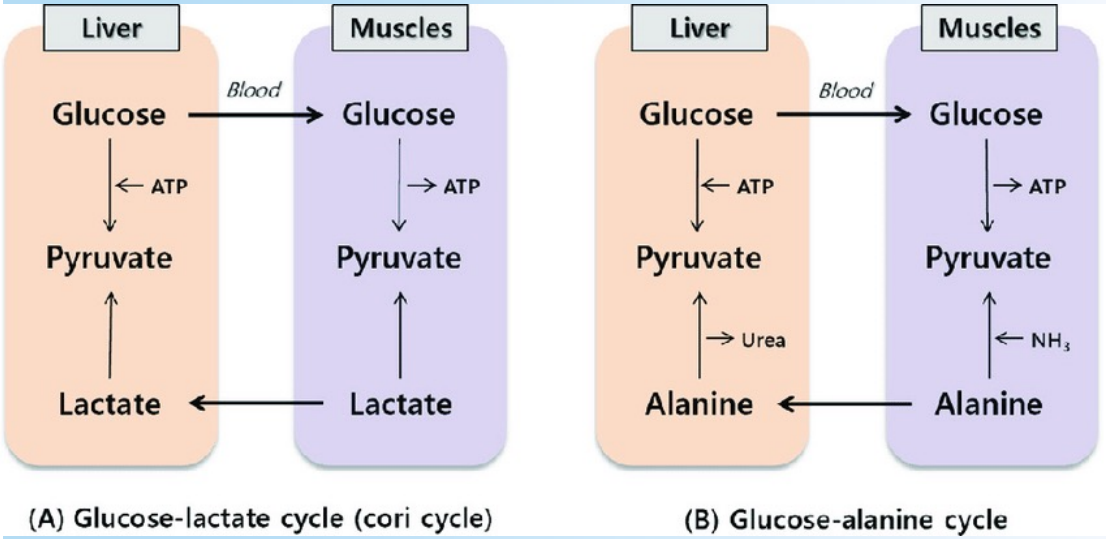
Main amino acid = ALALINE

Can use others as they enter through TCA cycle → Oxaloacetate EXCEPT for Leucine and Lysine



Comparing Cori Cycle & Alanine cycle





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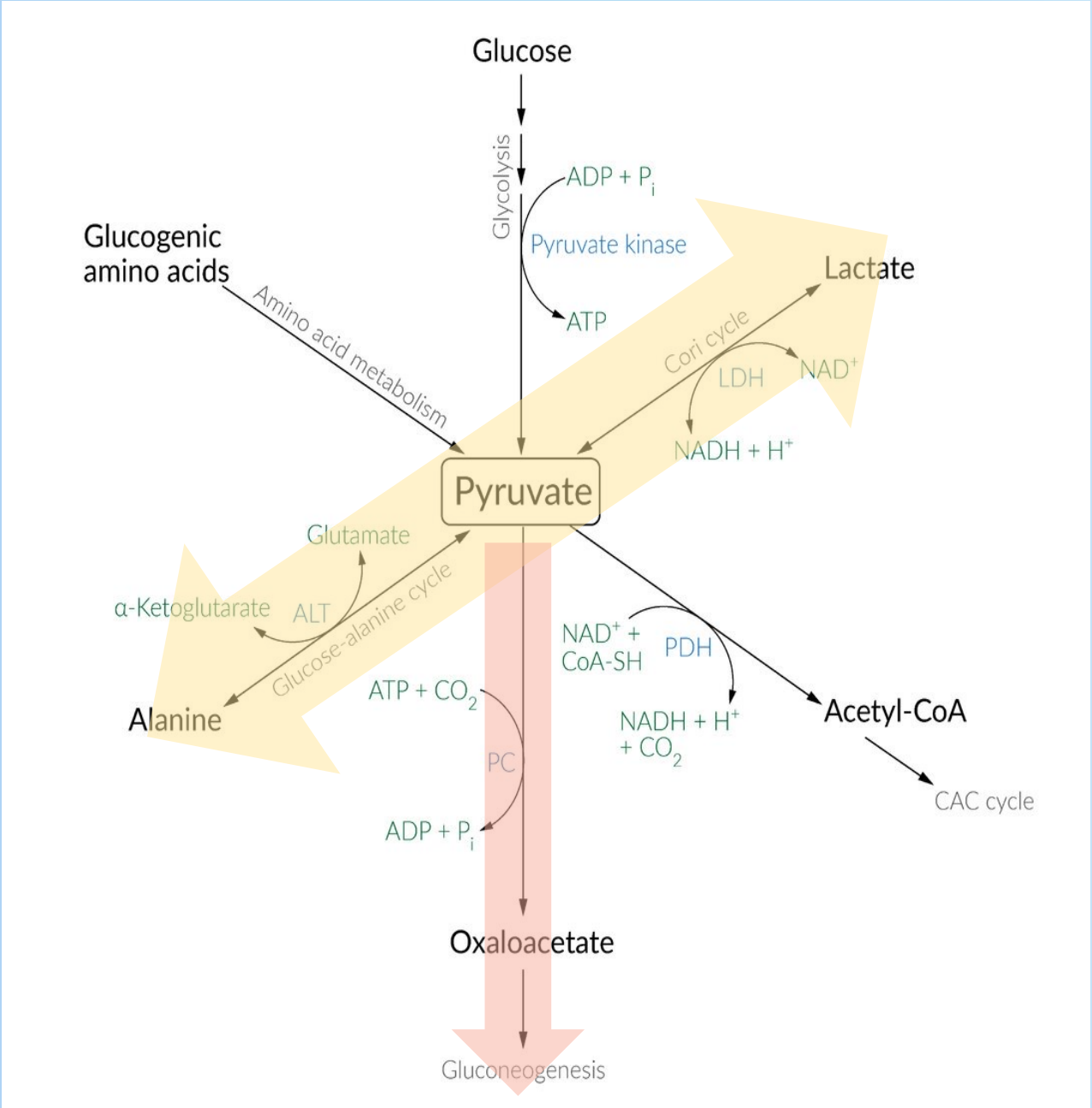
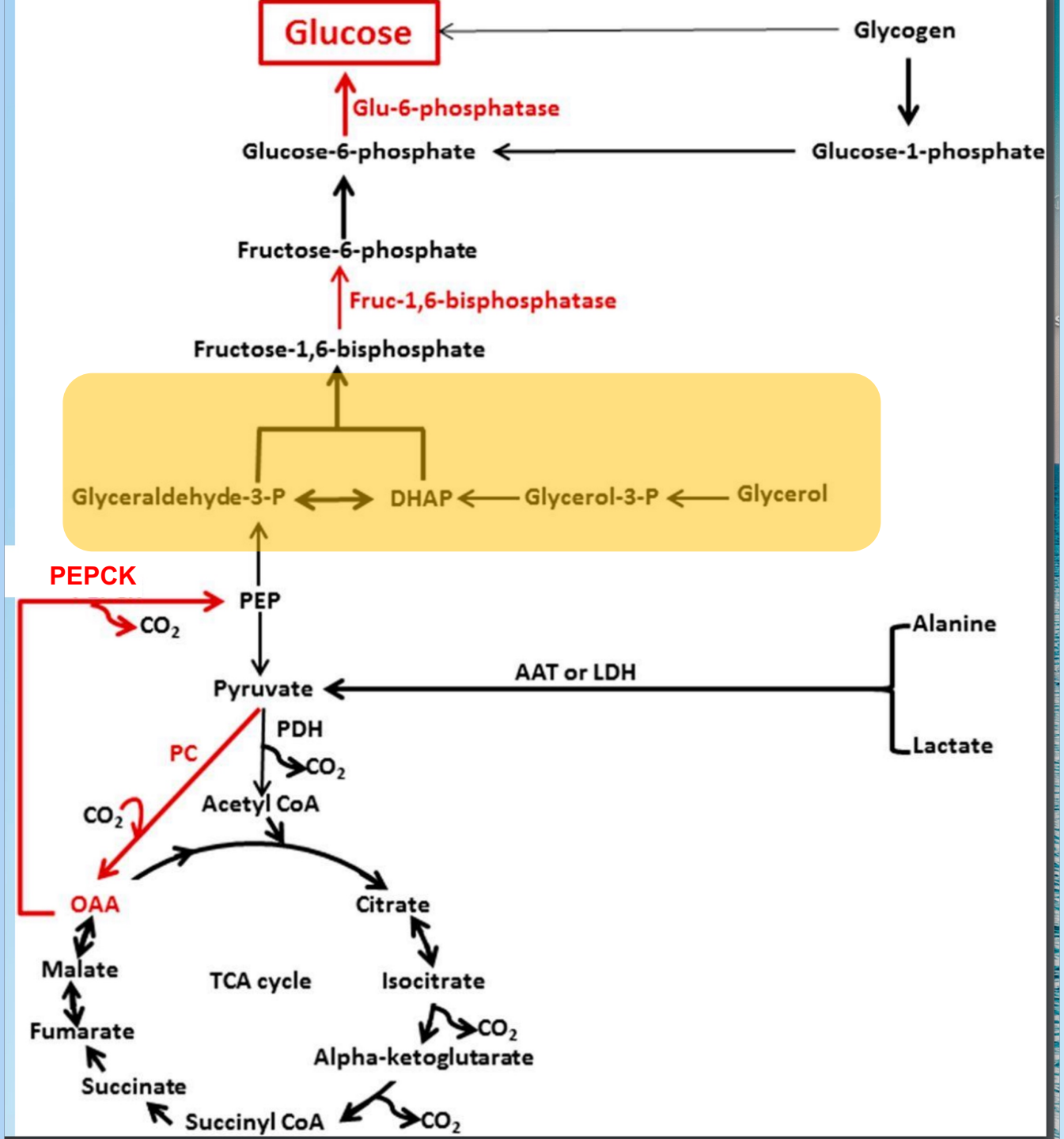

Glucose
Glycolysis
ADP + P_i
Pyruvate kinase
ATP
Glucogenic amino acids
Amino acid metabolism
Lactate
Cori cycle
LDH
NAD^+
$NADH + H^+$
Pyruvate
Glutamate
α-Ketoglutarate
ALT
Glucose-alanine cycle
Alanine
NAD^+ + CoA-SH
PDH
$NADH + H^+ + CO_2$
Acetyl-CoA
CAC cycle
$ATP + CO_2$
PC
ADP + P_i
Oxaloacetate
Gluconeogenesis

Precursor

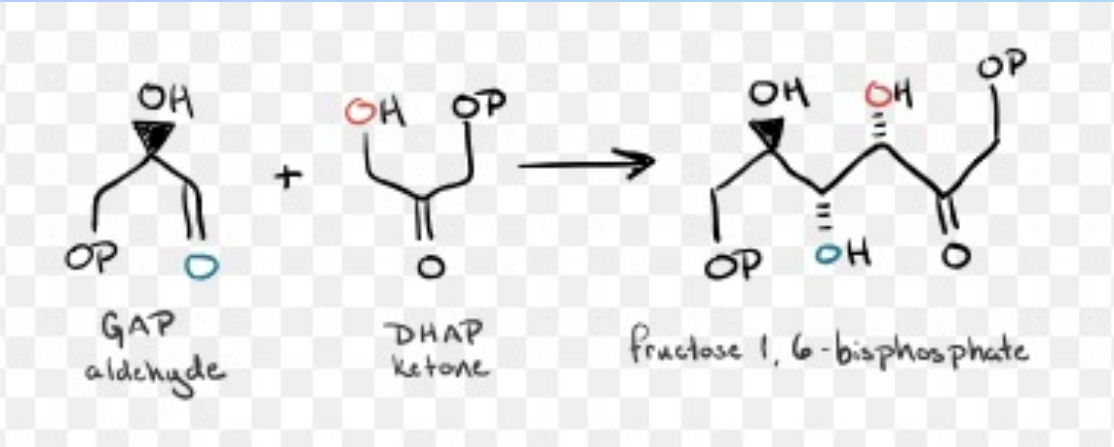


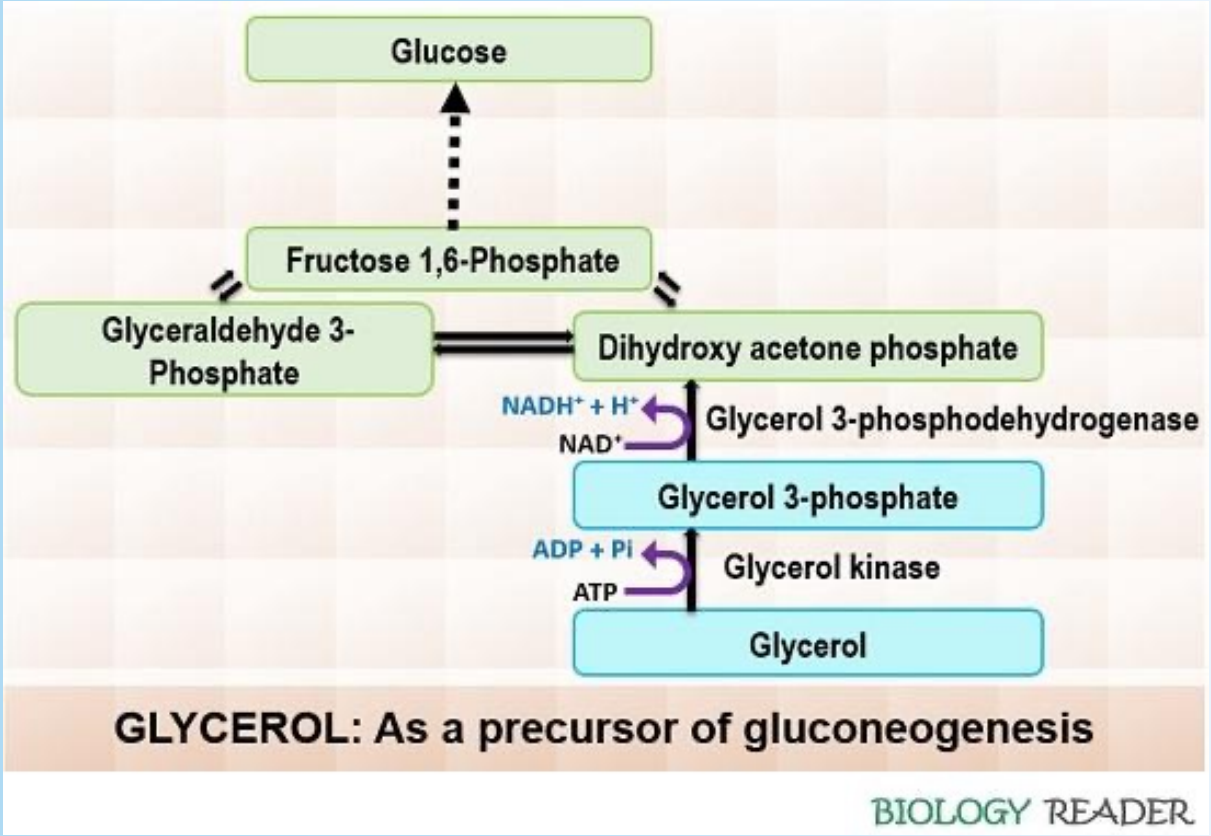
Glycerol precursor

Enzymes

- Glycerol kinase (adds P)
  - only found in liver/kidney
  - Uses an ATP
- Glycerol phosphate dehydrogenase

GAP + DHAP = F1,6BP



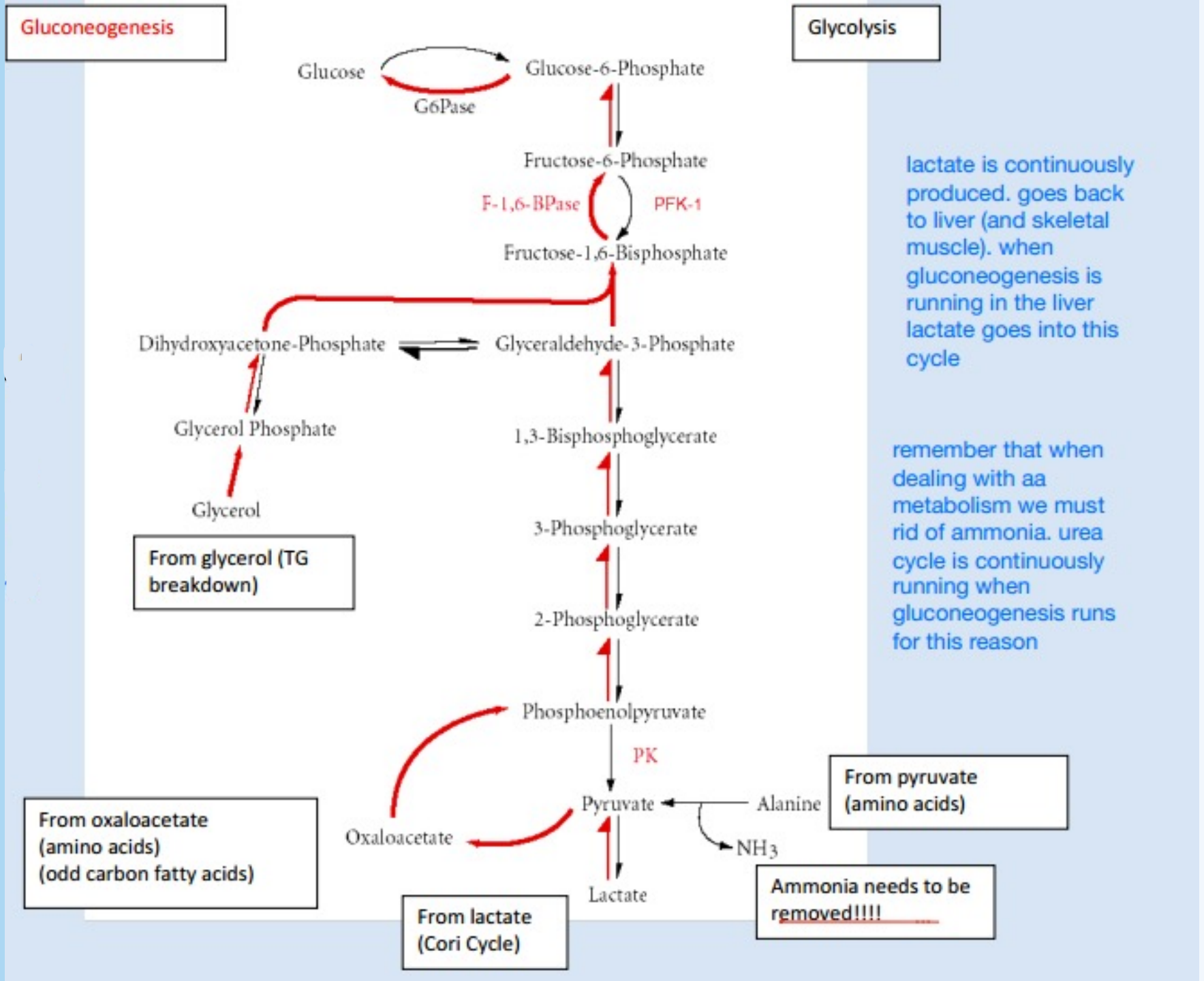


Precursors ✓

→ steps of gluconeogenesis

LIVER
(kidney)

↓ Insulin
↑ Glucagon
↑ Epinephrin



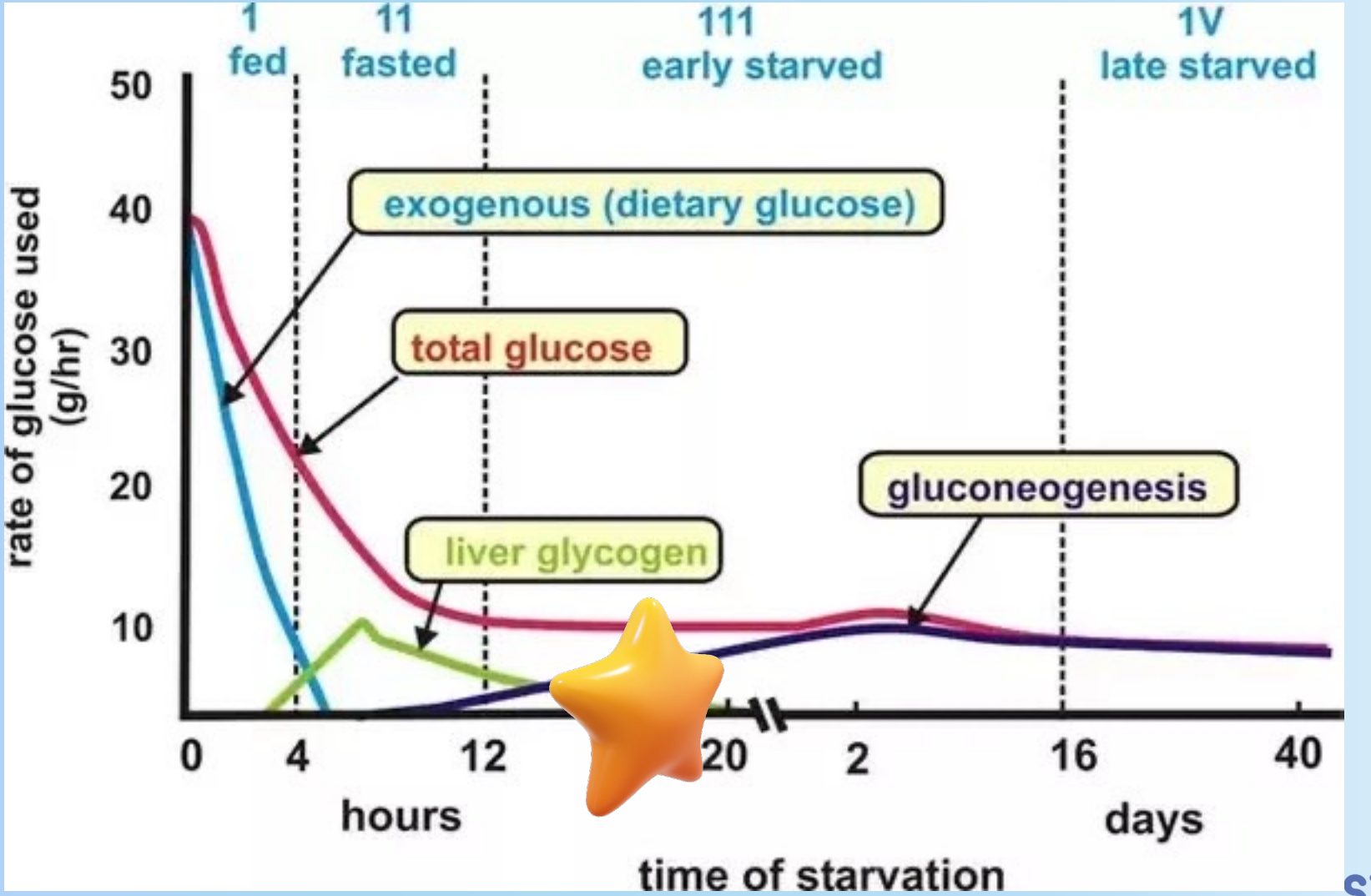
Glycogenolysis

Glycogen → Glucose

Glycogenolysis

Glucose: ↑

Glucagon & Epinephrine: ↑



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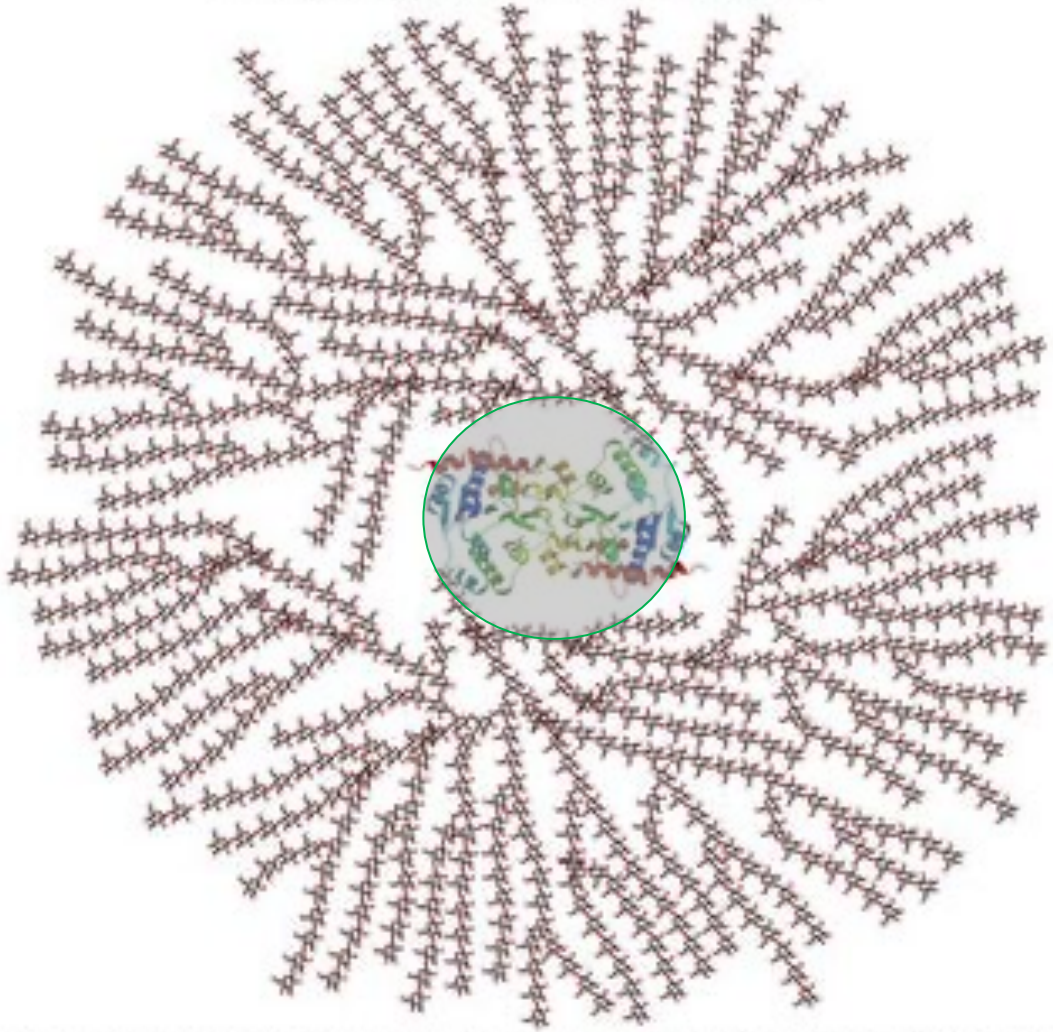
Glycogen structure



A core protein of glycogenin is surrounded by branches of glucose units.
The entire globular complex may contain approximately 30,000 glucose units.

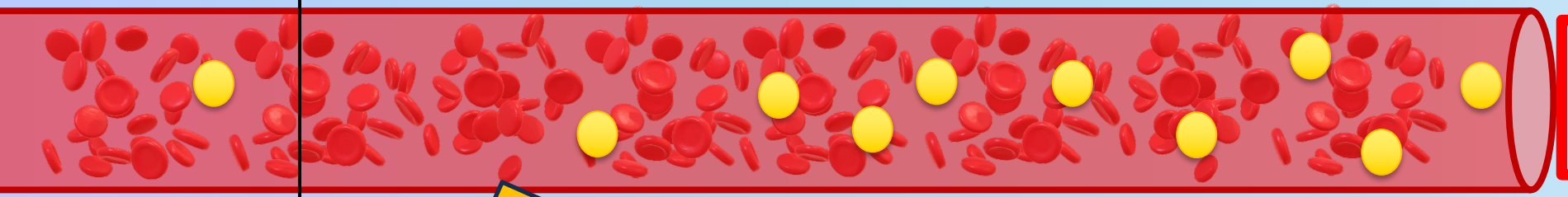
- Glycogen is smaller and more efficient to store
- Fats aren't adequate source, lead to ketone bodies which lowers pH = acidosis
- Glycogen exists as granules in cell cytoplasm with enzymes for both glycogenesis and glycogenolysis.

Glucose around glycogenin in

- linear α 1,4 bonds
- branched α1,6 bonds

Fasting/Starved

Make



Blood Glucose Range
70-100 mg/dL

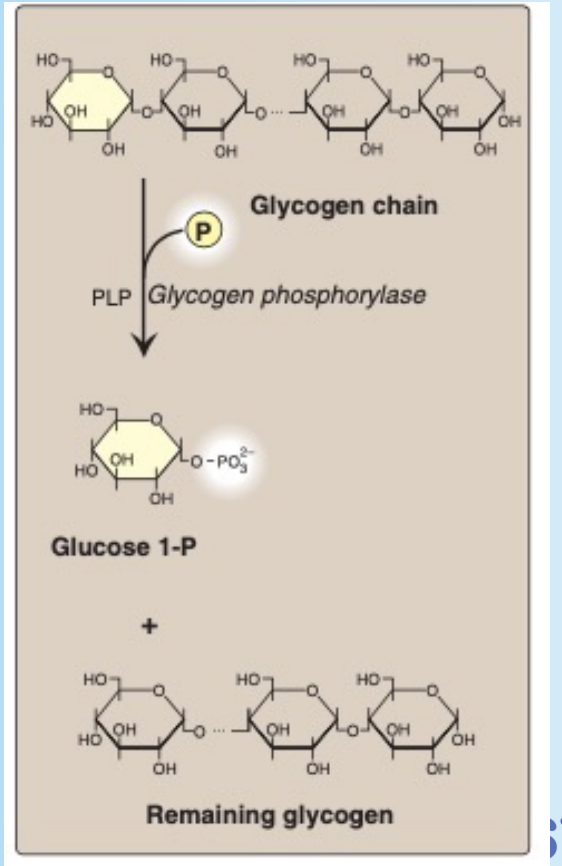
↓ Insulin
↑ Glucagon
↑ Epinephrin

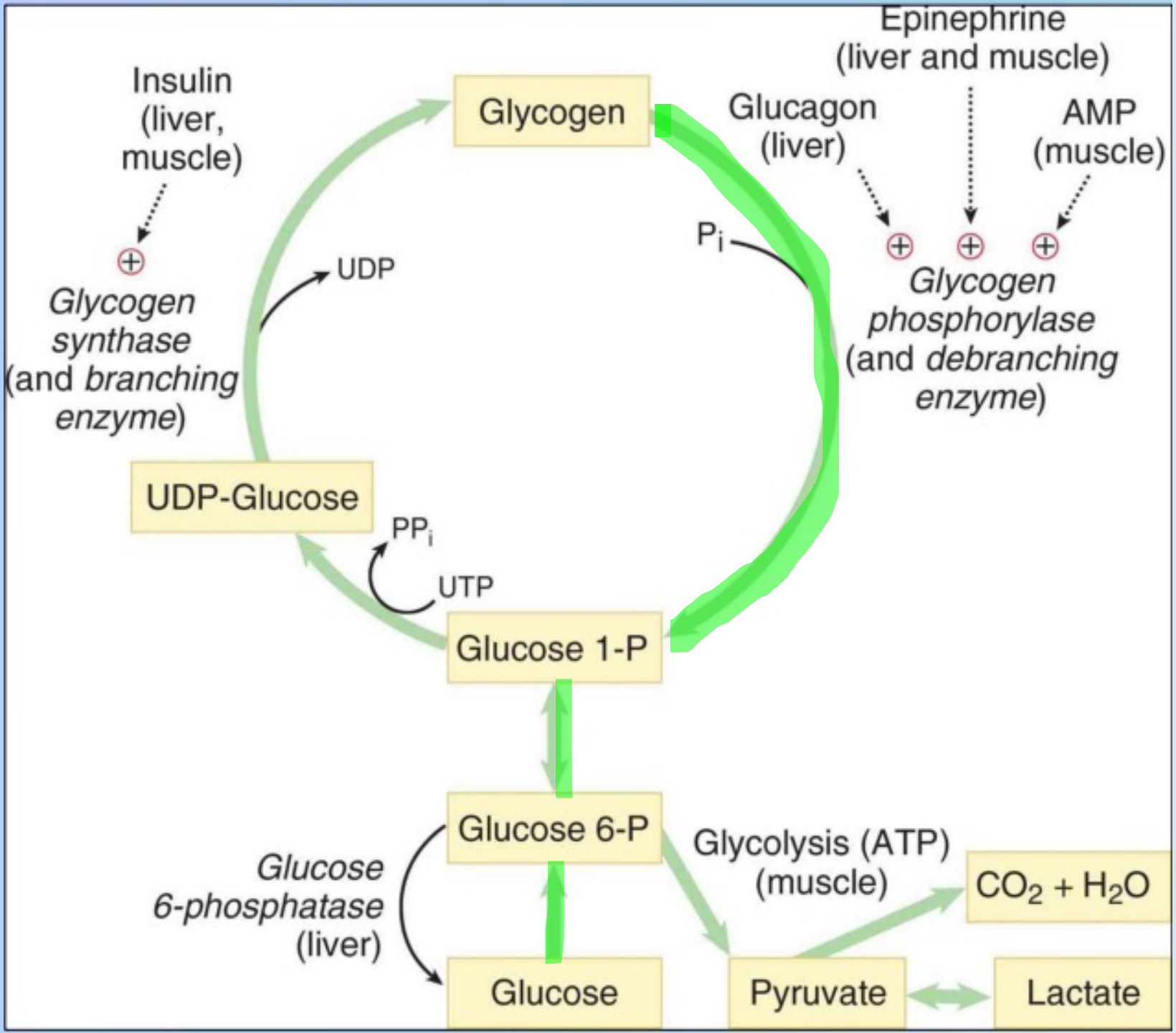
Glycogenolysis

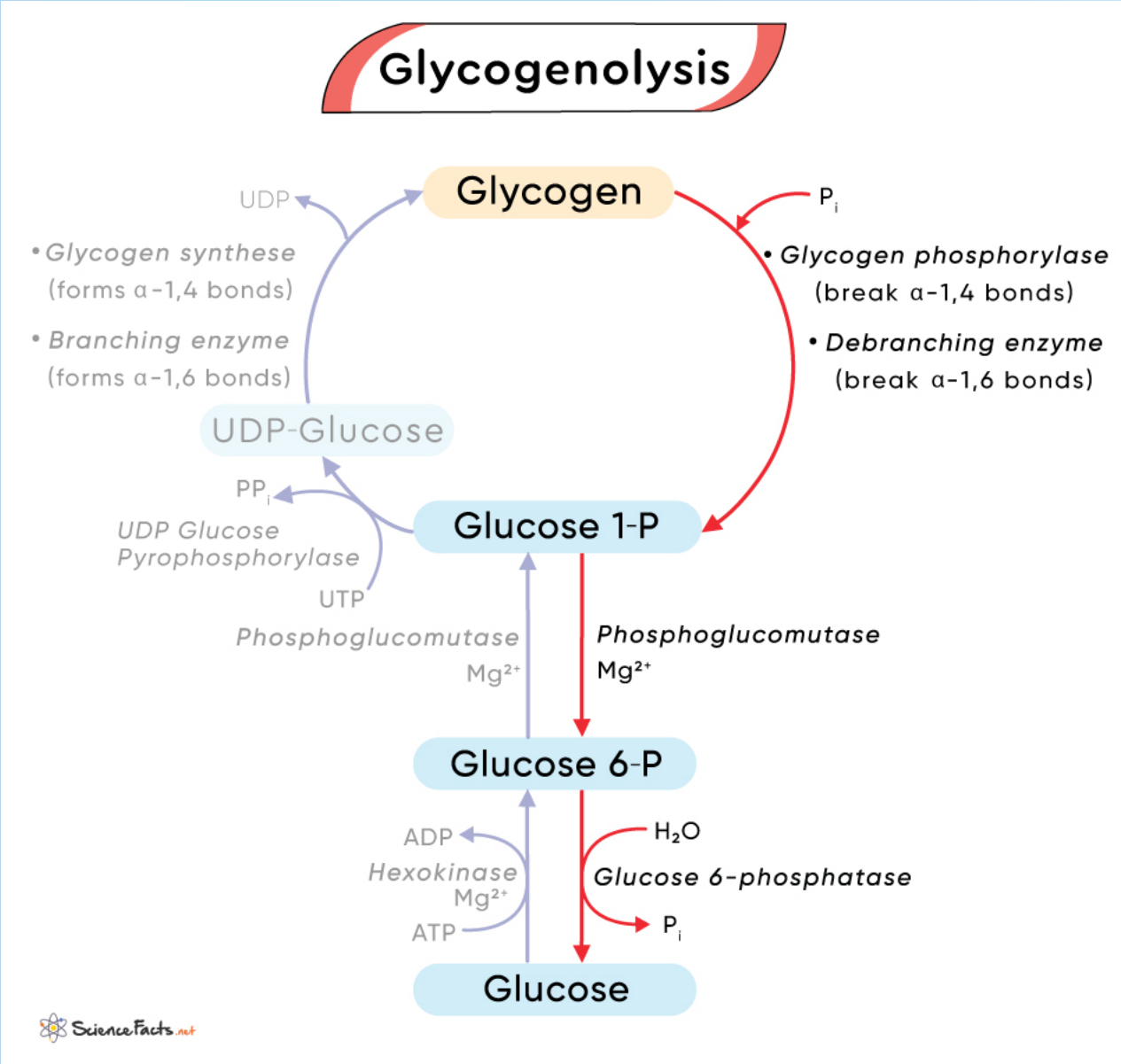
Break down glycogen → glucose

α1,6 bonds = free glucose
α1,4 bonds = glucose-1-phosphate

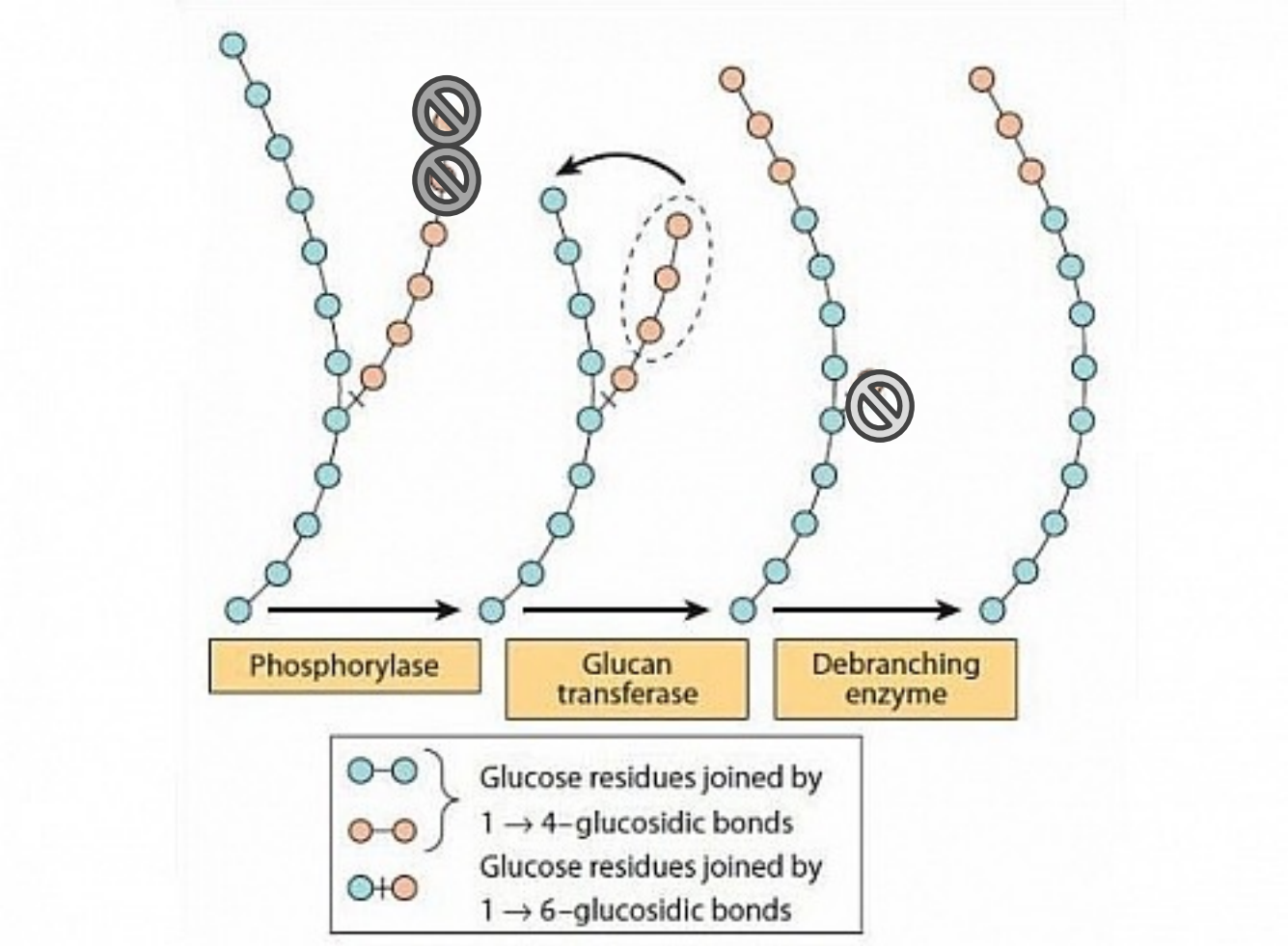
Convert G1P → Glucose




Epinephrine
(liver and muscle)
Insulin
(liver,
muscle)
Glycogen
Glucagon
(liver)
AMP
(muscle)
Pi
UDP
Glycogen
synthase
(and branching
enzyme)
Glycogen
phosphorylase
(and debranching
enzyme)
UDP-Glucose
PPi
UTP
Glucose 1-P
Glucose 6-P
Glycolysis (ATP)
(muscle)
CO2 + H2O
Glucose
6-phosphatase
(liver)
Glucose
Pyruvate
Lactate


Glycogenolysis
Glycogen
UDP
• Glycogen synthese
(forms α-1,4 bonds)
• Branching enzyme
(forms α-1,6 bonds)
P_i
• Glycogen phosphorylase
(break α-1,4 bonds)
• Debranching enzyme
(break α-1,6 bonds)
UDP-Glucose
PP_i
UDP Glucose
Pyrophosphorylase
UTP
Glucose 1-P
Phosphoglucomutase
Mg^{2+}
Phosphoglucomutase
Mg^{2+}
Glucose 6-P
ADP
Hexokinase
Mg^{2+}
ATP
H_2O
Glucose 6-phosphatase
P_i
Glucose
ScienceFacts.net

Glycogenolysis step simplified

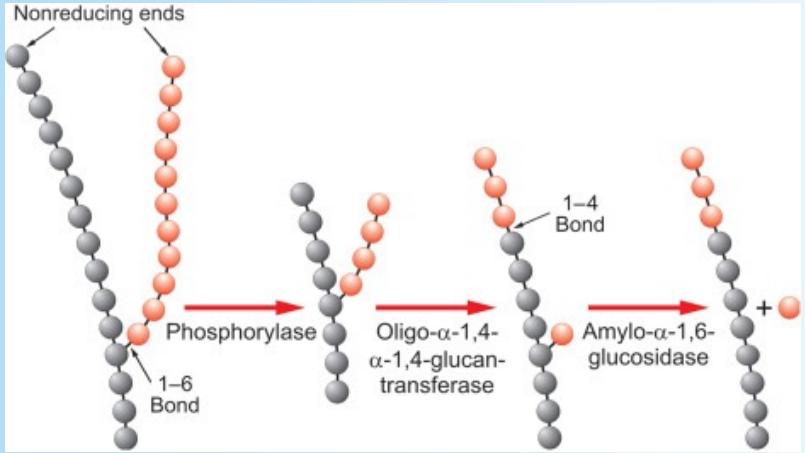


Take them off 1 at a time till we get to 4

→ Move over 3, leaving 1

→ Cut the 1 leftover

→ Repeat



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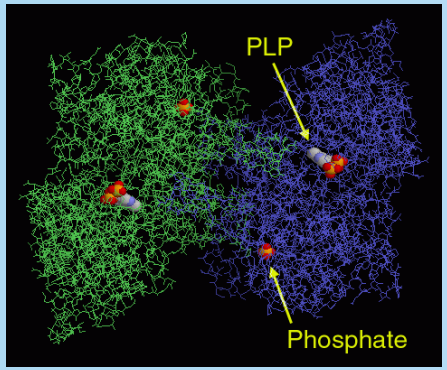
Glucagon Phosphorylase

RATE LIMITING STEP



Glycogen Phosphorylase has A and B

a = Active

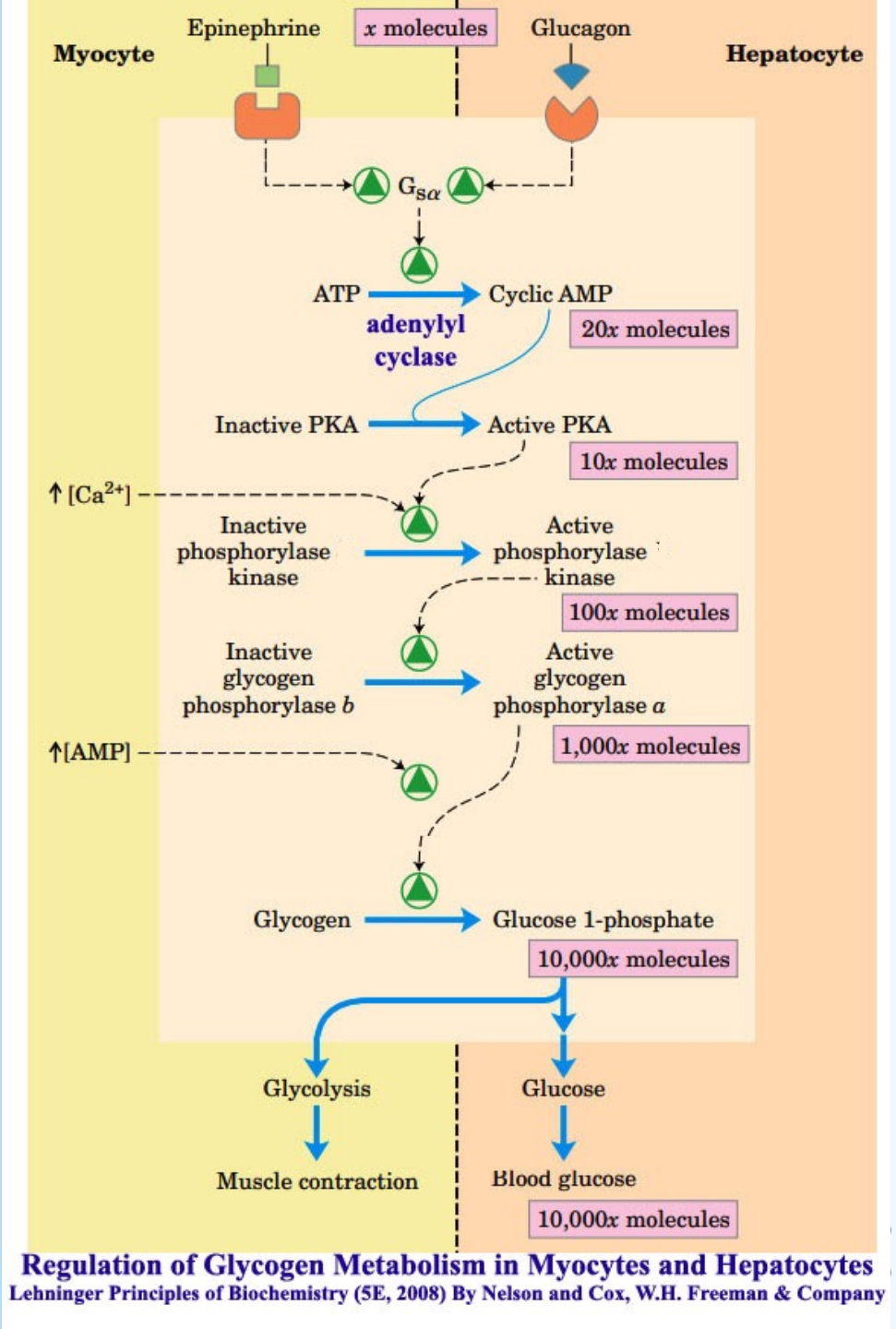
b= inactive

Has to be phosphorylated to be active

Phosphorylase kinase (adds P) turns it “on”

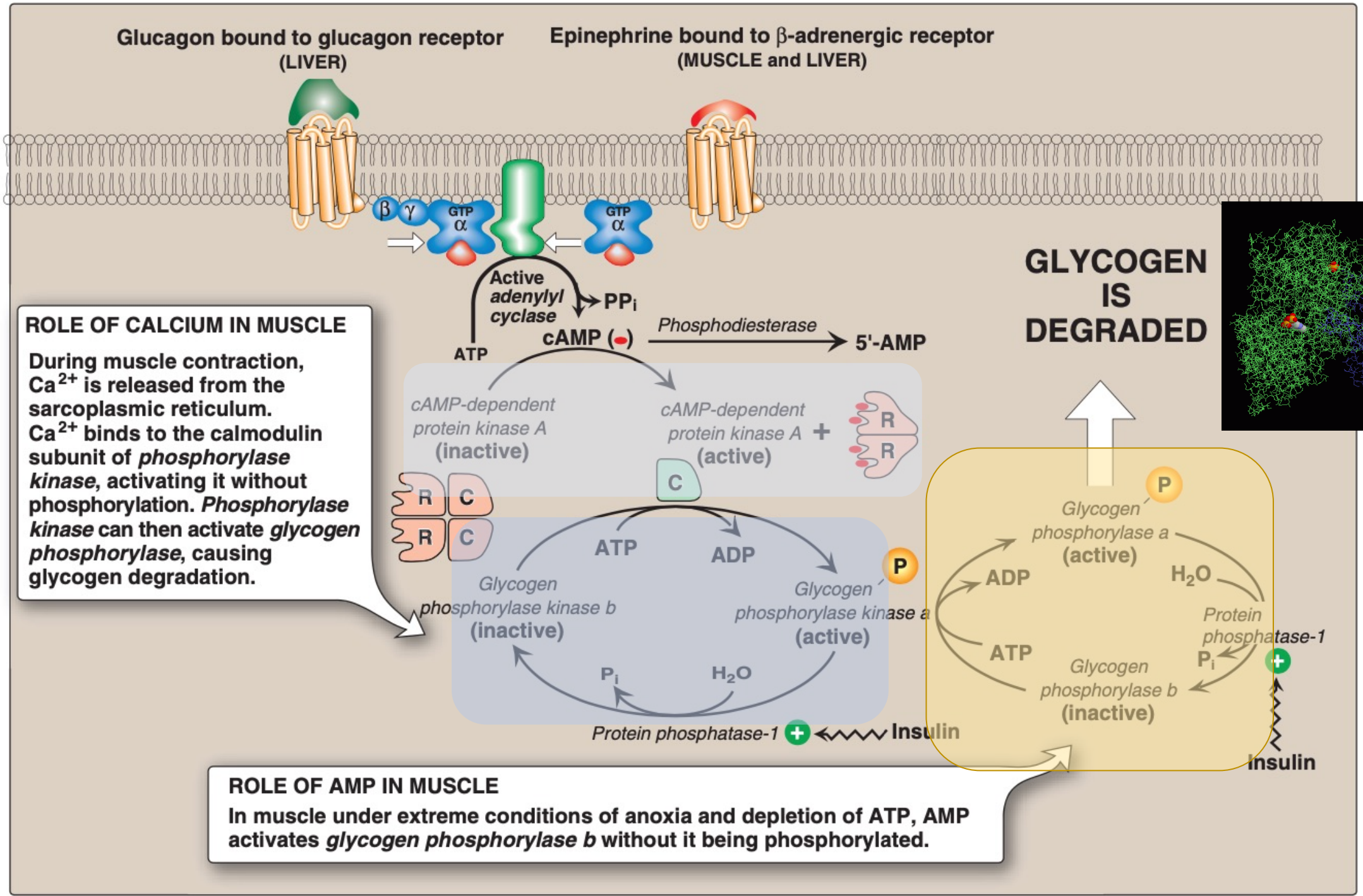
Phosphorylase Kinase b also needs to be activated so needs to be phosphorylated too

PKA (protein kinase A) adds P; turns it “on”



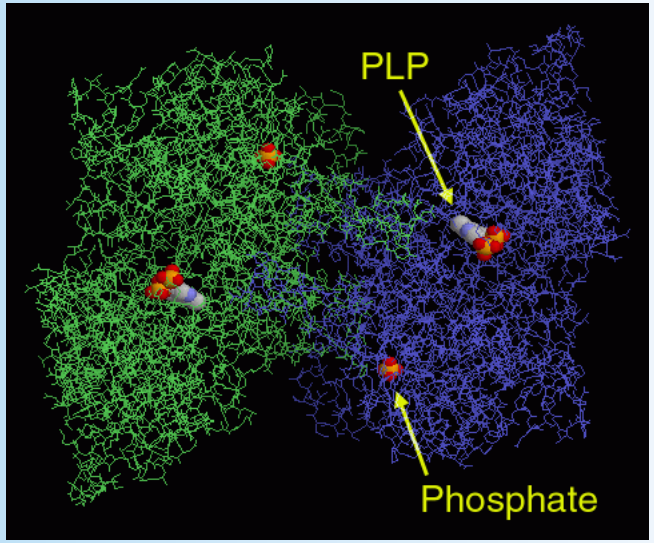
Regulation of Glycogen Metabolism in Myocytes and Hepatocytes

Lehninger Principles of Biochemistry (5E, 2008) By Nelson and Cox, W.H. Freeman & Company

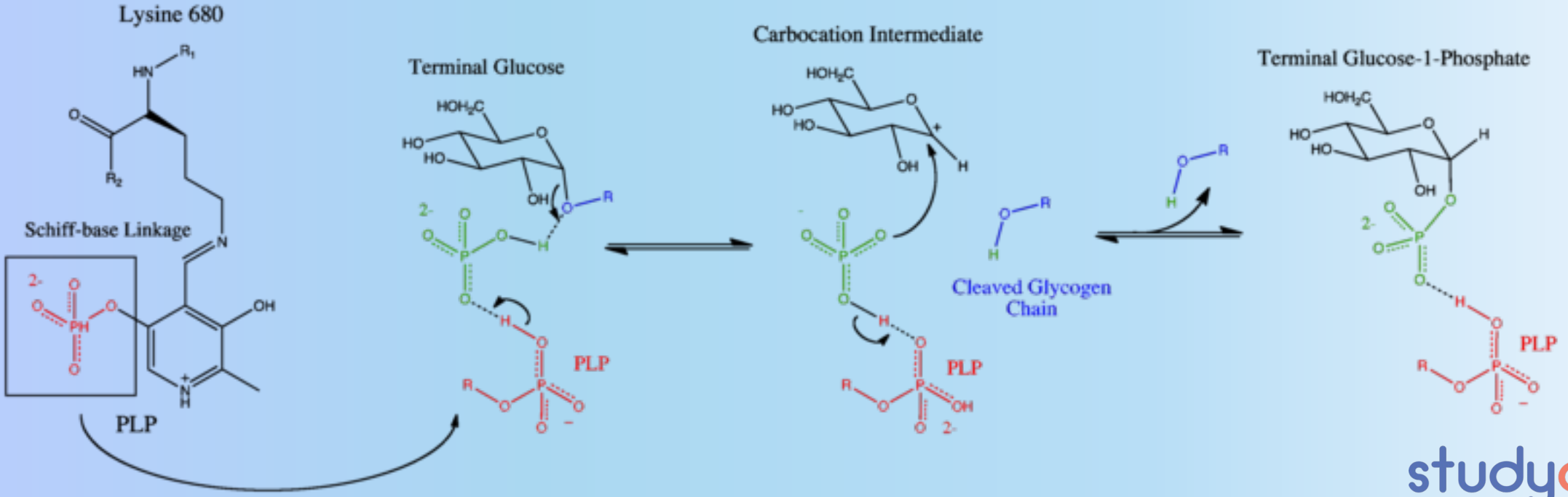

Glucagon bound to glucagon receptor
(LIVER)
Epinephrine bound to β-adrenergic receptor
(MUSCLE and LIVER)
β
γ
GTP
α
GTP
α
Active
adenylyl
cyclase
PPi
ATP
cAMP (-)
Phosphodiesterase
5'-AMP
ROLE OF CALCIUM IN MUSCLE
During muscle contraction, Ca2+ is released from the sarcoplasmic reticulum. Ca2+ binds 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
IS
DEGRADED
PLP
Phosphate
P
Glycogen
phosphorylase a
(active)
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.

Glucagon Phosphorylase

Phosphate between compounds

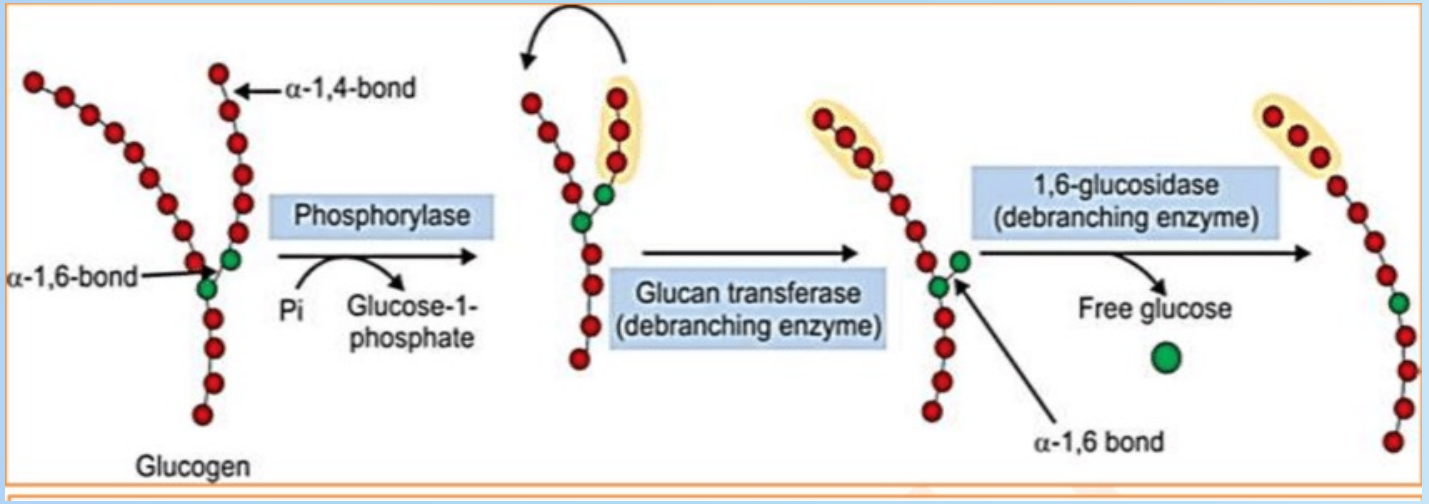


- Breaks α1,4 bonds
- Requires a coenzyme: PLP (derivative of B6)
- Phosphate form is active



Debranching enzyme

Enzyme with 2 catalytic sites

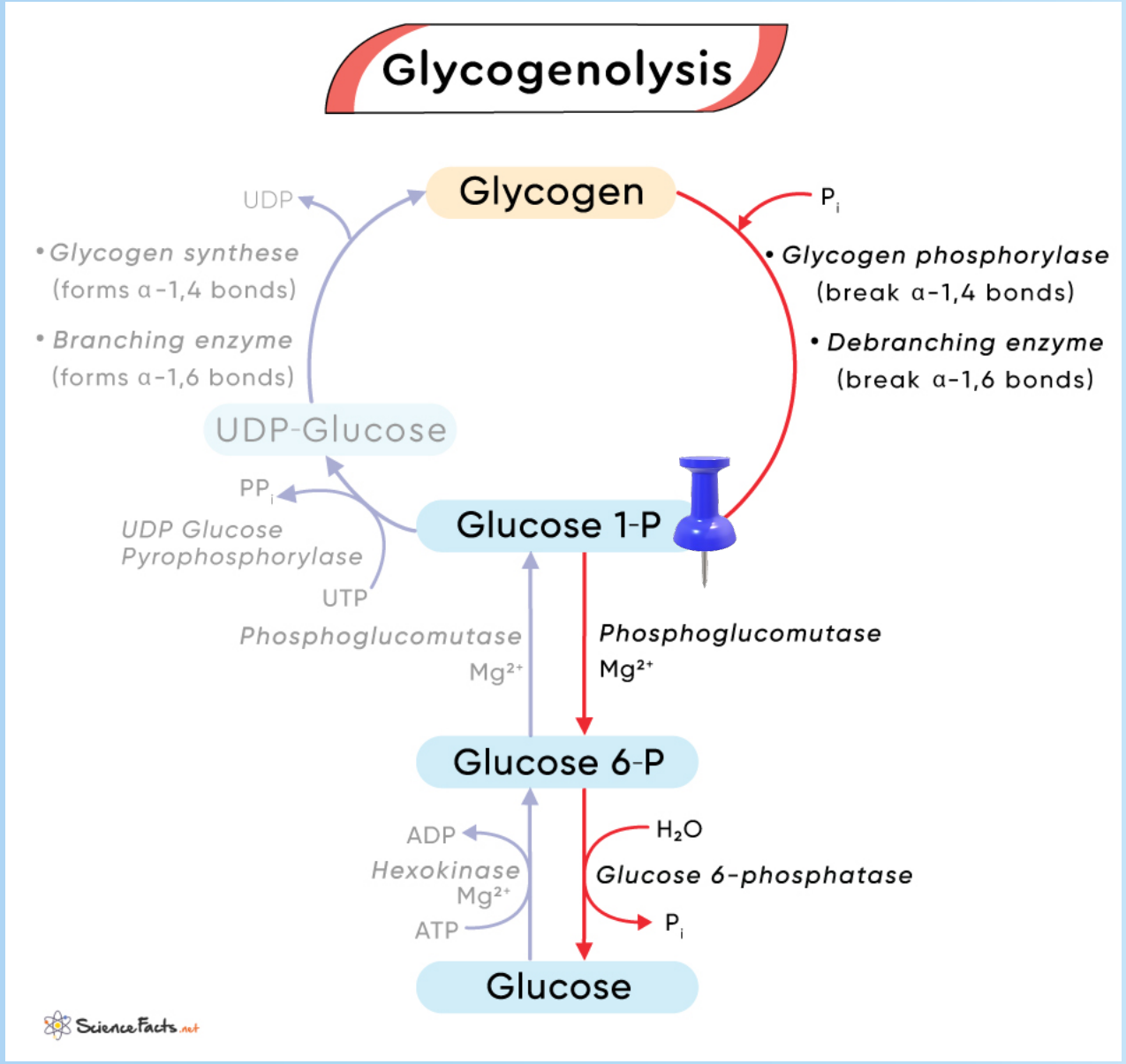


Glucan Transferase Activity

- Moves trisaccharide unit

1,6 Glycosidase Activity

- Cleaves branch and leaves free glucose


Glycogenolysis
Glycogen
UDP
• Glycogen synthese
(forms α-1,4 bonds)
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• Debranching enzyme
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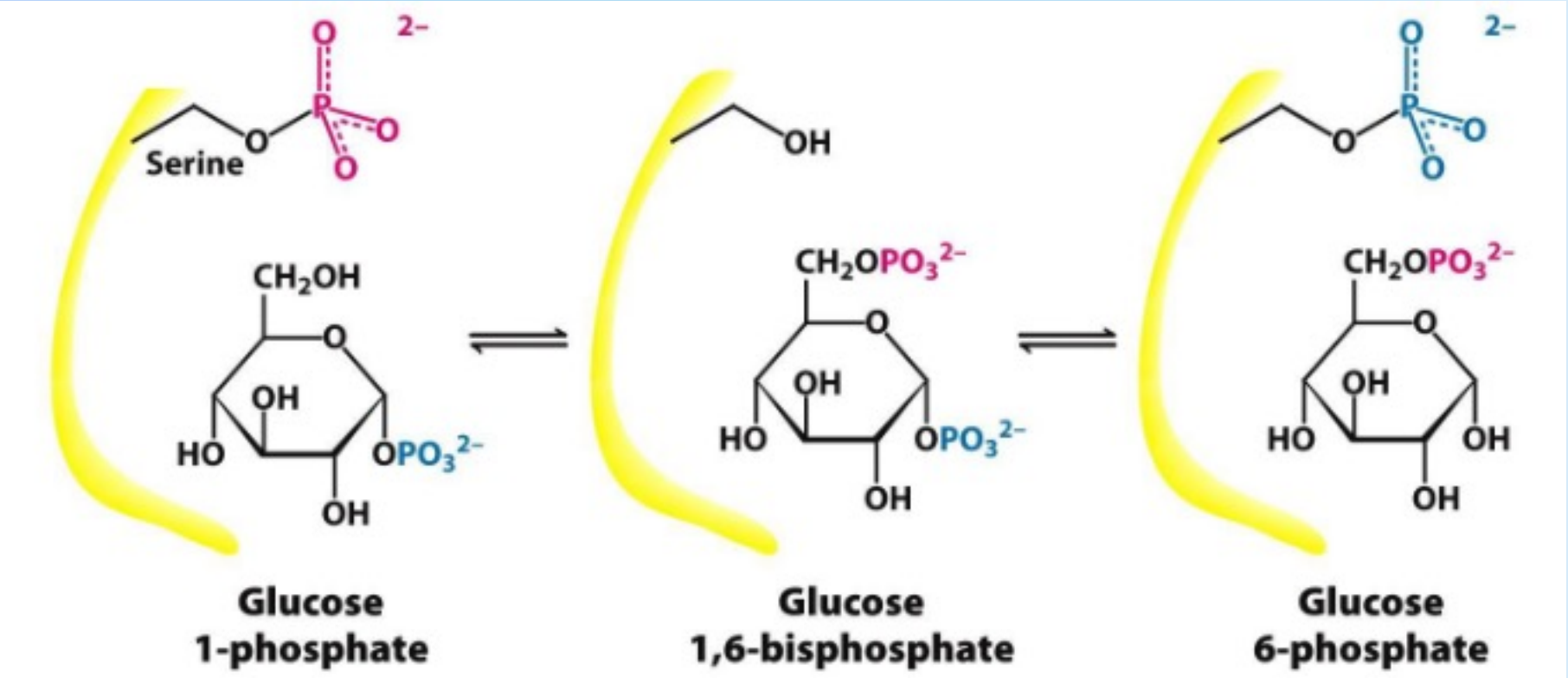
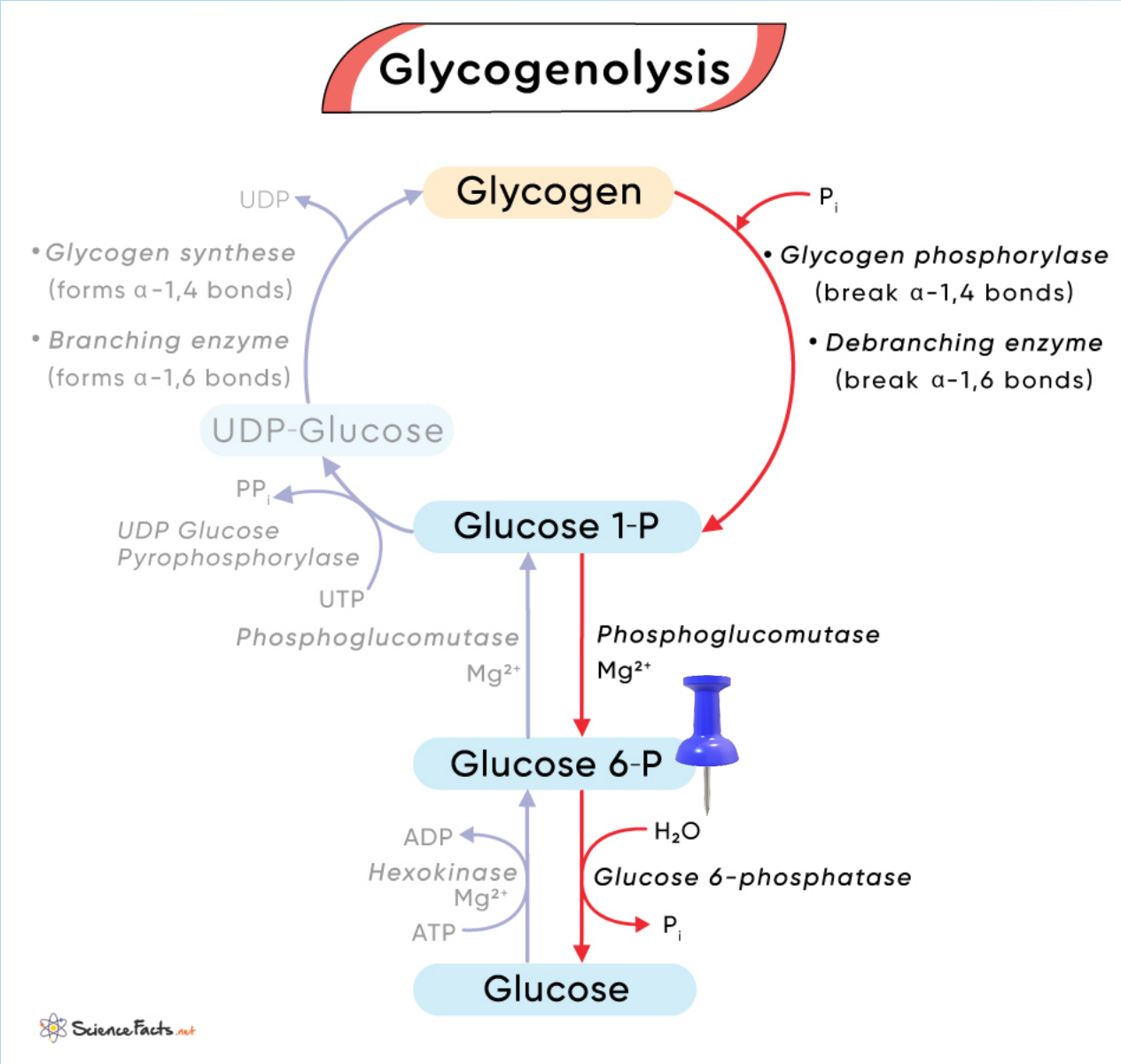
UDP-Glucose
PP_i
UDP Glucose
Pyrophosphorylase
UTP
Glucose 1-P
Phosphoglucomutase
Mg^{2+}
Phosphoglucomutase
Mg^{2+}
Glucose 6-P
ADP
Hexokinase
Mg^{2+}
ATP
H_2O
Glucose 6-phosphatase
P_i
Glucose
ScienceFacts.net

Phosphoglucomutase

Phosphate glucose mutate

"mutate the phosphate on the glucose"




Glycogenolysis
Glycogen
UDP
• Glycogen synthese
(forms α-1,4 bonds)
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(forms α-1,6 bonds)
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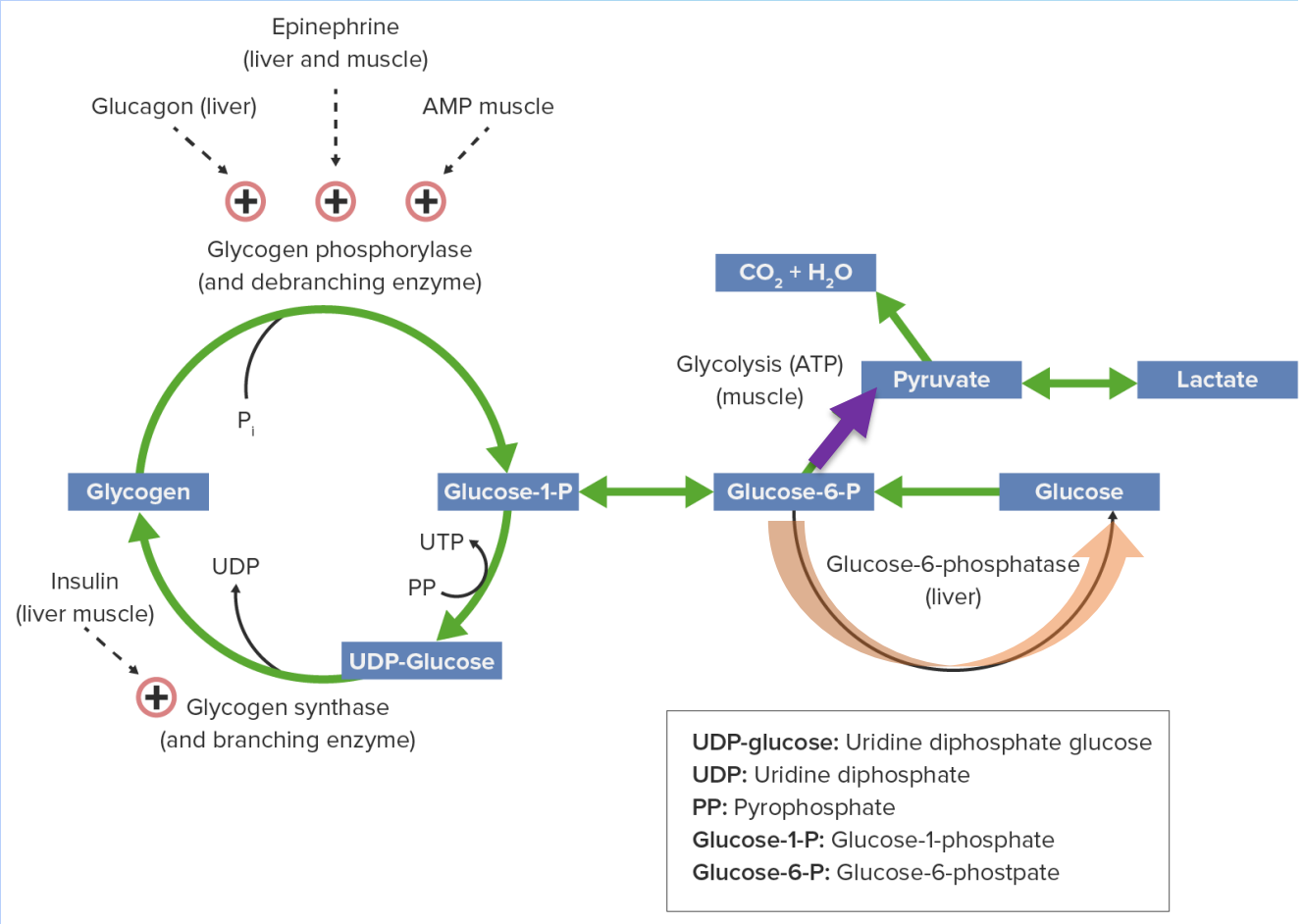
(break α-1,4 bonds)
• Debranching enzyme
(break α-1,6 bonds)
UDP-Glucose
PP_i
UDP Glucose
Pyrophosphorylase
UTP
Glucose 1-P
Phosphoglucomutase
Mg^{2+}
Phosphoglucomutase
Mg^{2+}
Glucose 6-P
ADP
Hexokinase
Mg^{2+}
ATP
H_2O
Glucose 6-phosphatase
P_i
Glucose
ScienceFacts.net



Phosphoglucomutase

Glc-1-P ----------> Glc-6-P ----------> Glycolysis

- Immediate source in muscle, goes straight to glycolysis

- Remember Glucose-6-phosphatase is **ONLY** in liver
- Only liver can provide glucose to bloodstream

Phosphoglucomutase **Glucose-6-Phosphatase**

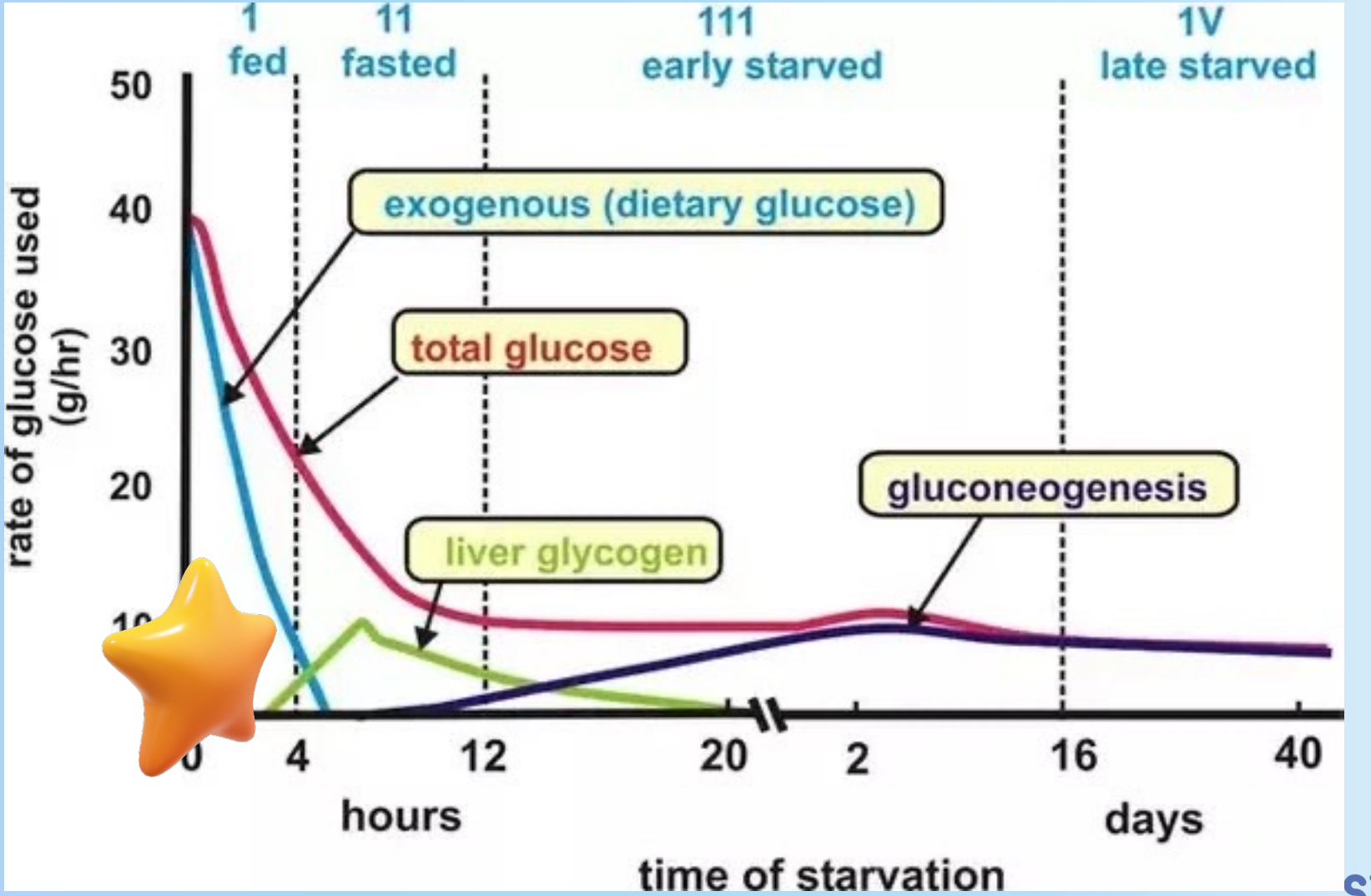
Glc-1-P ----------> Glc-6-P ----------> Glucose

Glycogenesis

Glucose → Glycogen

Glycogenesis

Glucose: ↑
Insulin: ↑



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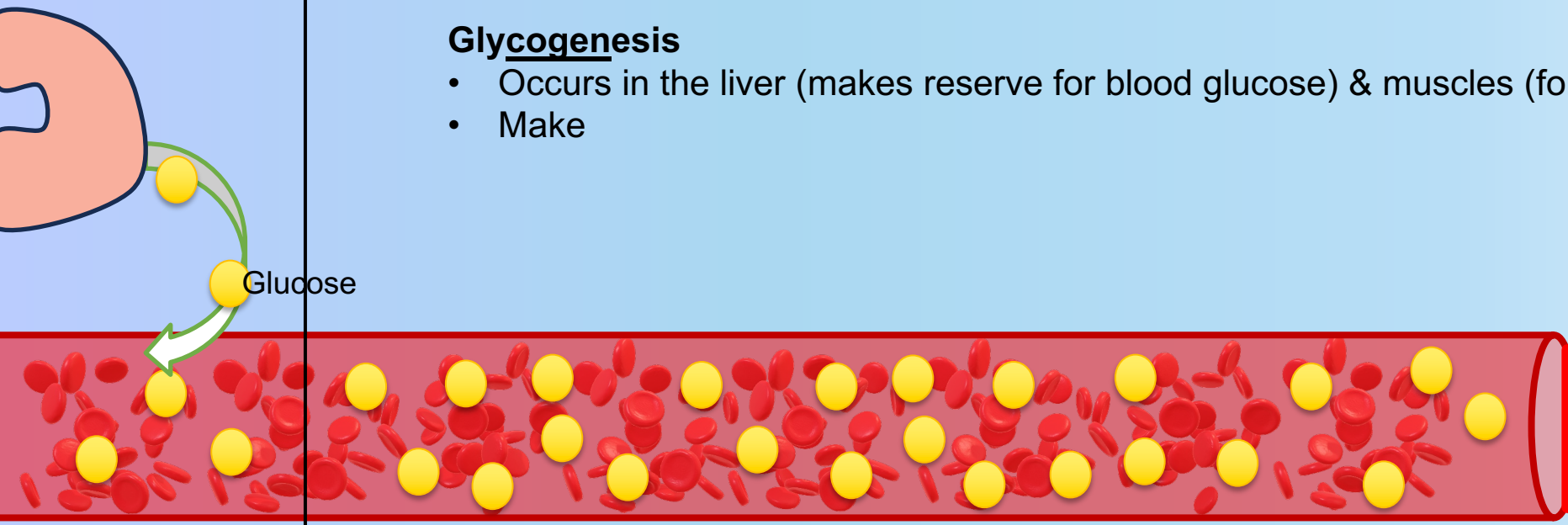
After meal/ Fed state

Glycolysis (just learned)

TAKE

Glycogenesis

- Occurs in the liver (makes reserve for blood glucose) & muscles (for energy*)
- Make



↑ Insulin
↓ Glucagon
↓ Epinephrin

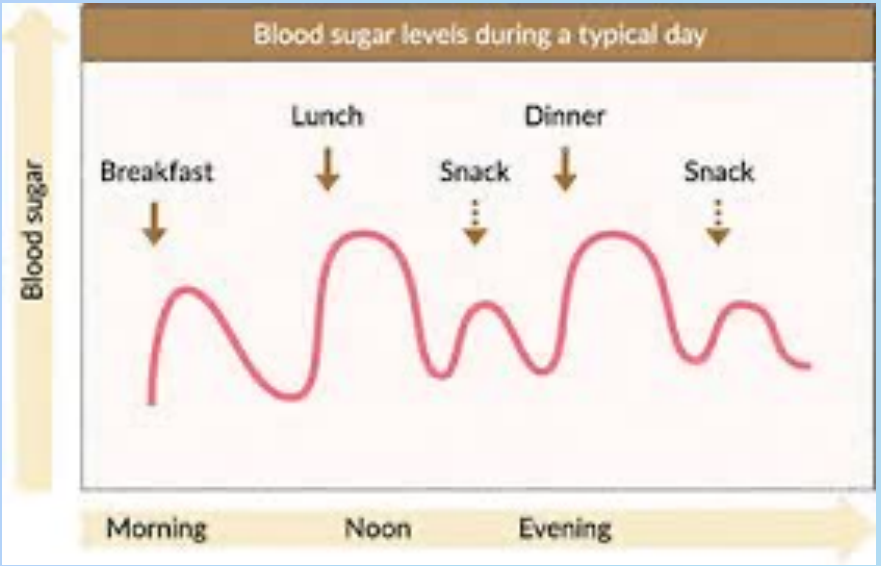


TABLE 18–1 Storage of Carbohydrate in a 70-kg Person

	Percentage of Tissue Weight	Tissue Weight	Body Content (g)
Liver glycogen	5.0	1.8 kg	90
Muscle glycogen	0.7	35 kg	245
Extracellular glucose	0.1	10 L	10

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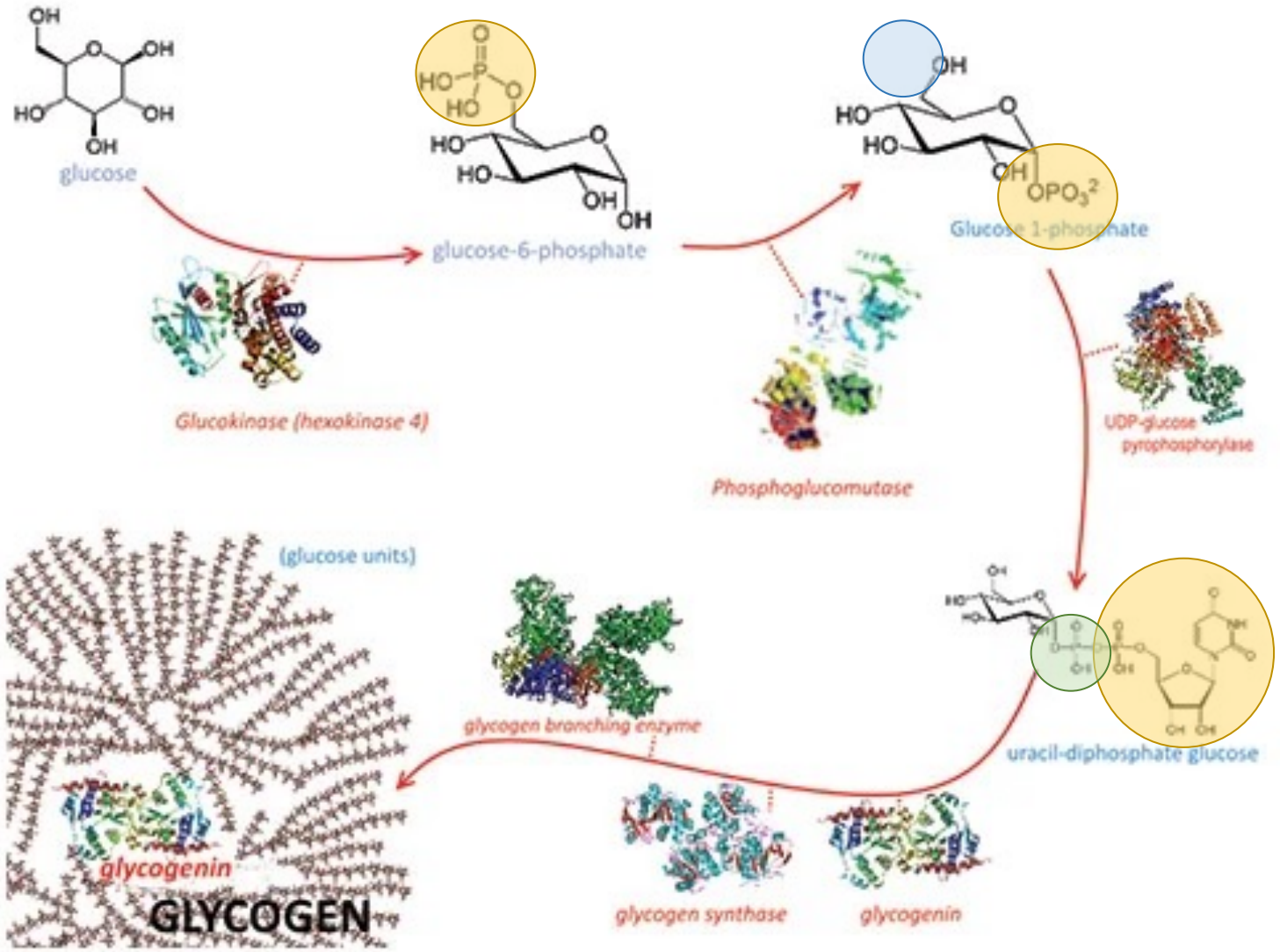


Glucose

↕ *Hexokinase* (in muscle)

↕ *Glucokinase* (in liver)

Glucose 6-phosphate

↕ *Phosphoglucomutase*

Glucose 1-phosphate

↕ *UDP-glucose pyrophosphatase*

UDP-glucose

↓ *Glycogen synthase*

α(1→4) glucosyl units

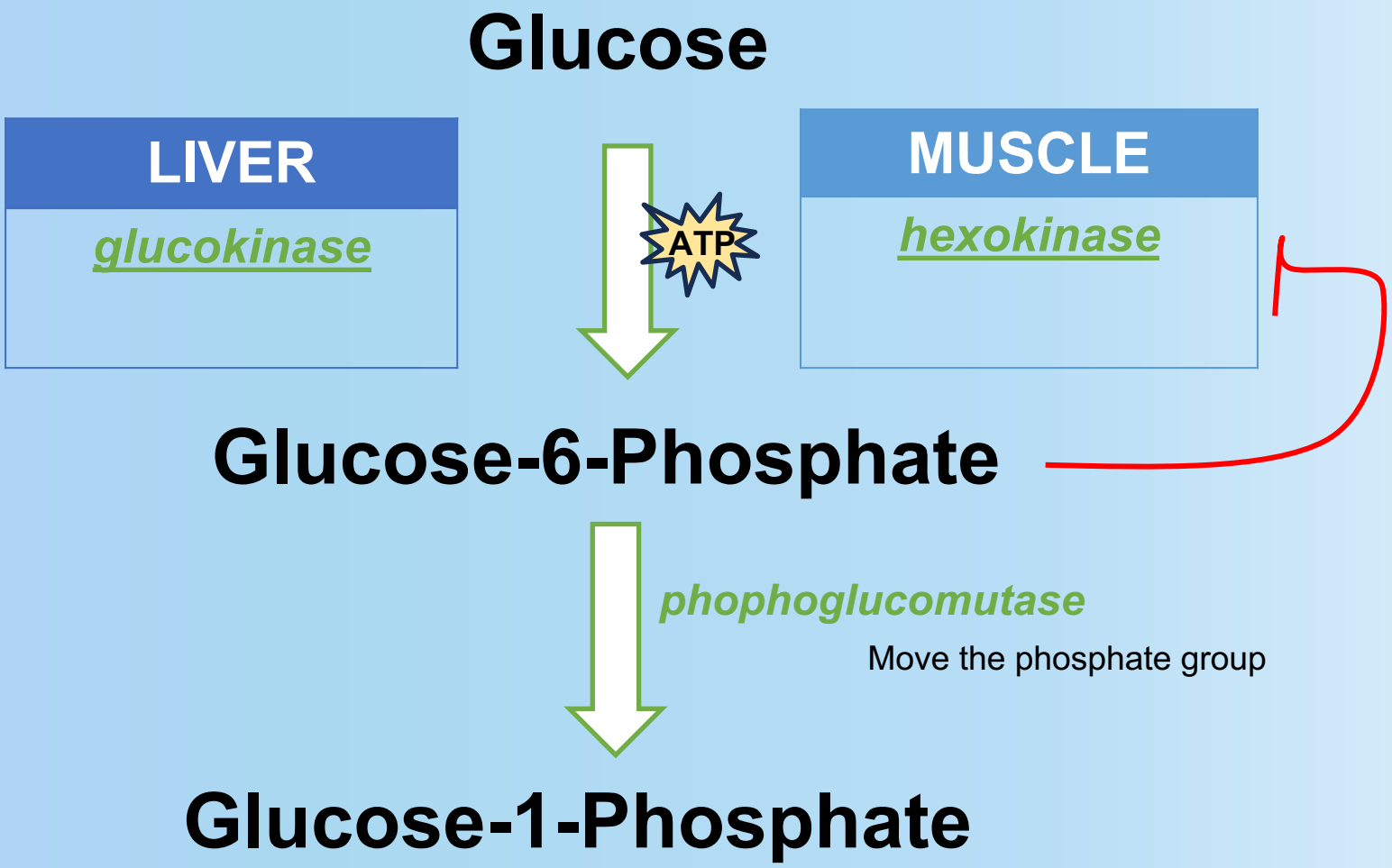
↓ *Branching enzyme*

Glycogen

[α(1→4) and α(1→6) glucosyl units]

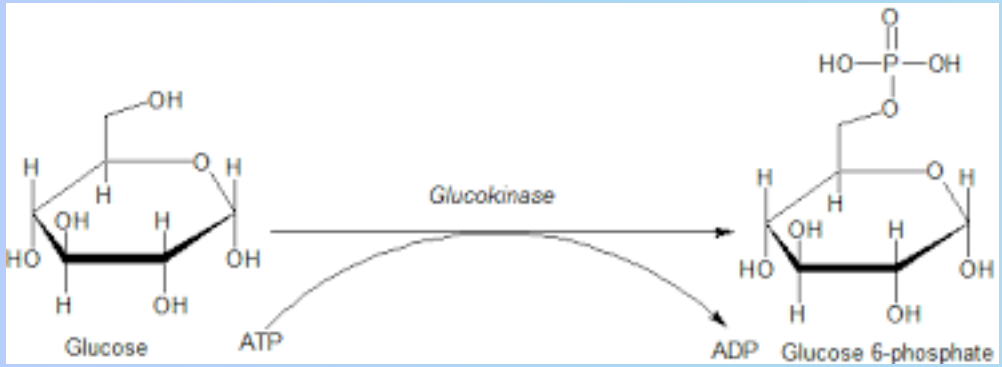
Glycogenesis

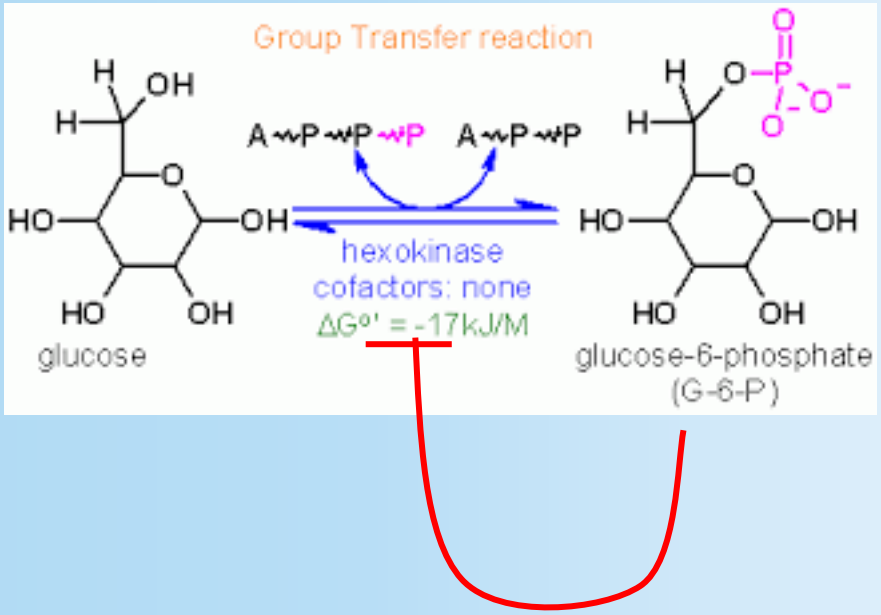
How do we make glycogen? "Glycogenesis"



Glucokinase/Hexokinase

- Add phosphate group to C6 ATP





Phosphoglucomutase

Phosphate glucose mutate

"mutate the phosphate on the glucose"

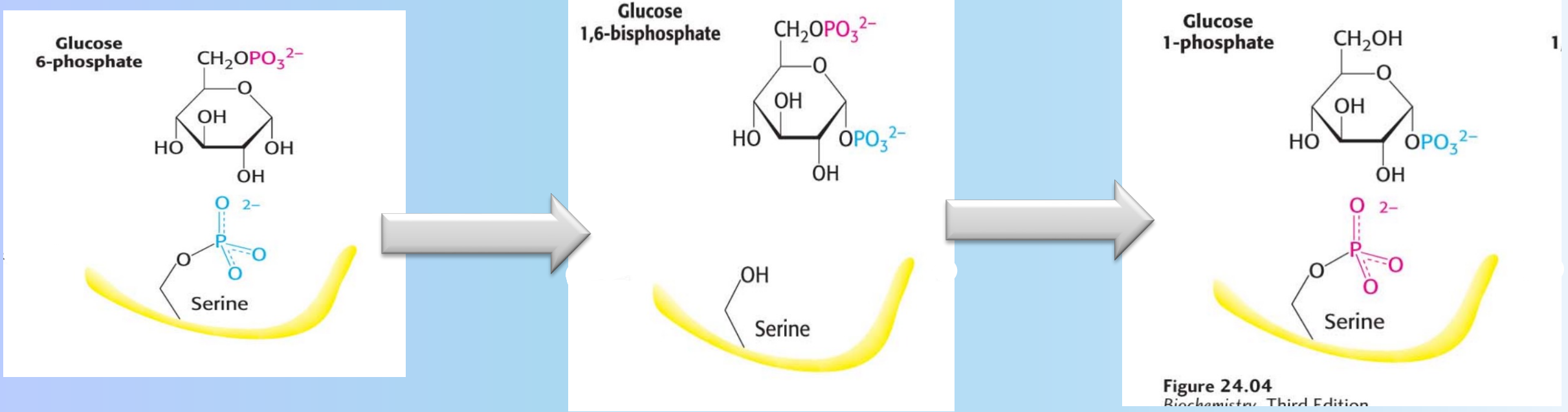
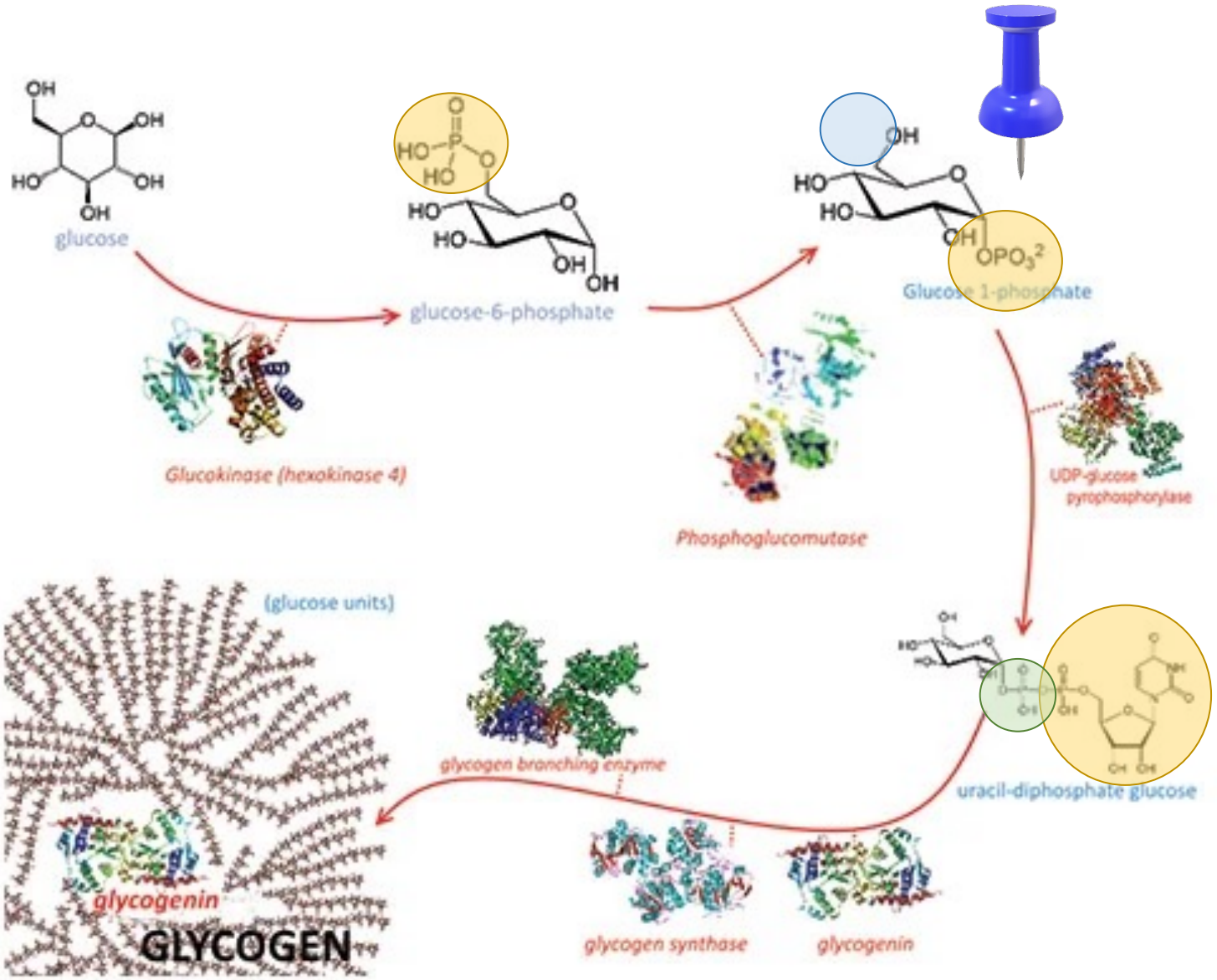
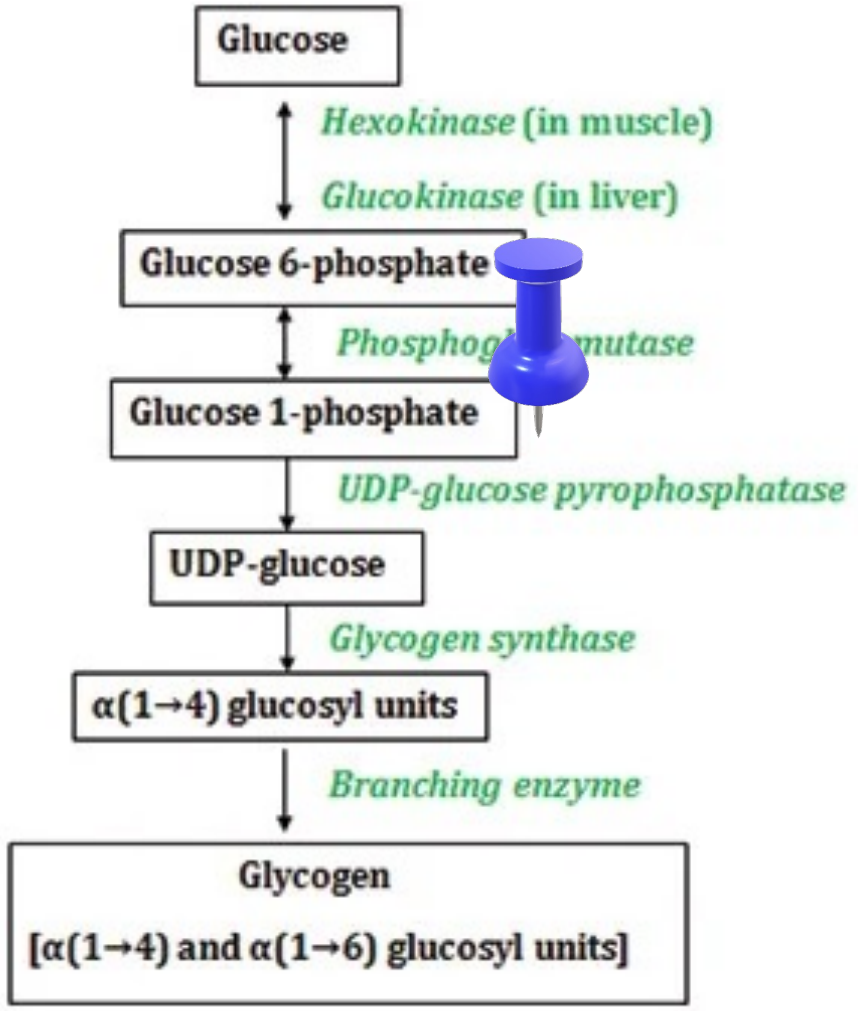


Figure 24.04

Biochemistry, Third Edition

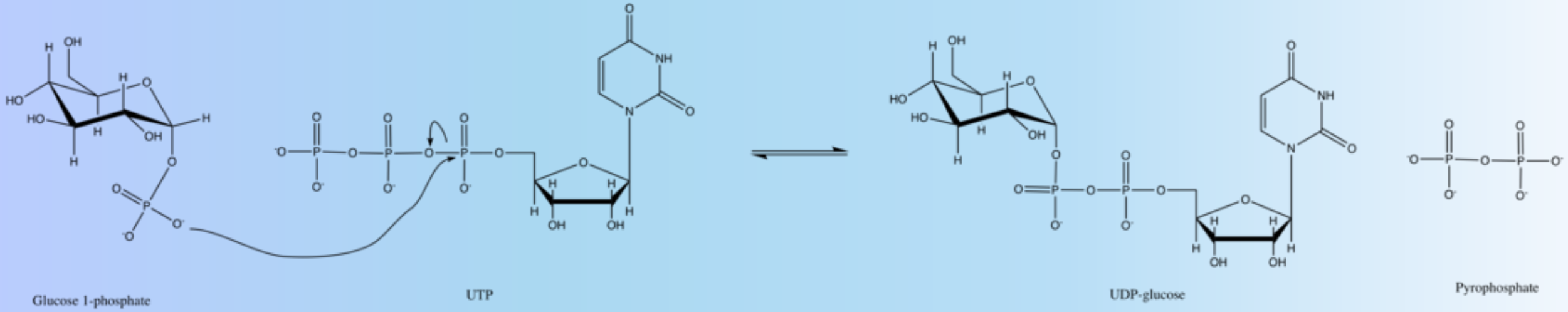




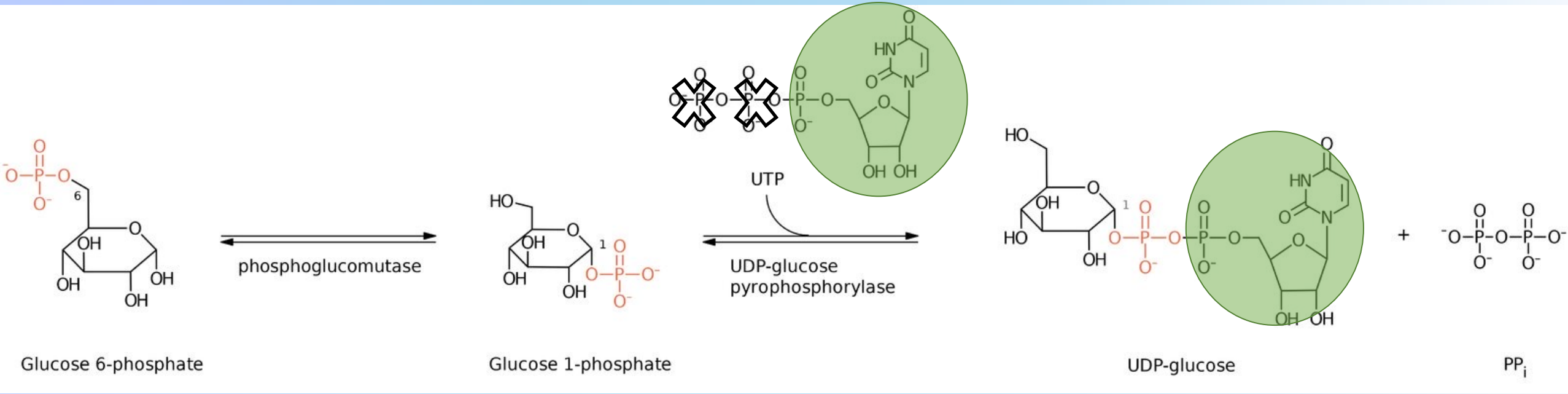
Glycogenesis

UDP Glucose pyrophosphatase

- G1P → UDP glucose
- “activates” the glucose



UDP Glucose pyrophosphorylase



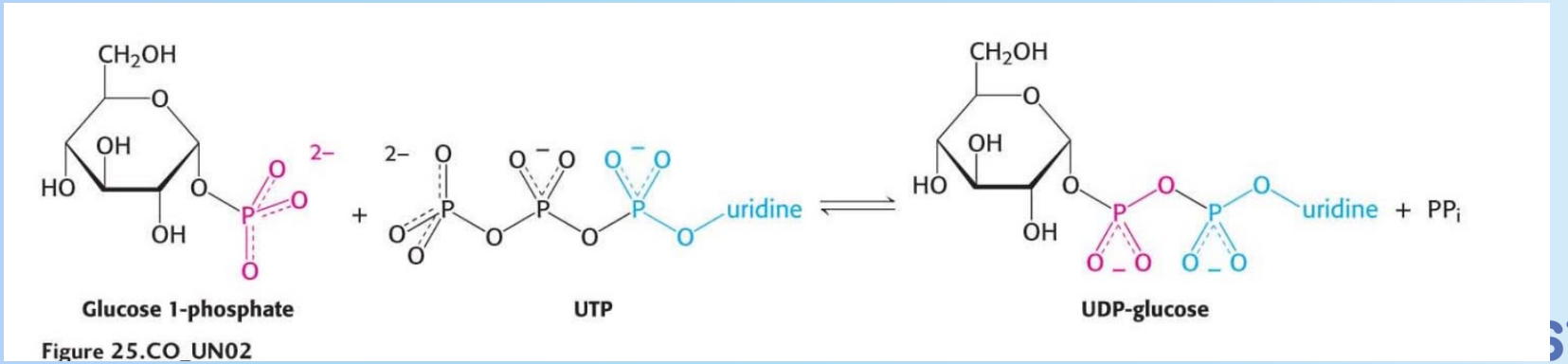
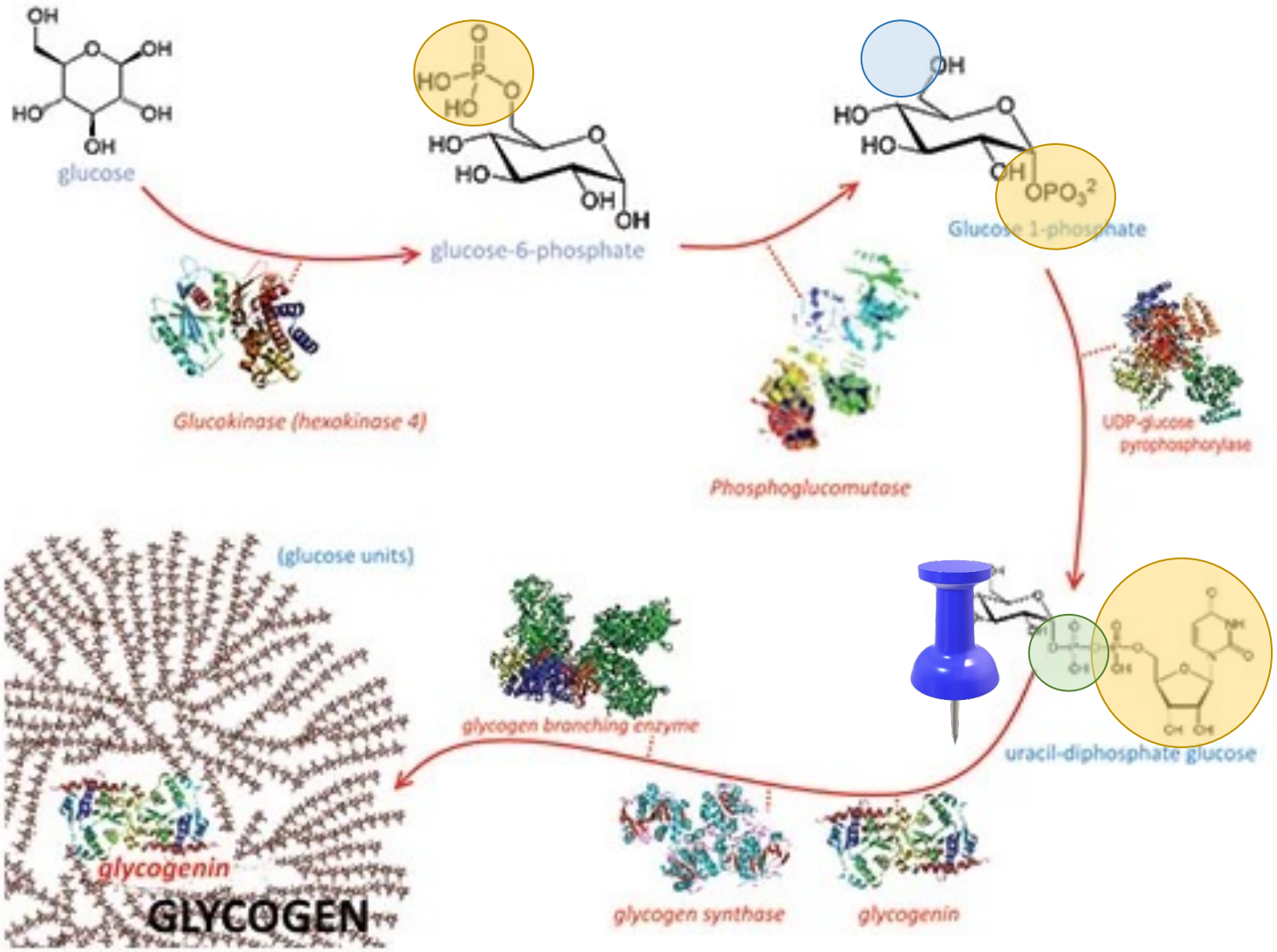
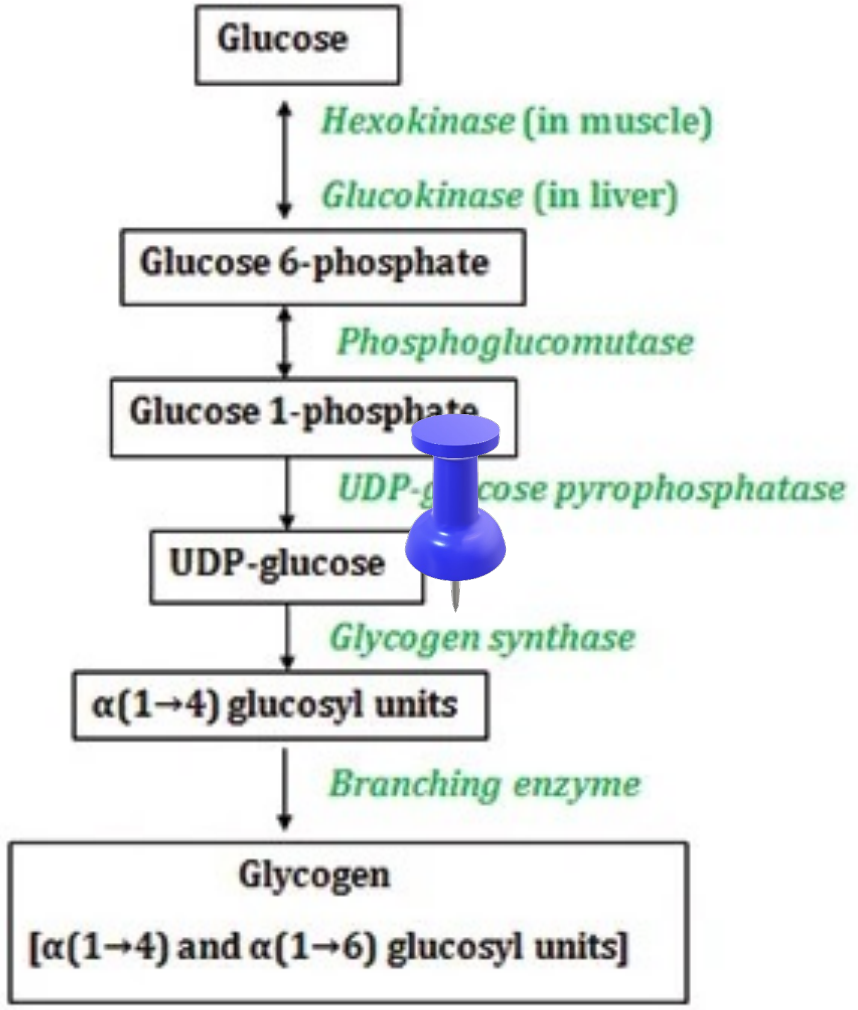


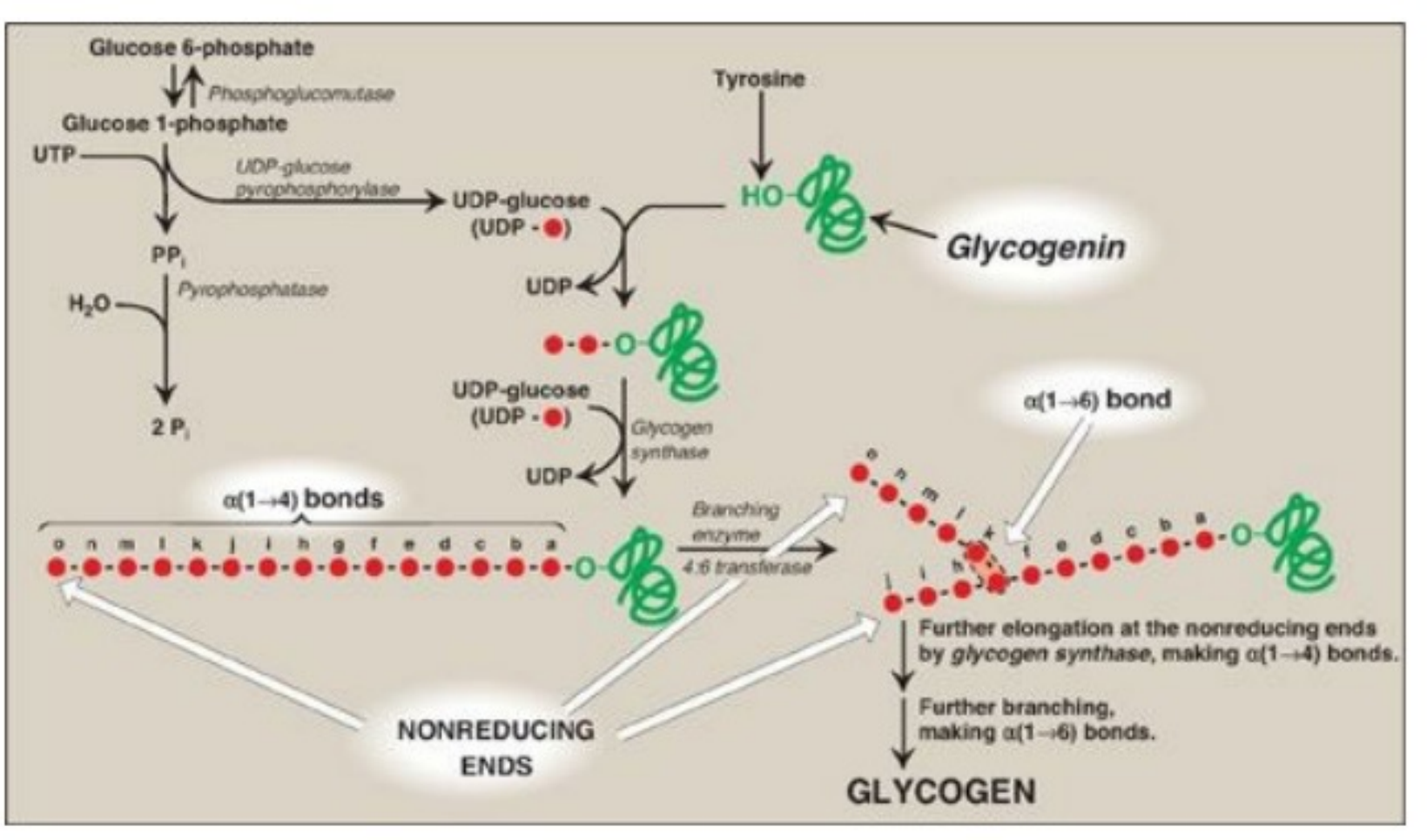
Figure 25.CO_UN02





Glycogenesis

Glycogenin



Protein and enzyme

Autoglucosylation: adds glucose onto itself

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Putting it all together

1. Add glucose to pre-existing glycogen fragment
2. If no fragment, glycogenin makes fragment, then we elongate:

STRAIGHT CHAIN (α1,4)
Glycogen synthase

α1,4 glycosidic bonds

Hydroxyl group of C1 of activated glucose to the C4 of the accepting glucose chain

Can only elongate an existing chain

RATE LIMITING STEP

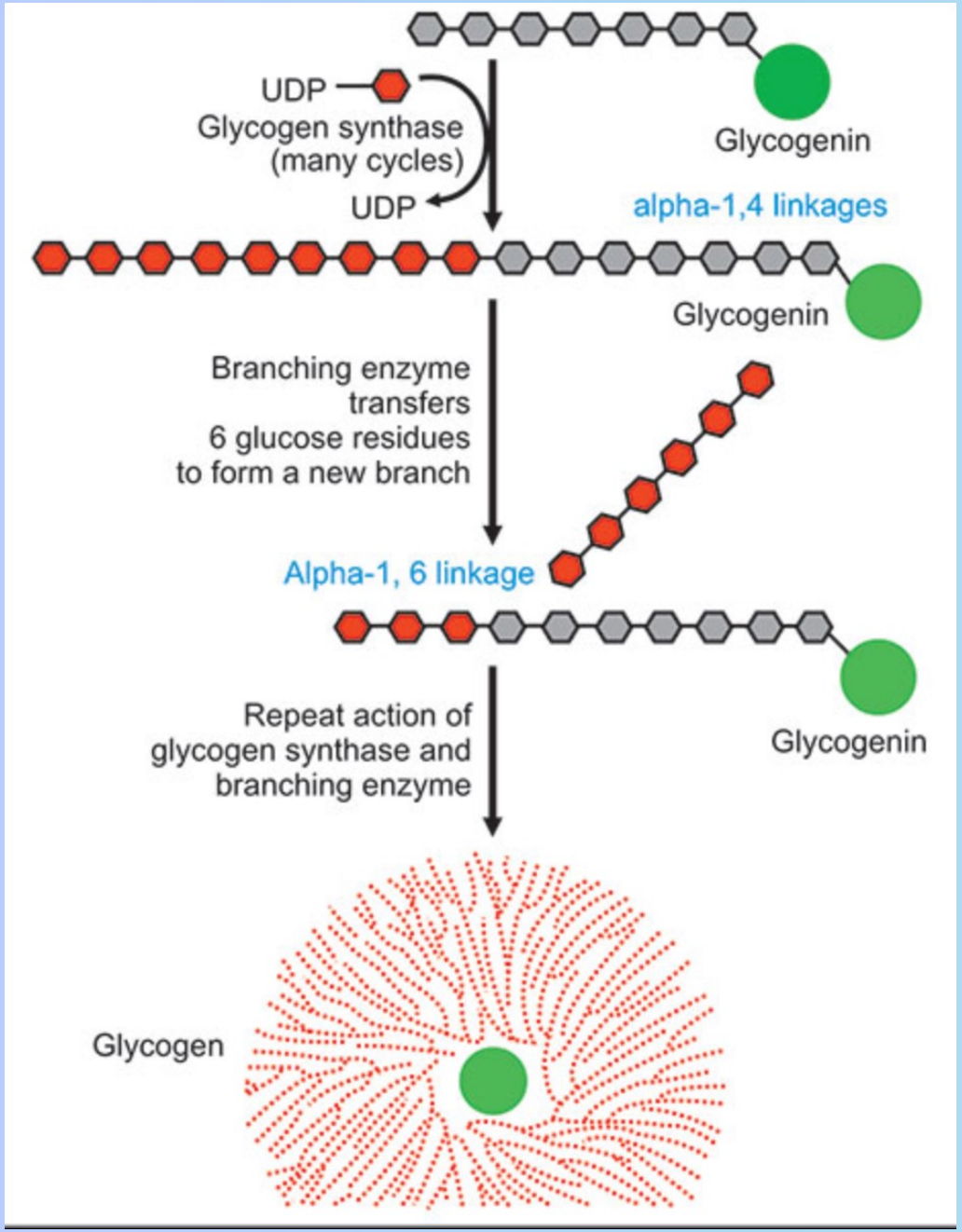
ACTIVE WITHOUT phosphate*

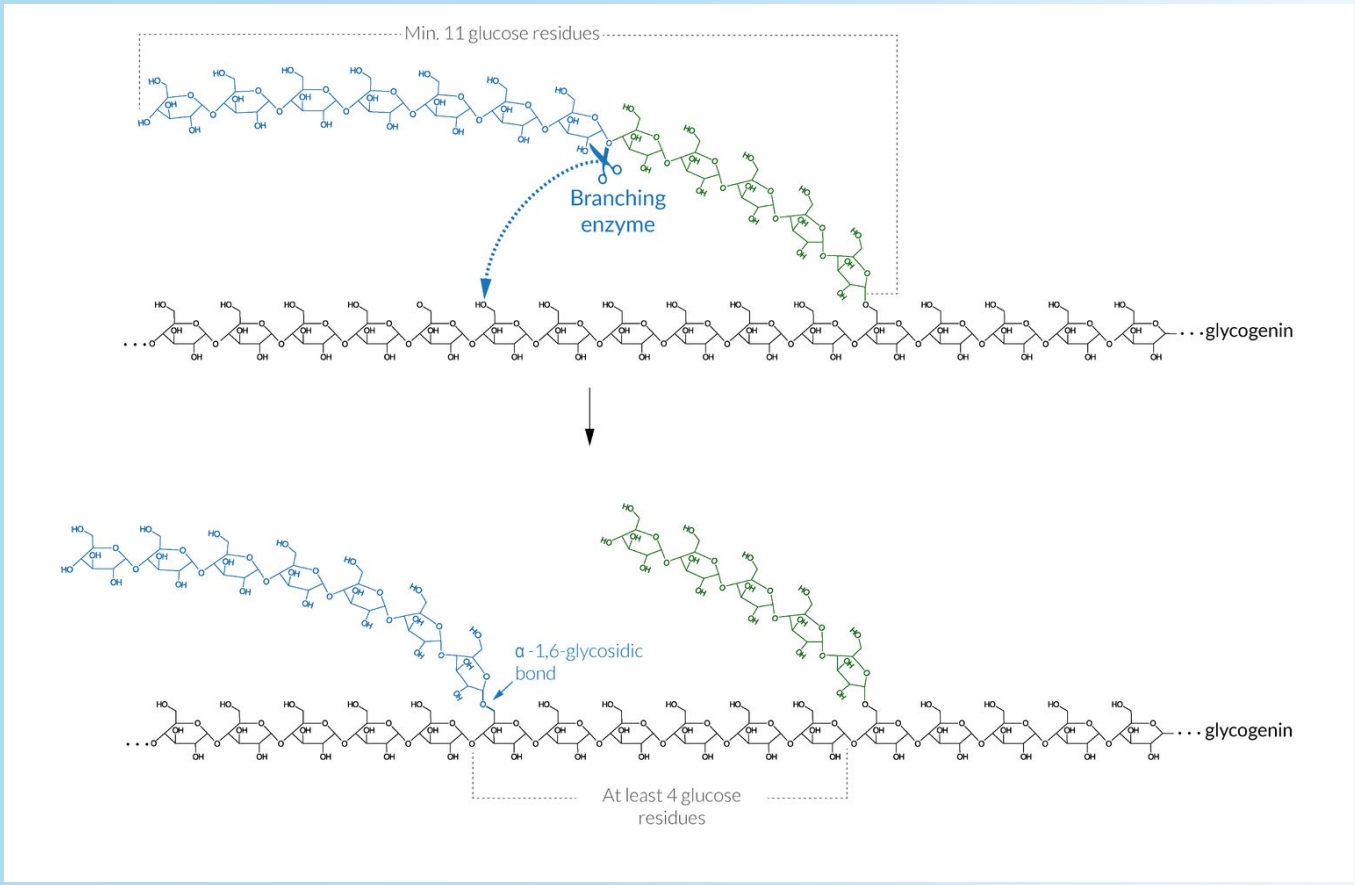
BRANCHED CHAIN (α1,6)
Branching enzyme

Branches every 8-12 glucose residues

Attaches as α1,6 glycosidic bonds.

Increases solubility and density


UDP
Glycogen synthase
(many cycles)
UDP
Glycogenin
alpha-1,4 linkages
Glycogenin
Branching enzyme
transfers
6 glucose residues
to form a new branch
Alpha-1, 6 linkage
Glycogenin
Repeat action of
glycogen synthase and
branching enzyme
Glycogen


Min. 11 glucose residues
Branching
enzyme
...glycogenin
α-1,6-glycosidic
bond
...glycogenin
At least 4 glucose
residues

Putting it all together

1. Add glucose to pre-existing glycogen fragment
2. If no fragment, glycogenin makes fragment, then we elongate:

STRAIGHT CHAIN (α1,4)
Glycogen synthase

α1,4 glycosidic bonds

Hydroxyl group of C1 of activated glucose to the C4 of the accepting glucose chain

Can only elongate an existing chain

RATE LIMITING STEP

ACTIVE WITHOUT phosphate*

BRANCHED CHAIN (α1,6)
Branching enzyme

Branches every 8-12 glucose residues

Attaches as α1,6 glycosidic bonds.

Increases solubility and density

Glycogen synthase

Insulin inhibits GSK3 (glycogen synthase kinsase 3)

keeps synthase without P

Has two forms: A and B

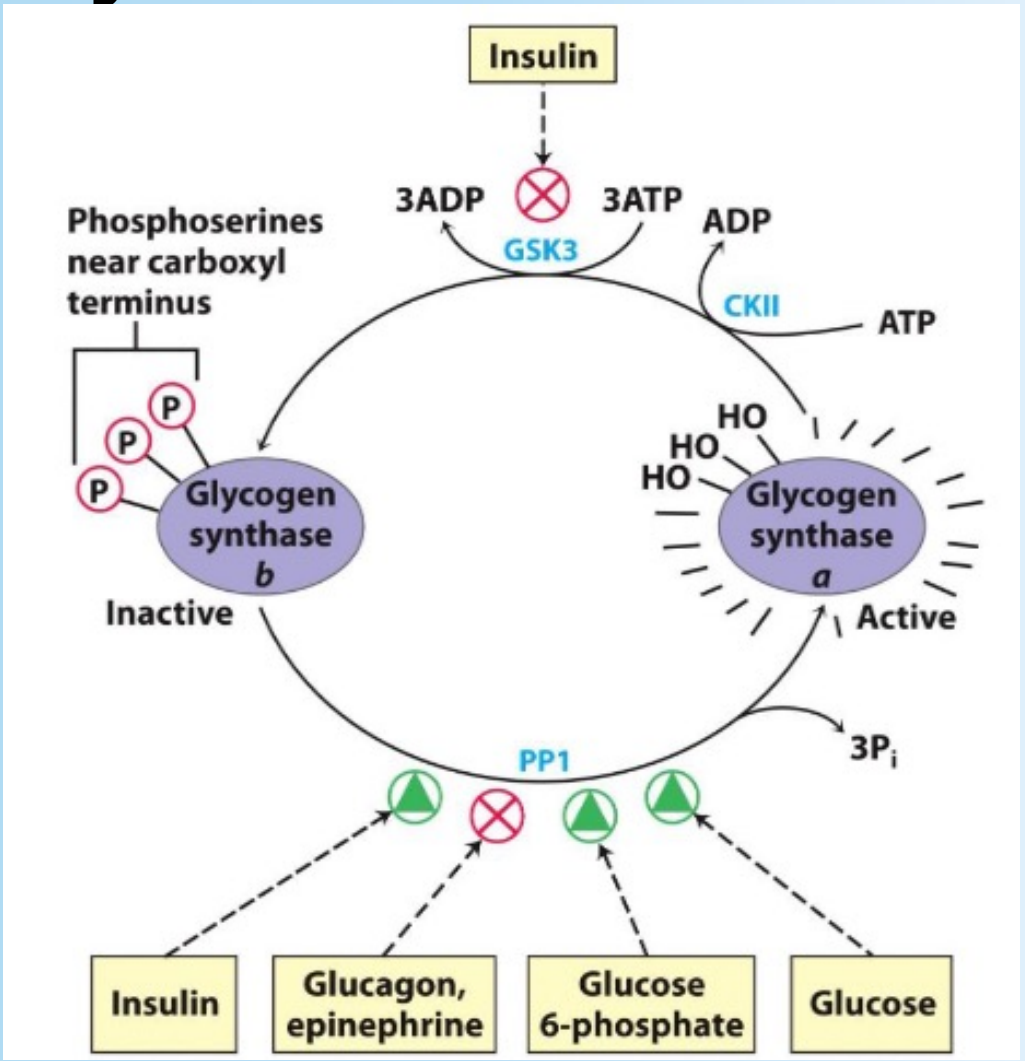
*** tricky*****

In general

A = active form

B= nonactive

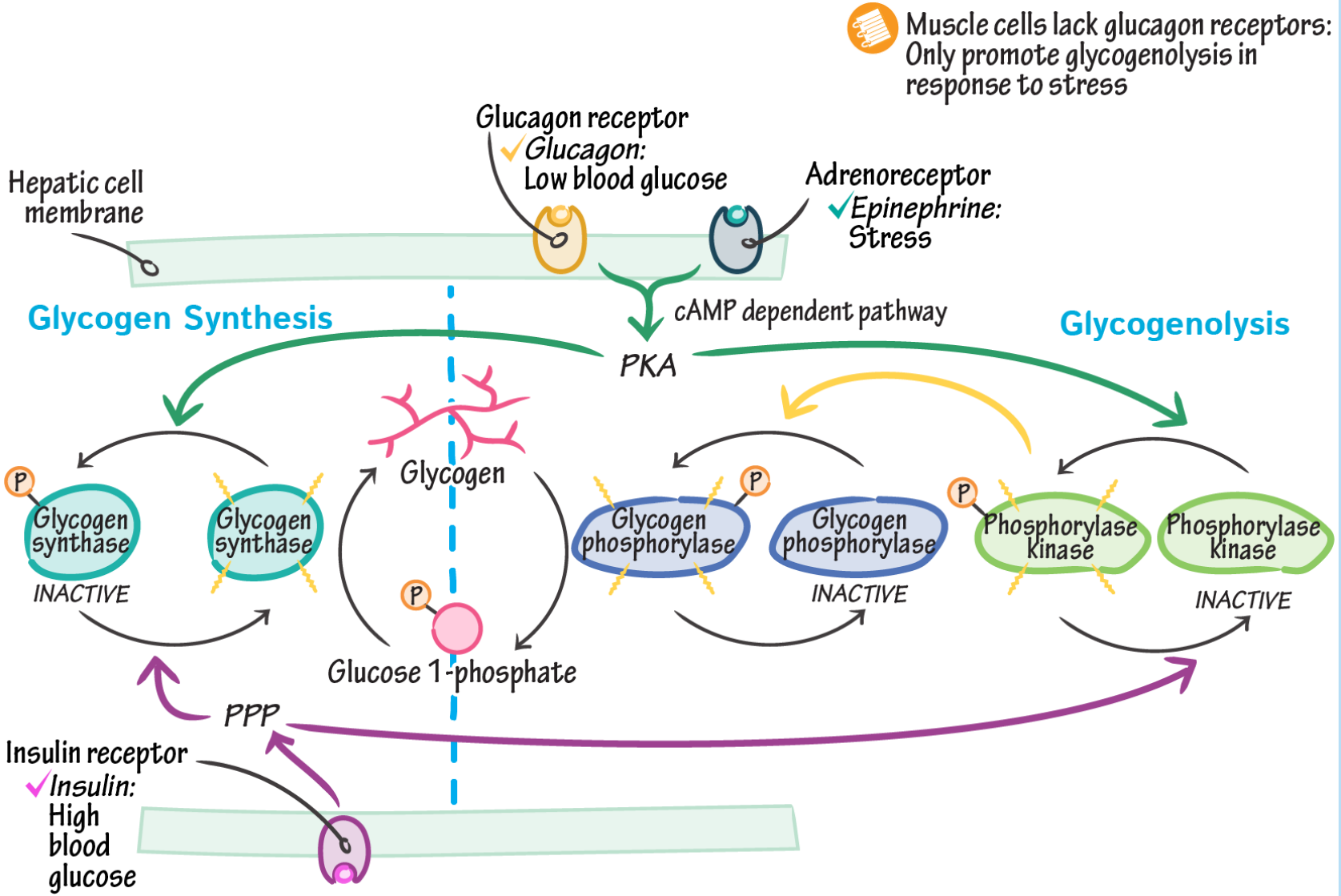
BUT the unphosphorylated form is the form wanted for glycogenesis.



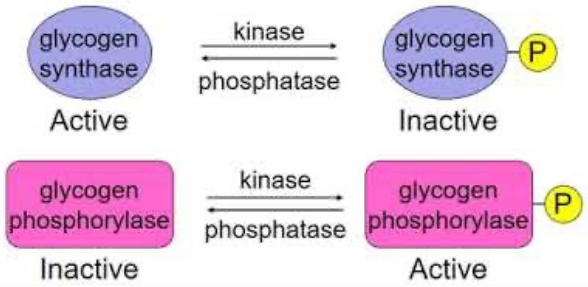
Glycogen Metabolism

Hormonal Regulation

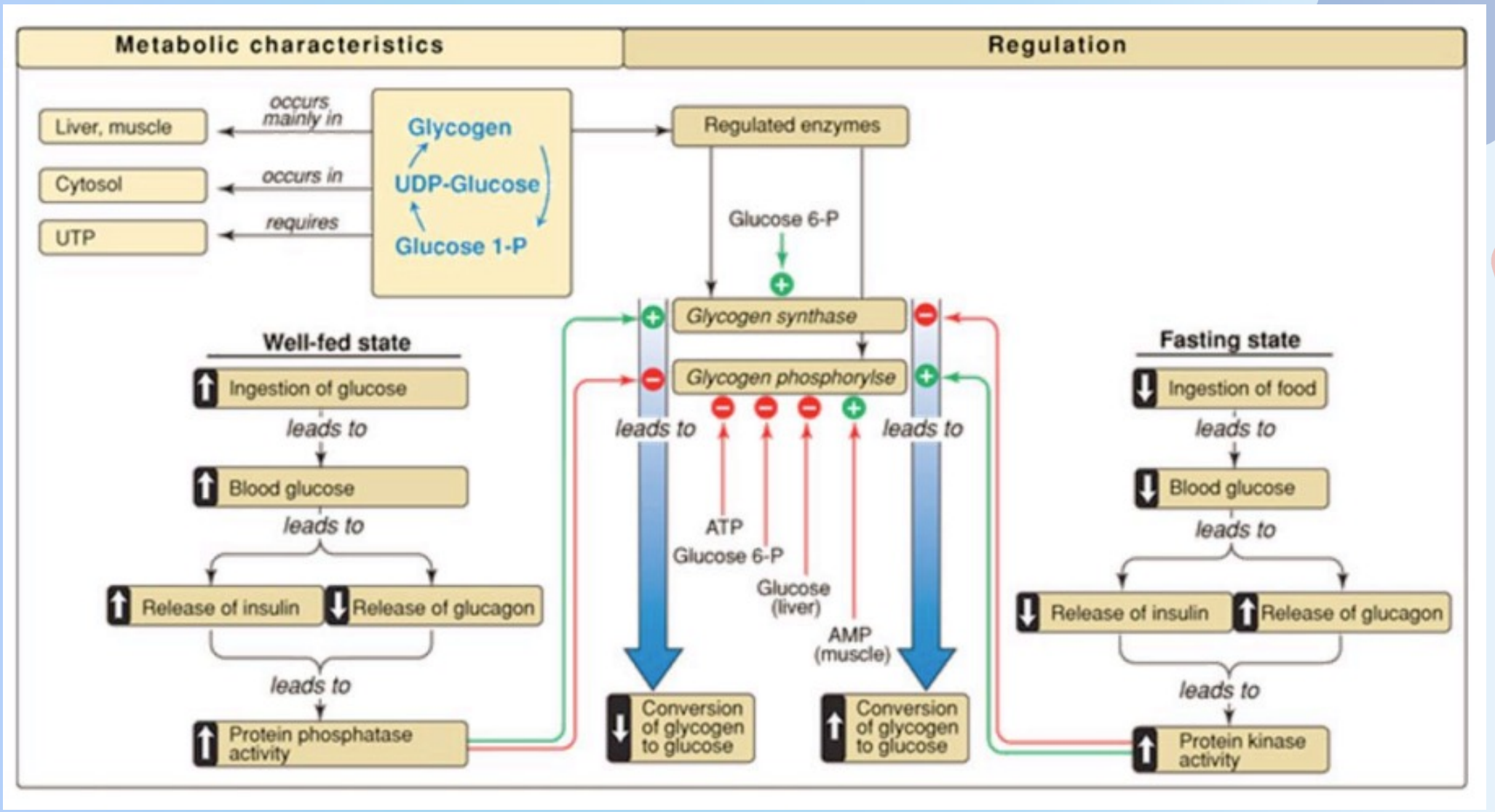
Muscle cells lack glucagon receptors: Only promote glycogenolysis in response to stress



Control by phosphorylation in liver & muscle



Hormone causing dephosphorylation	Tissue	Hormones causing phosphorylation
Insulin	Liver	Glucagon, epinephrine
Insulin	Muscle	Epinephrine


Metabolic characteristics
Regulation
Liver, muscle
occurs mainly in
Cytosol
occurs in
UTP
requires
Glycogen
UDP-Glucose
Glucose 1-P
Regulated enzymes
Glucose 6-P
Glycogen synthase
Glycogen phosphorylse
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
ATP
Glucose 6-P
Glucose (liver)
AMP (muscle)
Conversion of glycogen to glucose
Conversion of glycogen to glucose
Fasting state
Ingestion of food
leads to
Blood glucose
leads to
Release of insulin
Release of glucagon
leads to
Protein kinase activity

Deficiencies

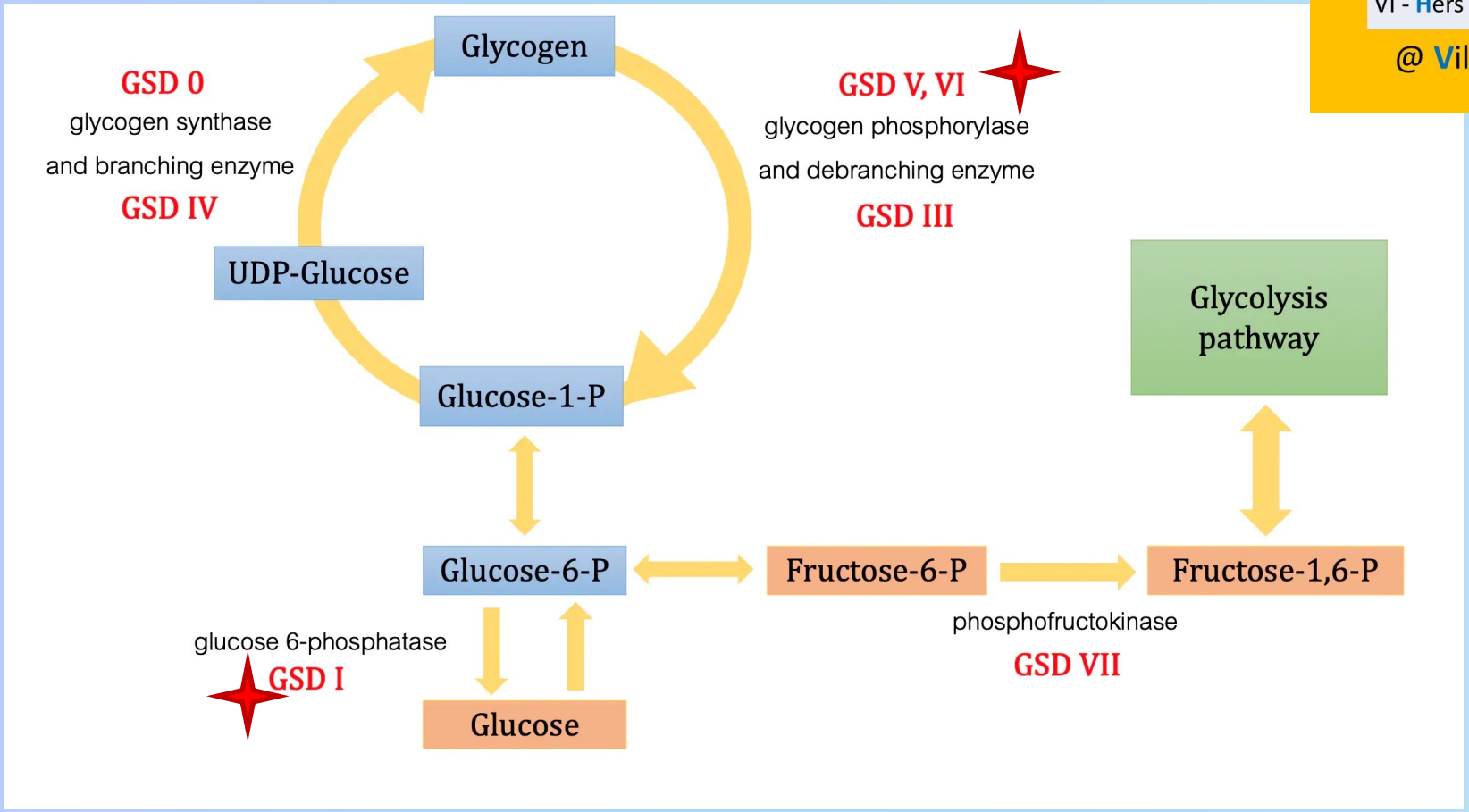
Glycogen Storage Disorders

Glycogen Storage Diseases

Type	Deficient Enzyme
I – Von Gierke	Glucose -6- Phosphate
II - Pompe	Lysosomal α 1,4 glycosidase
III - Cori	Debranching Enzyme
IV - Anderson	Branching Enzyme
V - McArdle	Muscle Glycogen Phosphorylase
VI - Hers	Hepatic Glycogen Phosphorylase

@ Villainous President Called And Molested Her.

www.dentaldevotee.blogspot.com



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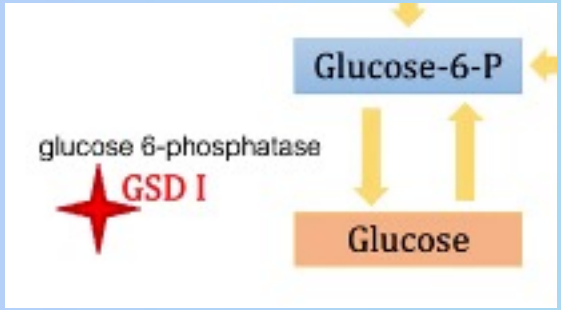
Type 1: Von Gierke Disease
Glucose-6-phosphatase deficiency

Glucose can't be made

Inherited as autosomal recessive disorder (both parents have to be carriers)

Deficient in liver, kidney and intestinal mucosa

- Glycogen and fat accumulate in liver → hepatomegaly
- No glucose = hypoglycemia

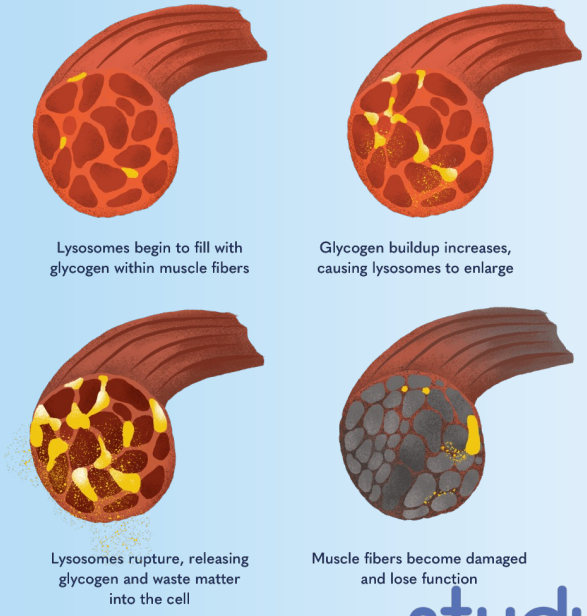


Type 2: Pompe Disease
Lysosomal GAA deficiency

Most severe disease

Affects muscle

Glycogen can't be broken down and accumulates - especially in heart muscle



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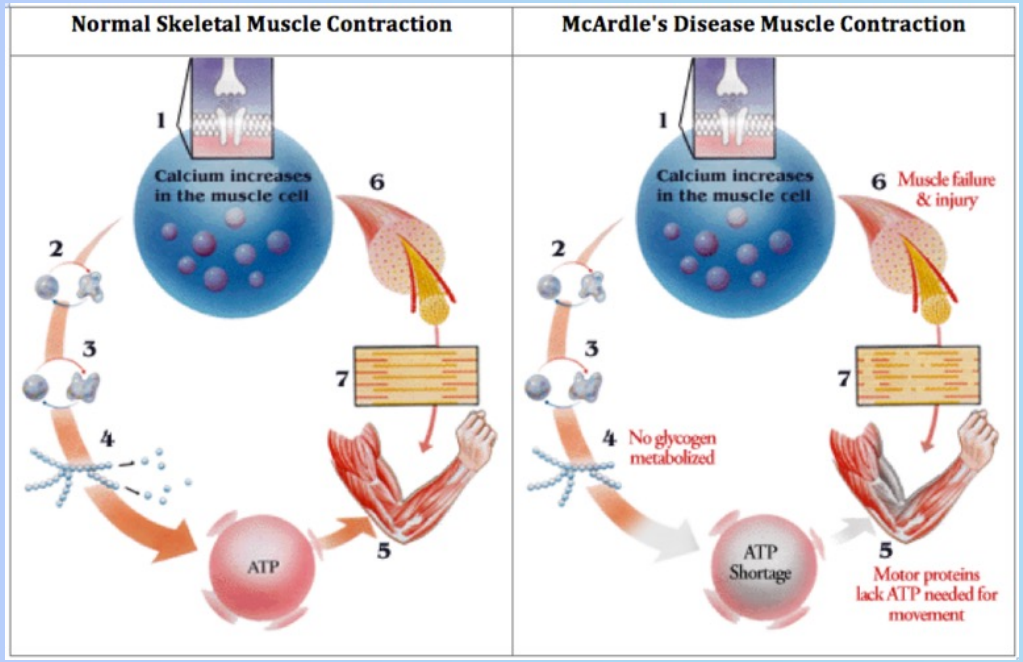
Type V: McArdle's Disease Myophosphorylase Deficiency

Autosomal recessive

Can't break down glycogen

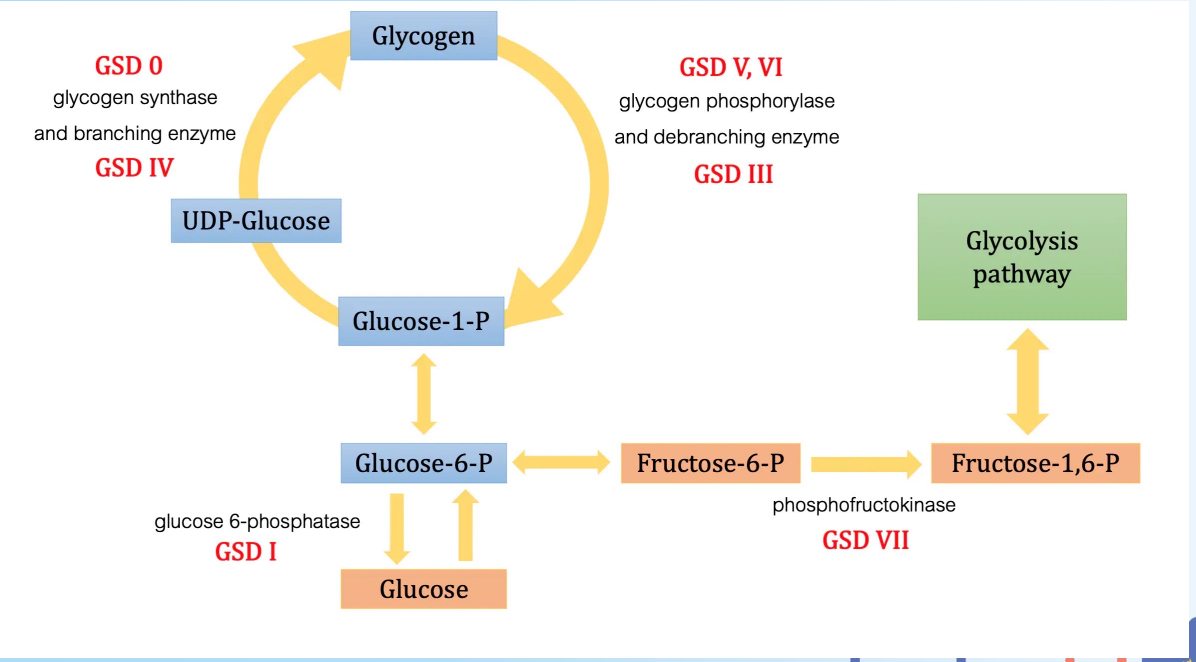
Deficiency of phosphorylase in <u>MUSCLE</u>



Type VI: Hers Disease Liver Phosphorylase Deficiency

Autosomal recessive (most) OR X-linked recessive

Can't break down glycogen in LIVER



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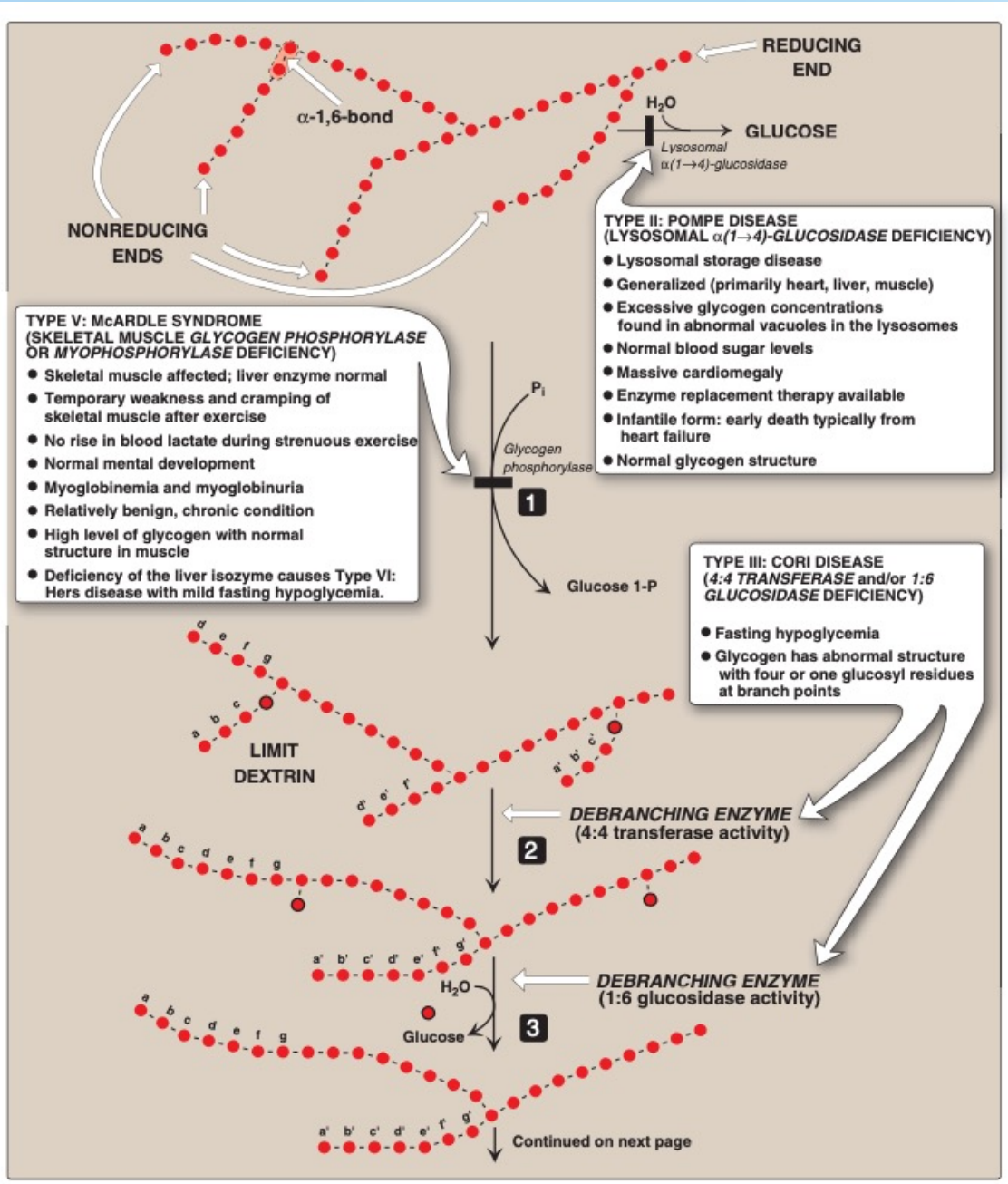

Figure 11.8
Glycogen degradation, showing some of the glycogen storage diseases (GSD). [Note: A GSD can also be caused by defects in *branching enzyme*, an enzyme of synthesis, resulting in Type IV: Andersen disease and causing death in early childhood.](*Continued on next page.*)

Type	Deficient enzyme	Signs and symptoms
I: Von Gierke (90% of all GSDs)	Glucose-6-phosphatase	- **Severe hypoglycemia** → hyperlipidemia - **Lactic acidosis** - Hepatomegaly - Hyperuricemia - Short stature/doll-like facies/protruding abdomen
II: Pompe	**Lysosomal** enzyme defect (acid maltase)	- **Cardiomegaly** → death by age 2 - **Hepatomegaly** - Muscle weakness
III: Cori disease	Debranching enzyme	- Mild hypoglycemia and hepatomegaly
IV: Andersen disease	Branching enzyme	- Infantile hypotonia, cirrhosis and death by 2 years
V: McArdle	Muscle glycogen phosphorylase (myophosphorylase)	- Muscle cramps and weakness on exercise - Myoglobinuria - No rise in lactate during exercise - Recovery or «second wind» after 10-15 minutes of exercise
VI: Hers	Hepatic glycogen phosphorylase	- Mild fasting hypoglycemia (compensated by gluconeogenesis) - Hepatomegaly and cirrhosis

Extra Resources

Ninja Nerd

AKLectures

Osmosis