Gluconeogenesis & Glycogen Metabolism

By Matt Hryniewicki

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PLAN

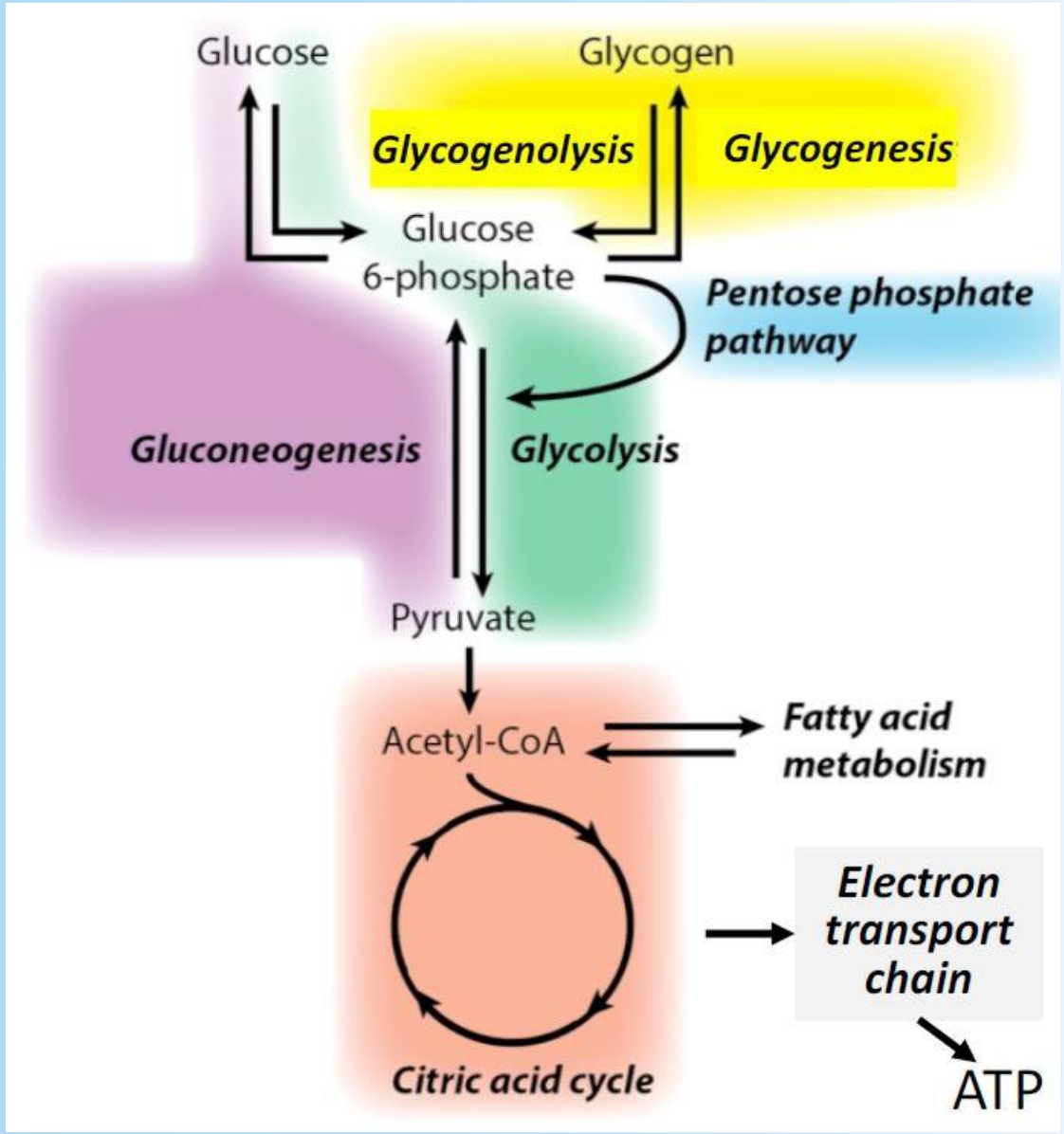
Quick Overview

Gluconeogenesis

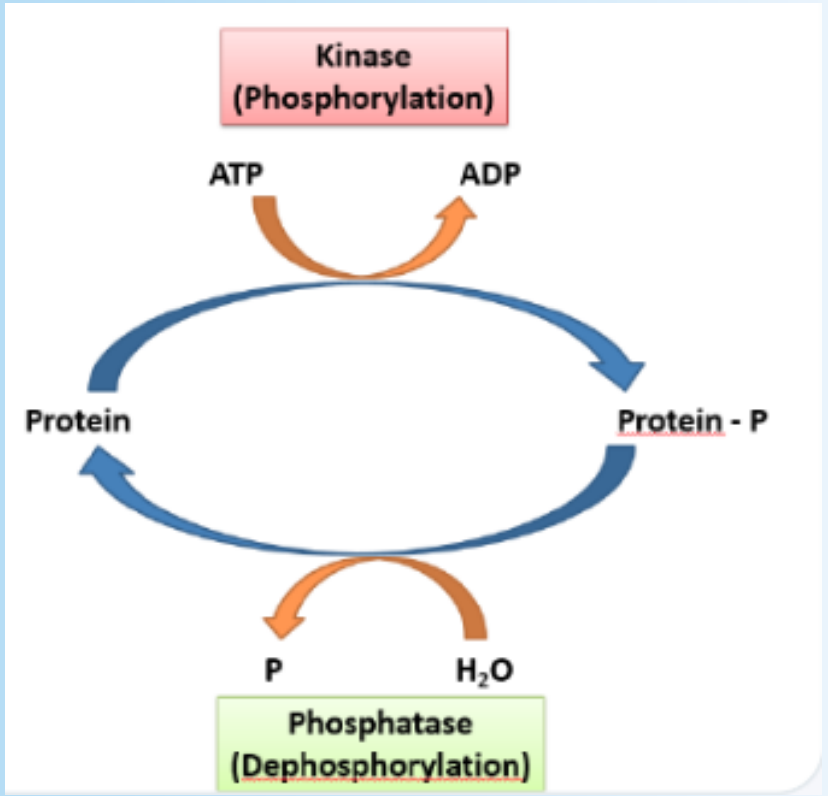
-----BREAK-----

Glycogenolysis + Glycogenesis

Glycogen Storage Diseases



Terminology



Kinase: Add phosphate from high energy molecule (ATP)

Phosphorylase: Adds phosphate from an inorganic phosphate

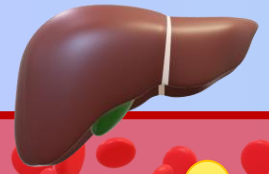
Phosphatase: Use water to remove phosphate -(P)

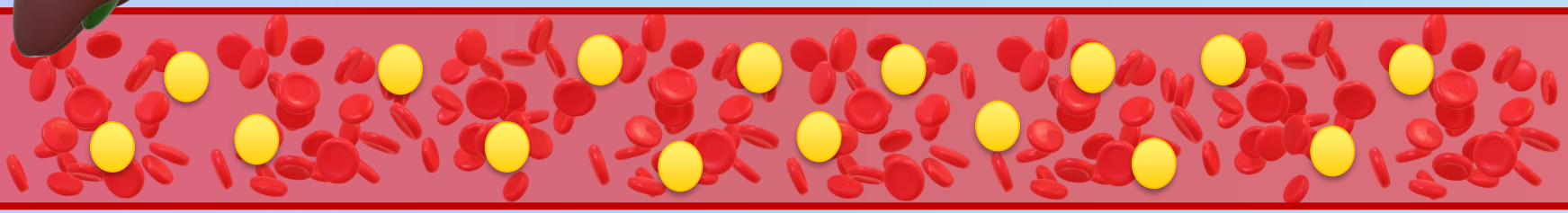
Homeostasis

Take

- **Glycolysis** glucose → pyruvate
- **Glycogenesis** glucose → glycogen

↑ Insulin
↓ Glucagon
↓ Epinephrin





Blood Glucose Range
70-100 mg/dL

Glucose

↓ Insulin
↑ Glucagon
↑ Epinephrin

Make

- **Gluconeogenesis** precursors → glucose
- **Glycogenolysis** glycogen → glucose

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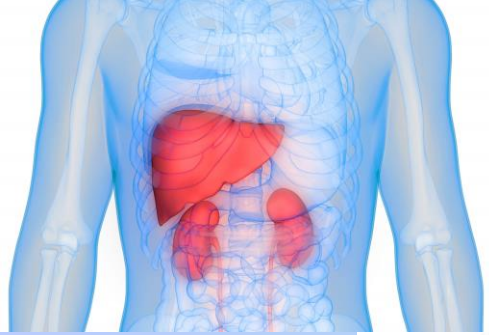
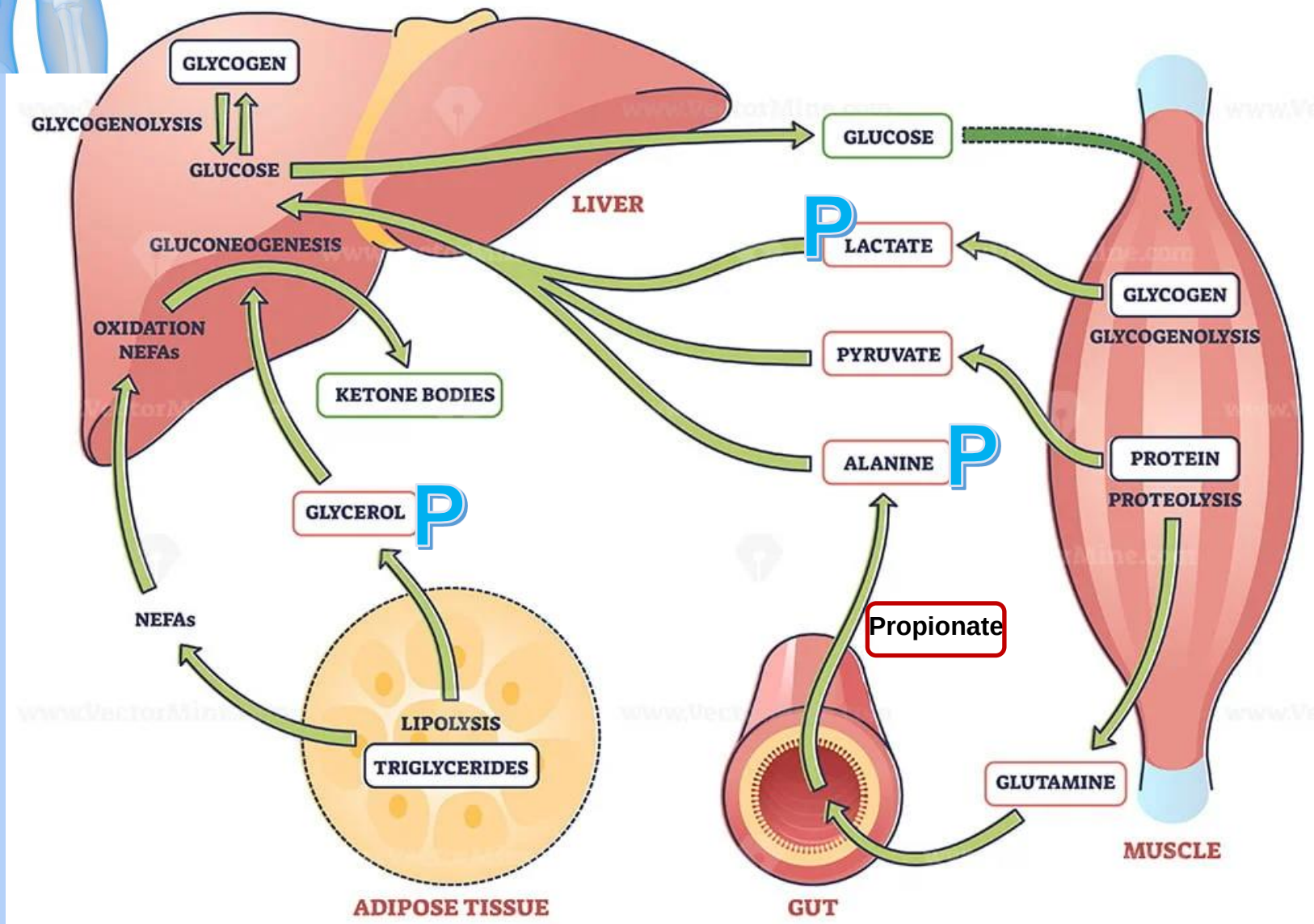
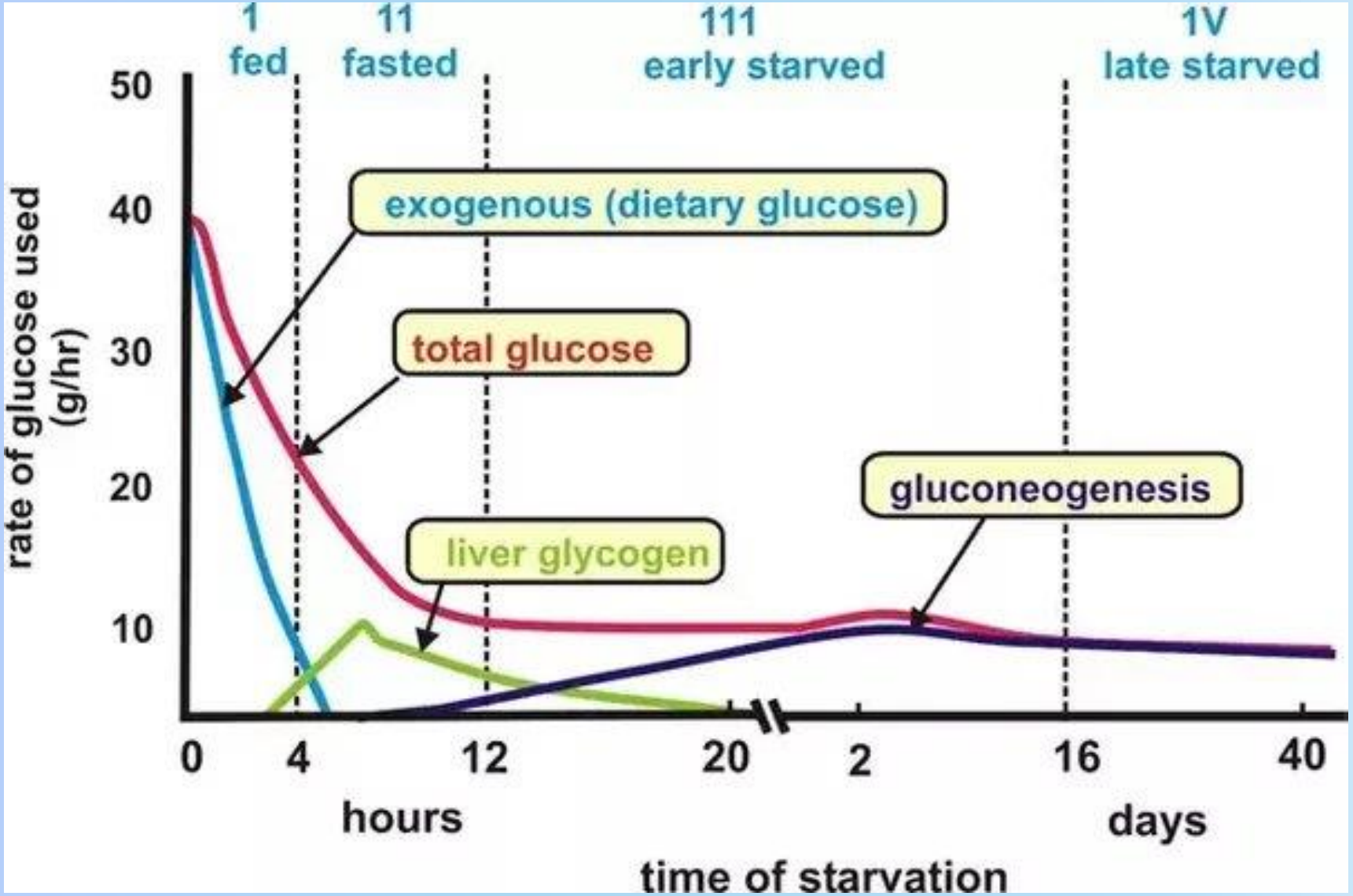
Gluconeogenesis

Noncarbohydrate Precursors → Glucose



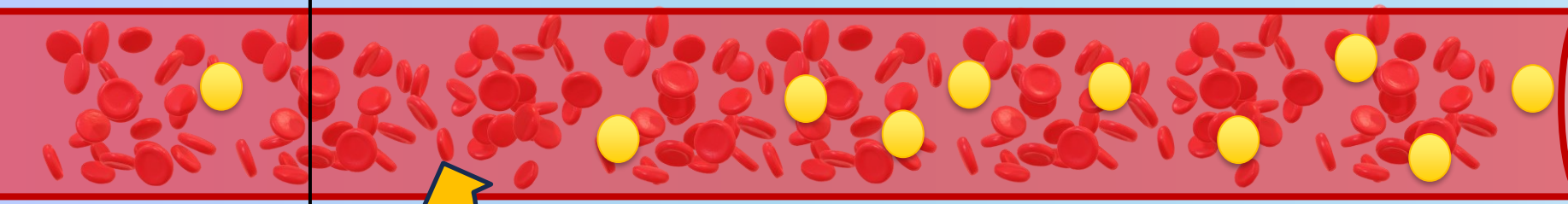
GLUCONEOGENESIS




1
fed
11
fasted
111
early starved
1V
late starved
rate of glucose used (g/hr)
50
40
30
20
10
exogenous (dietary glucose)
total glucose
liver glycogen
gluconeogenesis
0
4
12
20
2
16
40
hours
days
time of starvation

Fasting/Starved

Make



Blood Glucose Range
70-100 mg/dL

↓ Insulin
↑ Glucagon
↑ Epinephrine

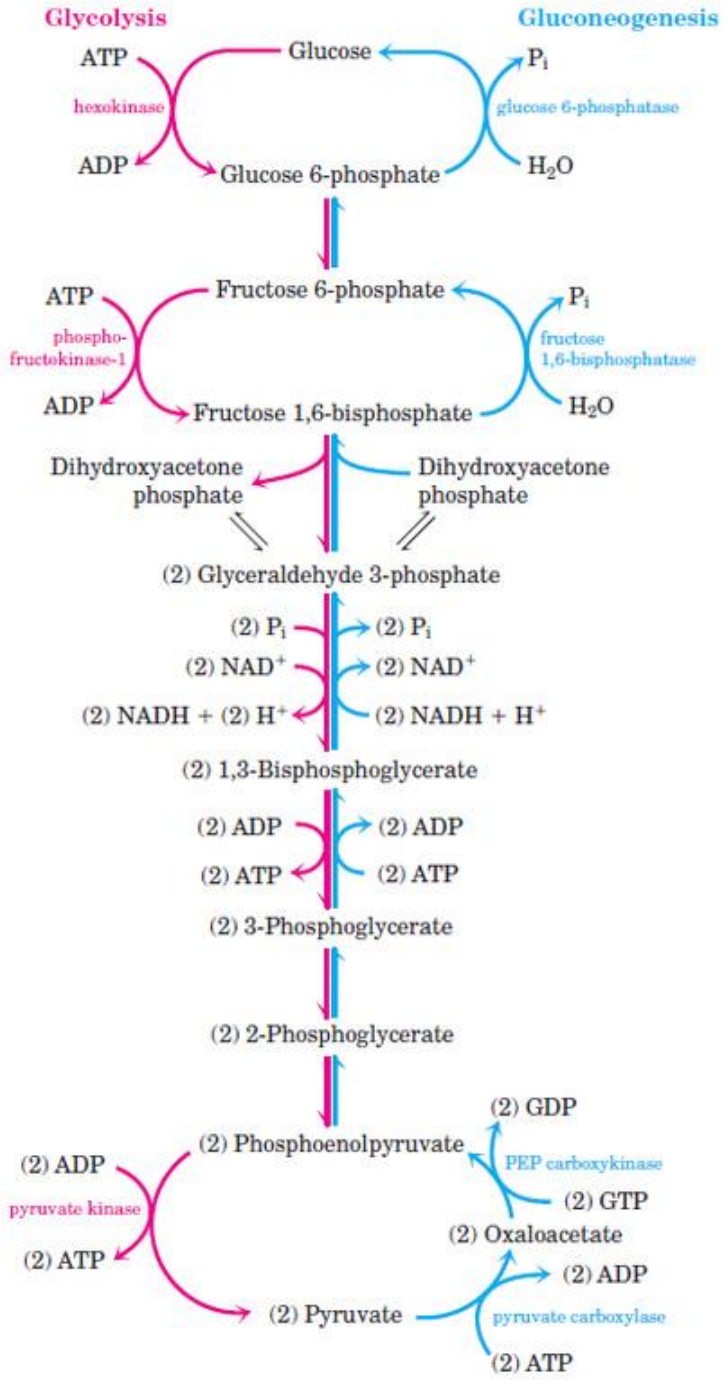
Gluconeogenesis

Majority occurs in liver; little bit in kidney

Making Glucose from 3 precursors
1. Lactate (anaerobic glycolysis of muscles and RBCs)
2. Glucogenic Amino Acids (breakdown of proteins)
3. Glycerol (breakdown of fats)

Bypassing 3 irreversible enzymes of glycolysis

Need 2 pyruvate per glucose



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

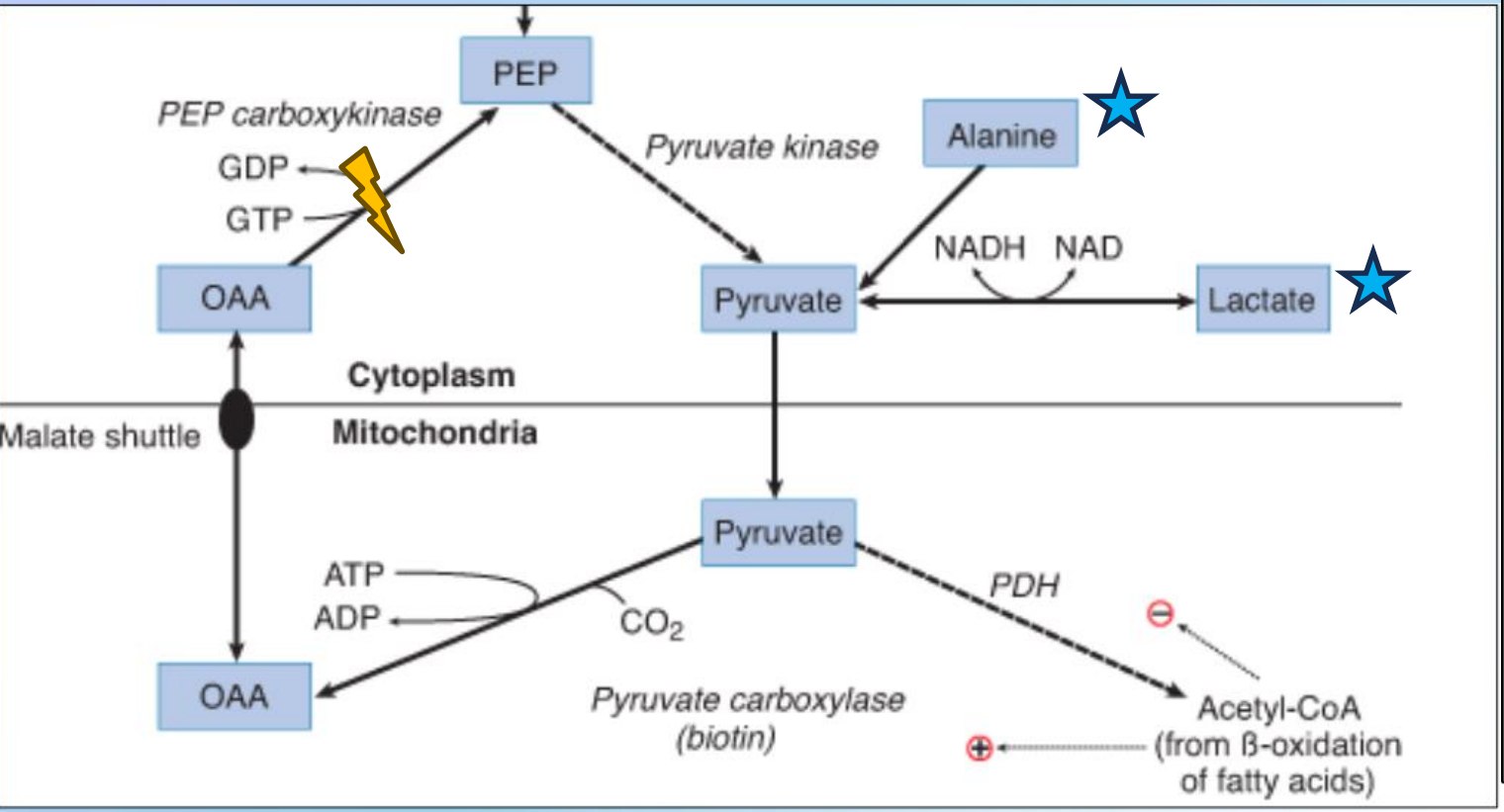
(4 steps)

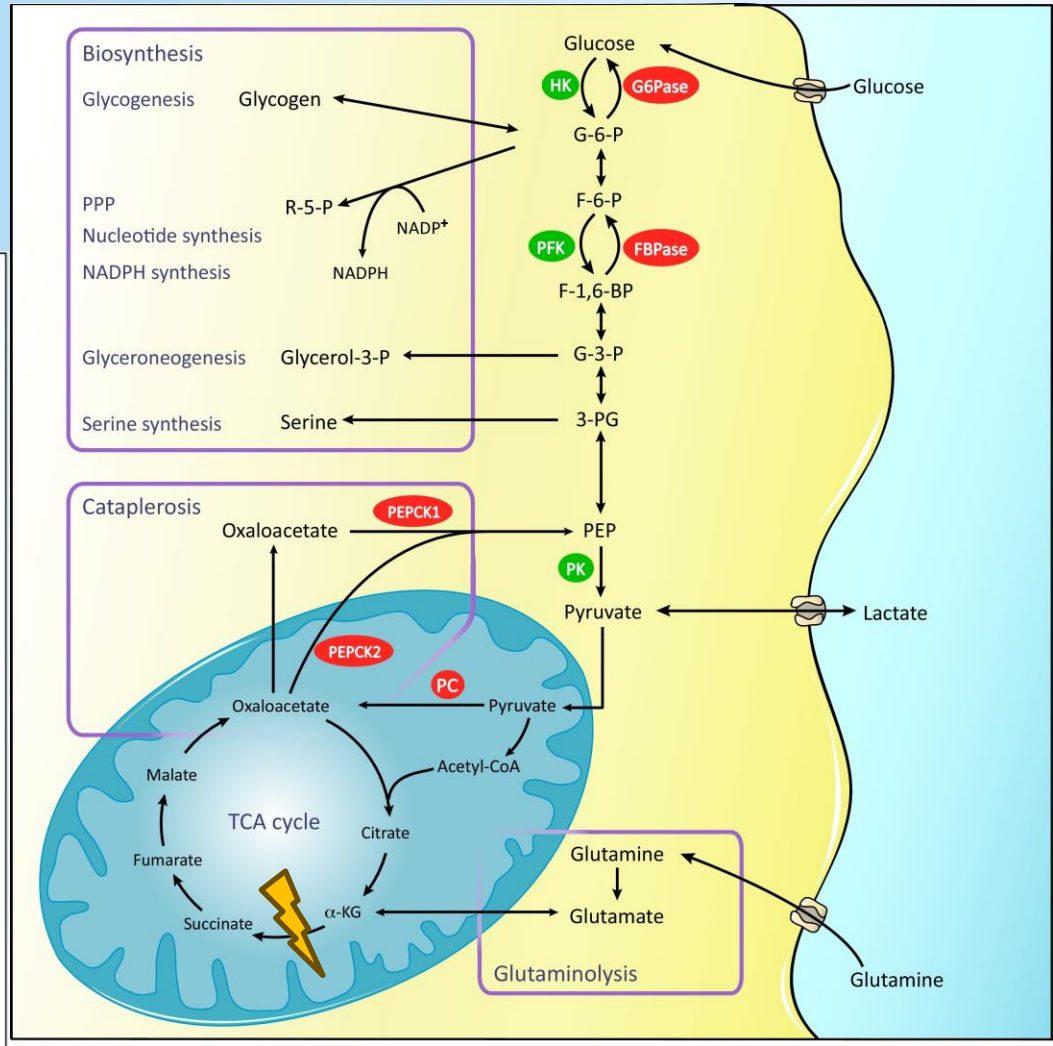
1 Pyruvate Kinase → **(a) Pyruvate carboxylase +**
(b) Phosphoenolpyruvate carboxyl kinase
(PEP Carboxyl Kinase)

1: Carboxylation of Pyruvate

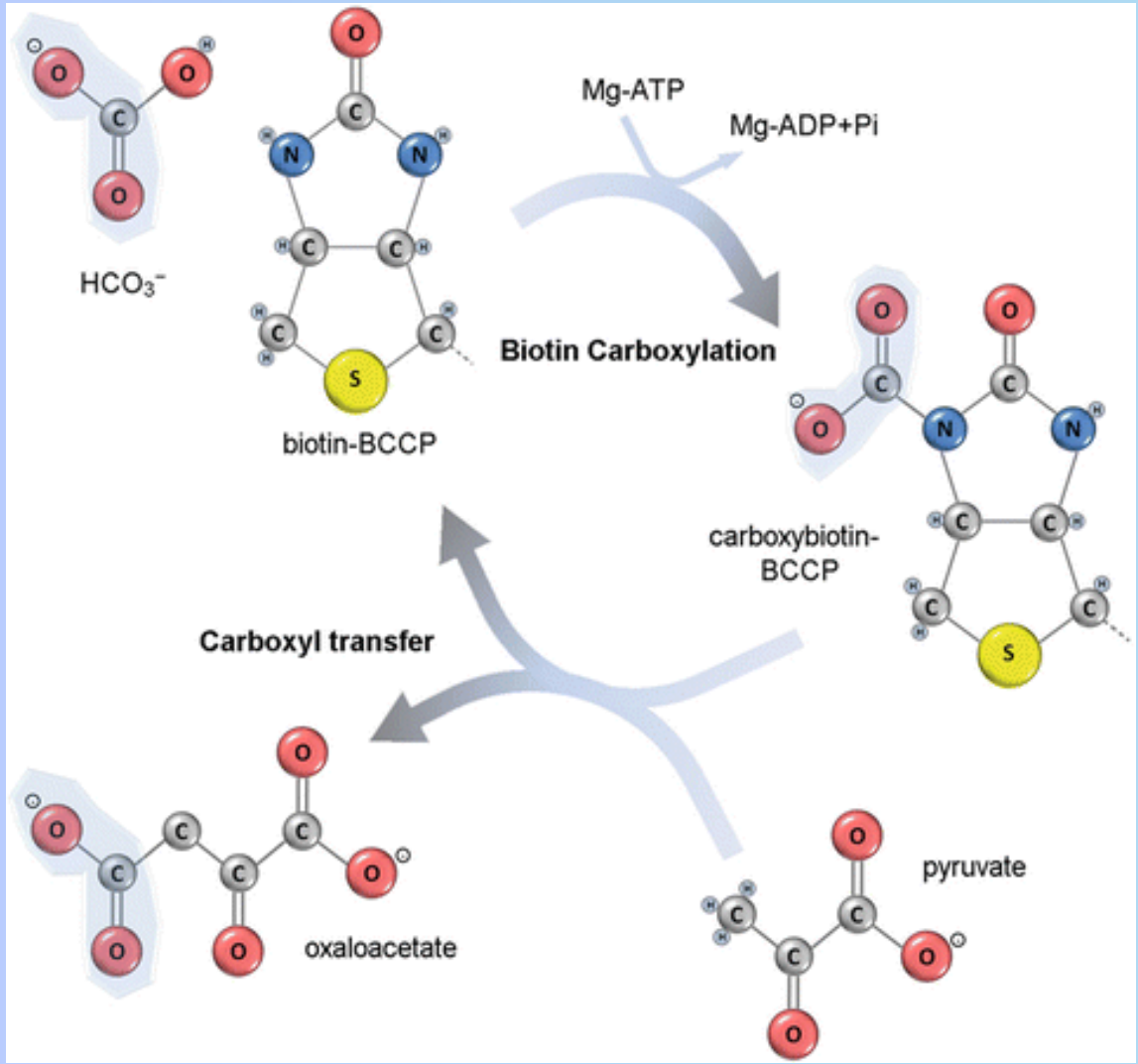
Energy: ATP, GTP
PC needs Biotin
High CoA: GO
Low CoA: STOP

1. **Pyruvate carboxylase**(+**biotin**) catalyzes carboxylation of pyruvate → OAA
2. OAA is reduced to malate
3. Export malate from mitochondrion → cytosol
4. Malate is oxidized to OAA
5. **Phosphoenolpyruvate carboxykinase (PEPCK)** decarboxylates and phosphorylates OAA → PEP using GTP as phosphate donor





Why is biotin important?



Biotin + bicarbonate + ATP → carboxybiotin

”loads the enzyme with CO_2”

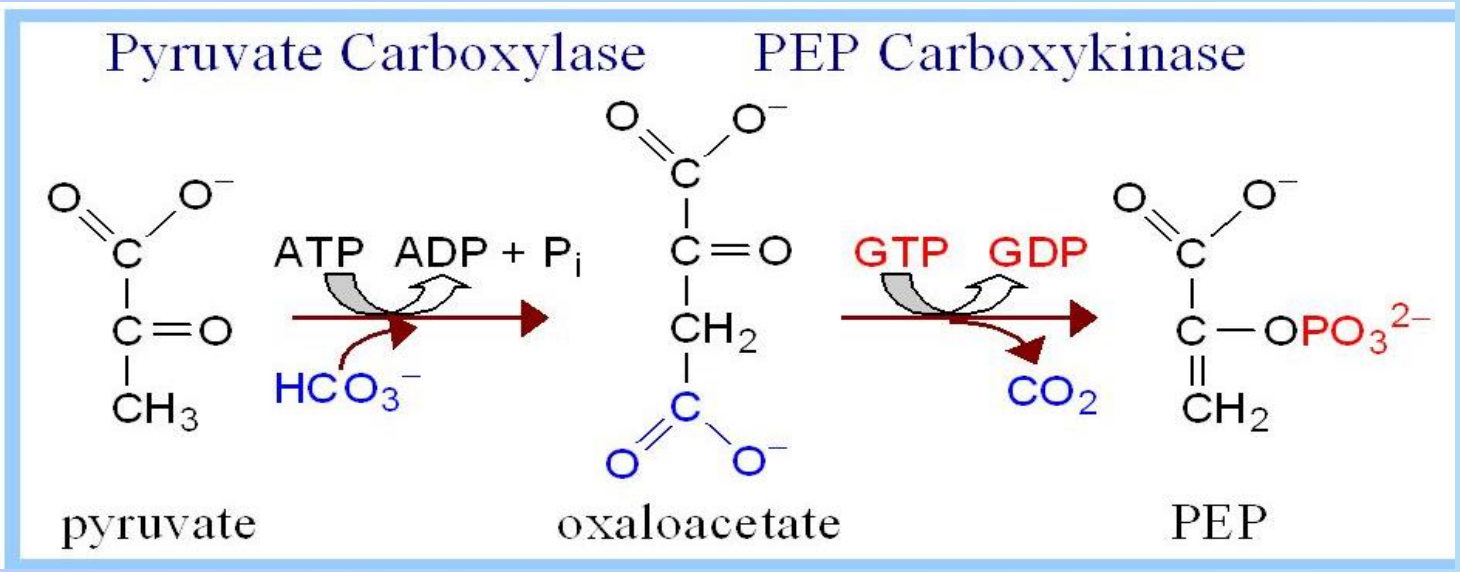
Pyruvate carboxylase then adds this CO_2 to pyruvate making OAA

Occurs in mitochondria

Highlights of Step 1

4 reactions are needed to bypass pyruvate kinase
(don't forget about the malate shuttle!)

Pyruvate Carboxylase	PEP carboxykinase
Occurs in mitochondria → (Malate shuttle)	Occurs in cytosol
Pyruvate → Oxaloacetate	Oxaloacetate → Phosphoenolpyruvate (PEP)
Carboxylates Requires ATP	Decarboxylates Requires GTP
Cofactor: Biotin **Acetyl CoA regulates this enzyme**	



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2: Dephosphorylation of Fructose 1,6 bisphosphate

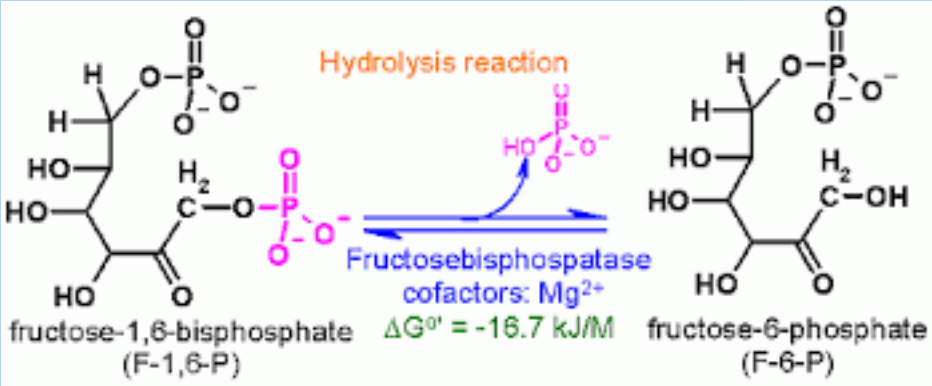
Enzyme: **fructose 1,6-bisphosphatase**

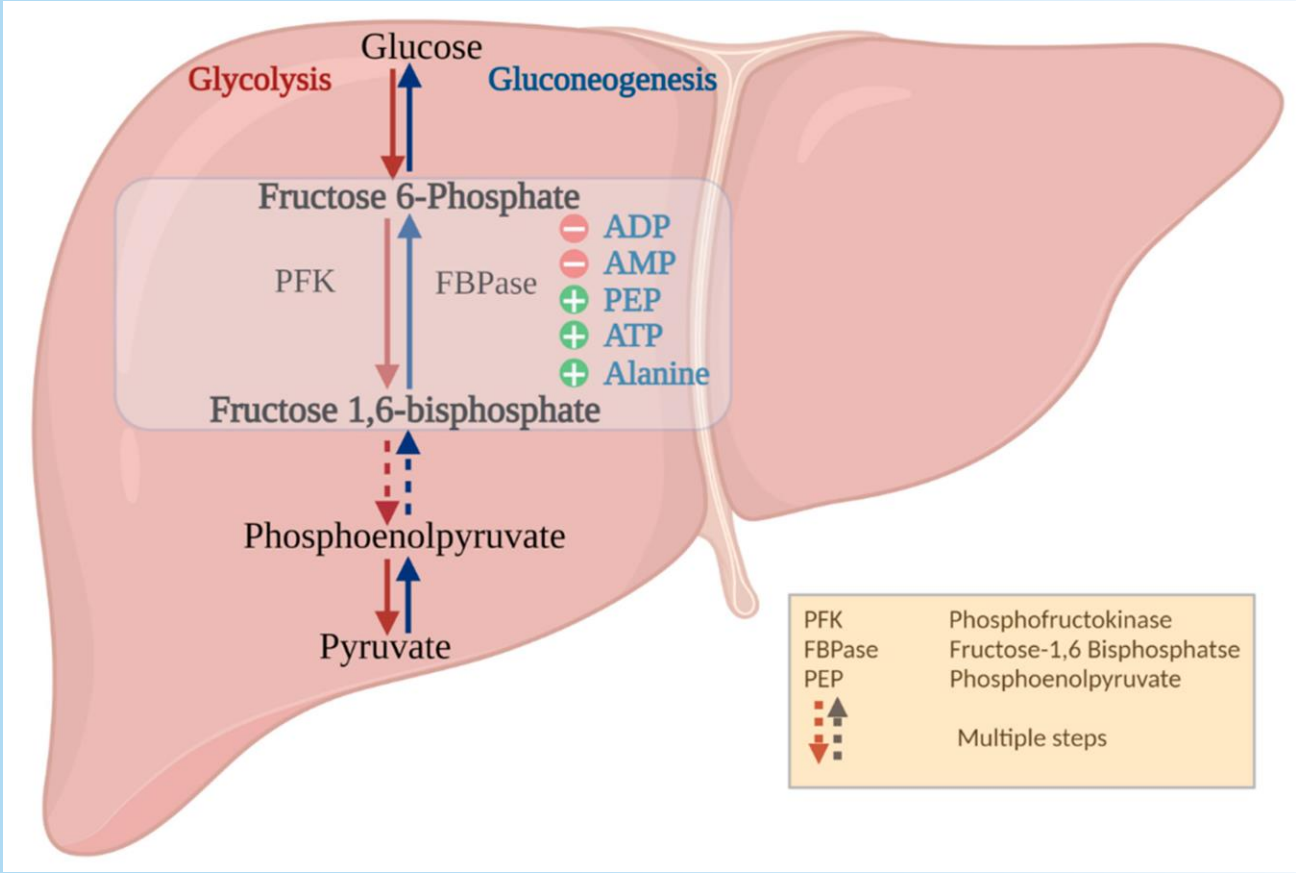
Bypasses phosphofructokinase-1

RATE LIMITING ENZYME

Inhibited by AMP & F2,6BP

Cytosol





3: Dephosphorylation of Glucose-6-phosphate

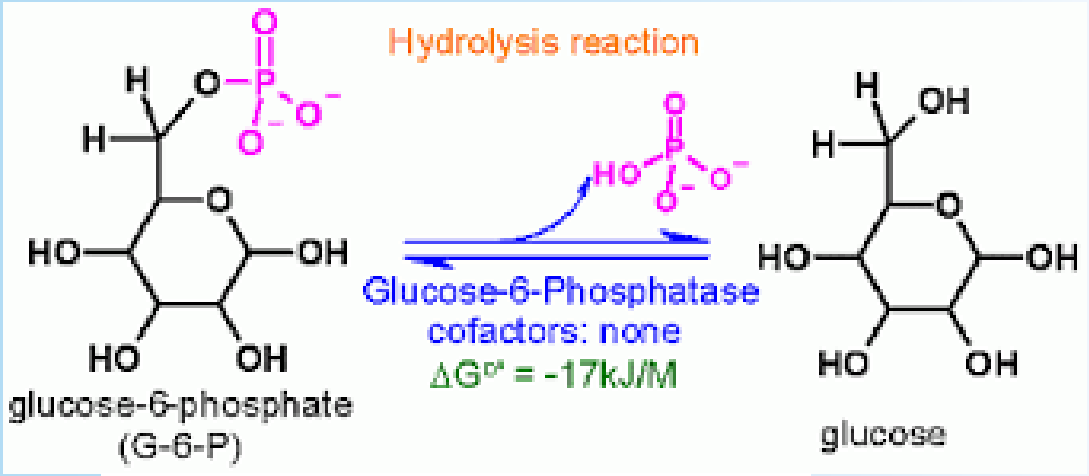
Enzyme: **Glucose-6-phosphatase**

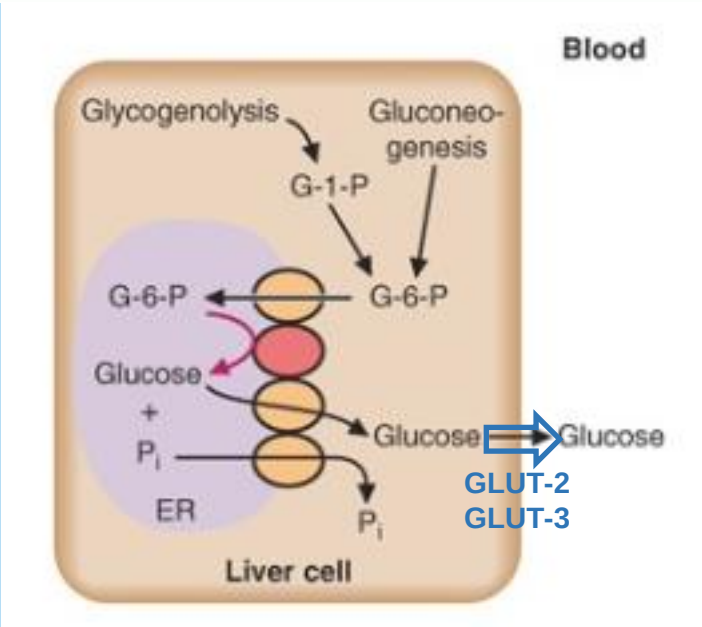
Bypasses Glucokinase

Only present in liver and kidney

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):

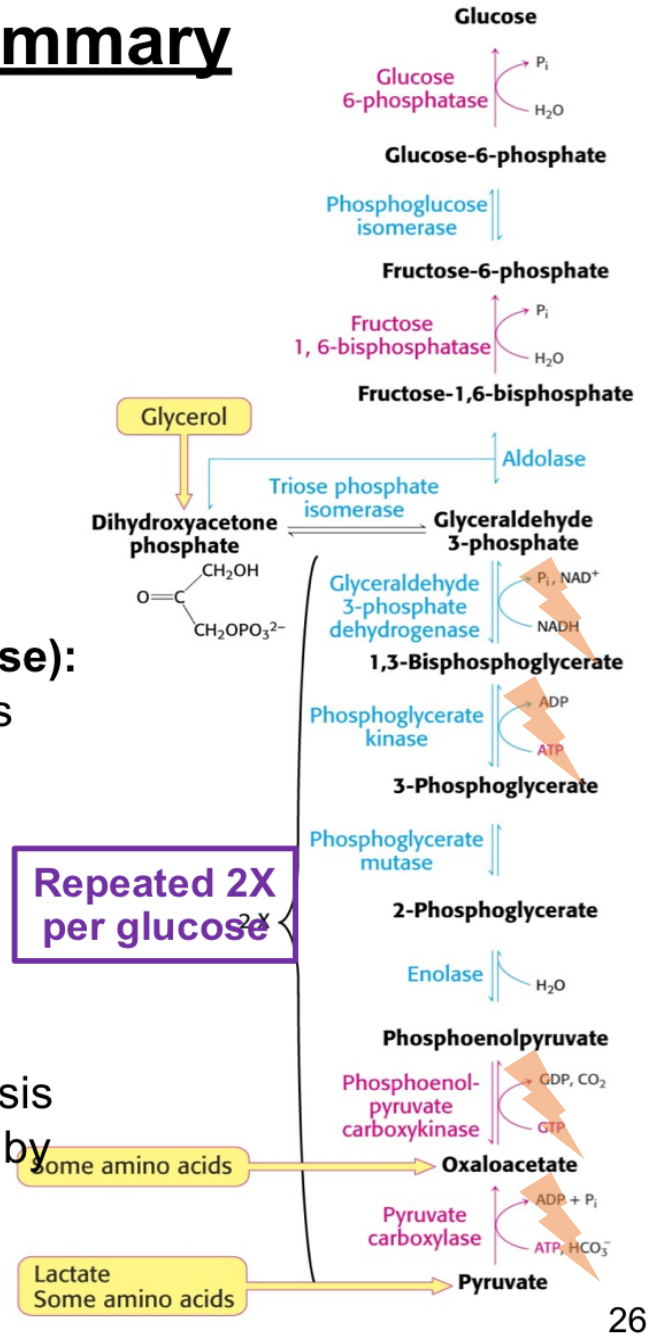
- PEP → Fructose-1,6-BP reactions shared with glycolysis
- Hydrolysis of 1 ATP & oxidation of 1 NADH
- Irreversible PFK-1 reaction bypassed by Fructose-1,6-Biphosphatase
- Glycerol enters at this step

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

Because 2x pyruvate for every glucose produced

Review of Regulation

GLUCAGON

Lowers **F2,6BP** -> activation of **F1,6-bisphosphatase** (also affected by epinephrine)

Stimulates production of cAMP → Stimulates conversion of hepatic PK to its inactive (phosphorylated form) → decreasing conversion of PEP to pyruvate → diverts PEP to synthesis of glucose

Increases transcription of **PEPCK**

Potent stimulator of the transport of glucogenic amino acids by the liver

Glucagon and epinephrine ↑↑ in response to decrease in blood glucose

SUBSTRATE AVAILABILITY

Decreased insulin favors mobilization of amino acids from muscle protein providing carbon skeleton for gluconeogenesis

Catabolism of fatty acids provides ATP and NADH required for gluconeogenesis

High amounts of **alanine** (amino acid) inhibit glycolysis at pyruvate kinase step: **"gluconeogenic signal"**

Cortisol released during stress and hypoglycemia, synthesizes more **PEPCK**, **PC**, and **F1,6-BP**

ACETYL COENZYME A

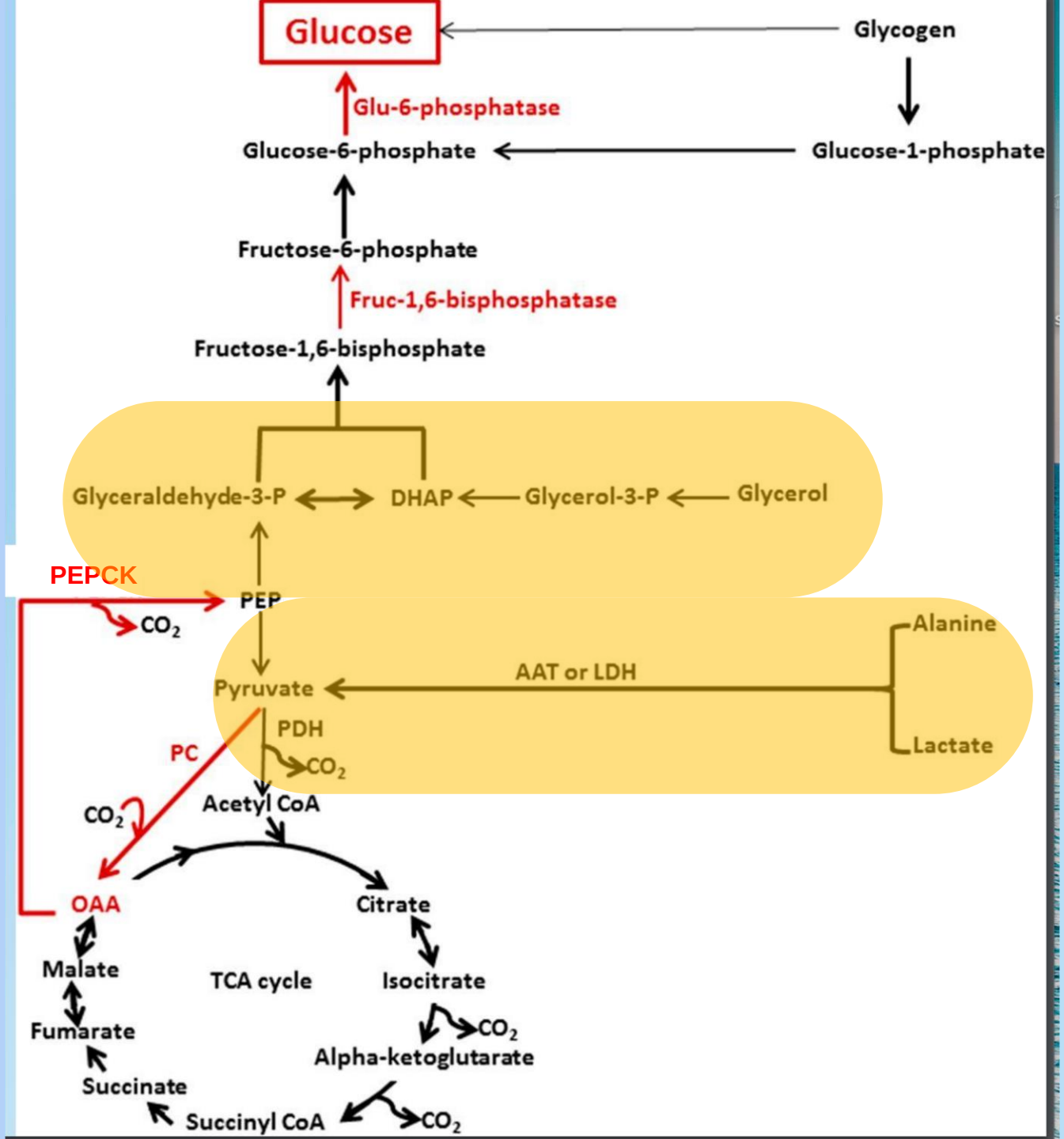
During fasting, allosteric activation of **pyruvate carboxylase** by acetyl CoA
(reciprocal inhibition of **pyruvate dehydrogenase**)
Increased lipolysis → fatty acids accumulation → lots of acetyl CoA made

AMP

- INHIBITS fructose 1,6-bisphosphatase

Gluconeogenesis	Fed state	Fasting state	Inducer	Repressor	Activator	Inhibitor
Pyruvate carboxylase	↓	↑	Glucocorticoids, glucagon, epinephrine	Insulin	Acetyl-CoA	ADP
Phosphoenolpyruvate carboxykinase	↓	↑	Glucocorticoids, glucagon, epinephrine	Insulin		
Glucose-6-phosphatase	↓	↑	Glucocorticoids, glucagon, epinephrine	Insulin		

Precursors



Lactate: provides carbon

Amino Acids: most importantly <u>alanine</u>

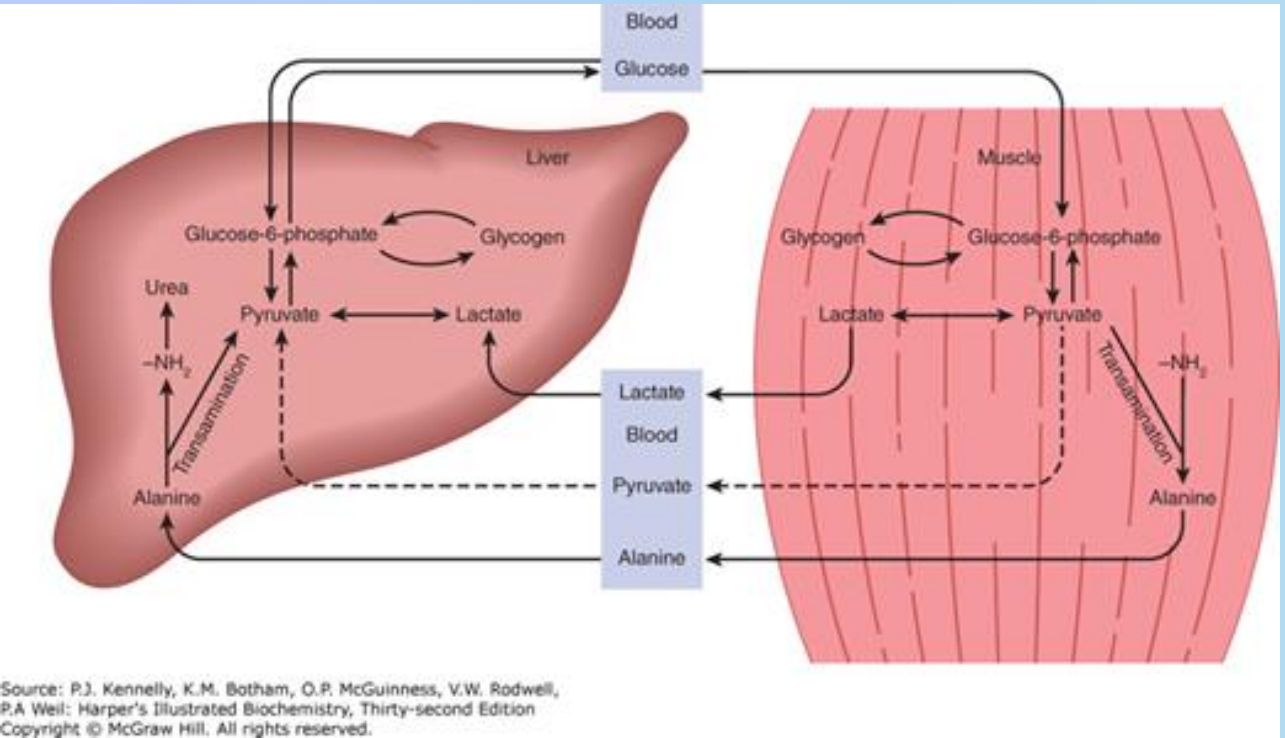
Glycerol

Lactate → Pyruvate

Muscles and RBCs (lack 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).

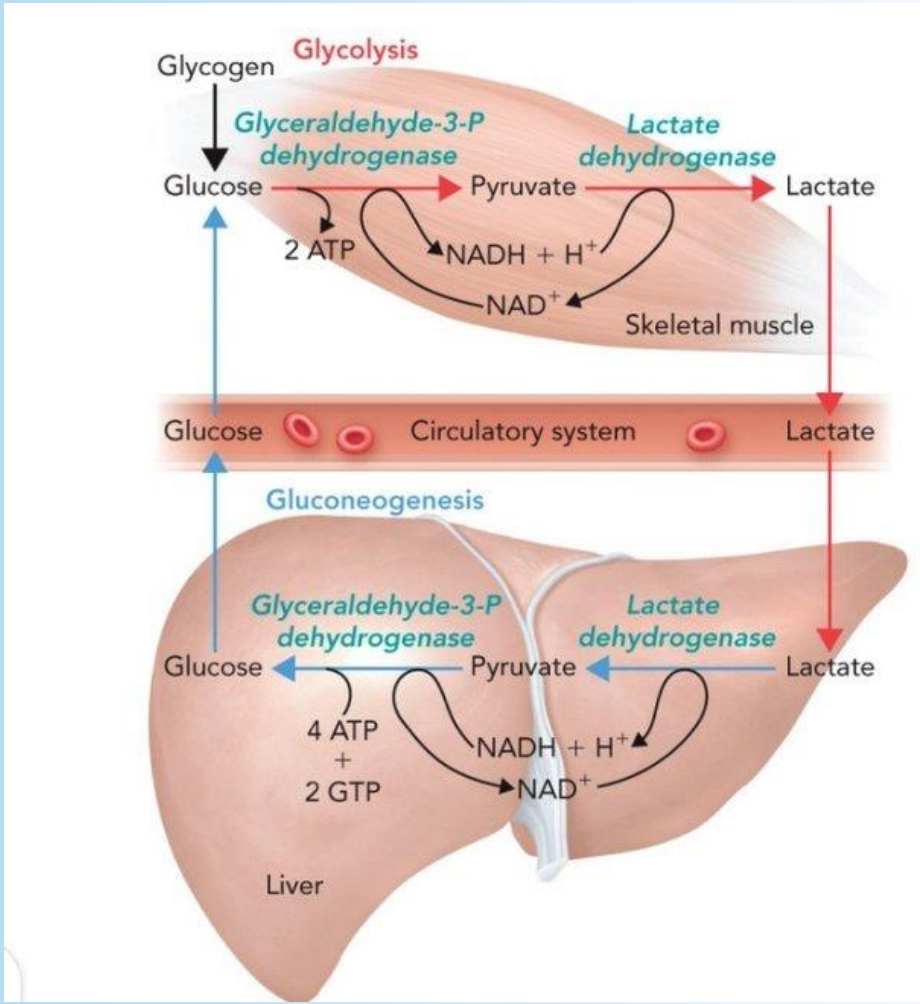
Take the lactate and turn it into pyruvate.



Source: P.J. Kennelly, K.M. Botham, O.P. McGuinness, V.W. Rodwell, P.A Weil: Harper's Illustrated Biochemistry, Thirty-second Edition

CORI

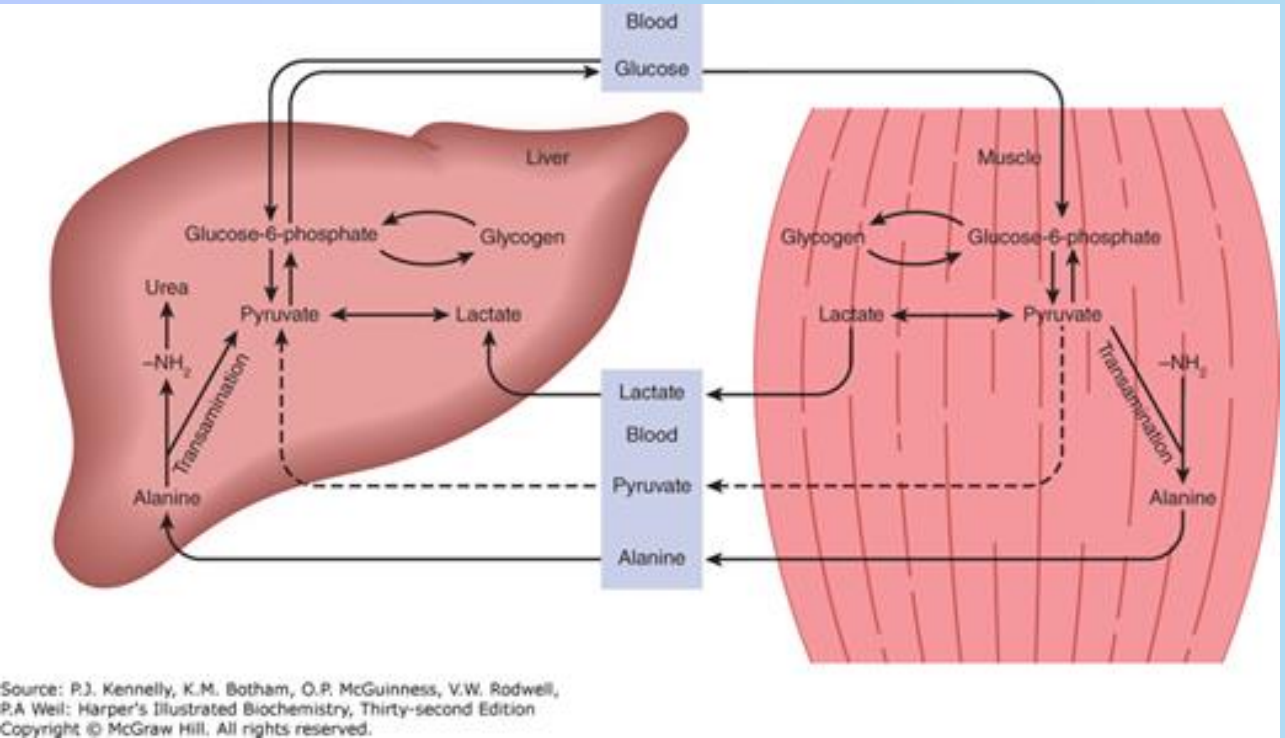
CYCLE



Glucose-Alanine Cycle

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

Excess pyruvate → alanine via ***Alanine aminotransferase (ALT)***
Alanine is transported to liver and transaminases back to pyruvate



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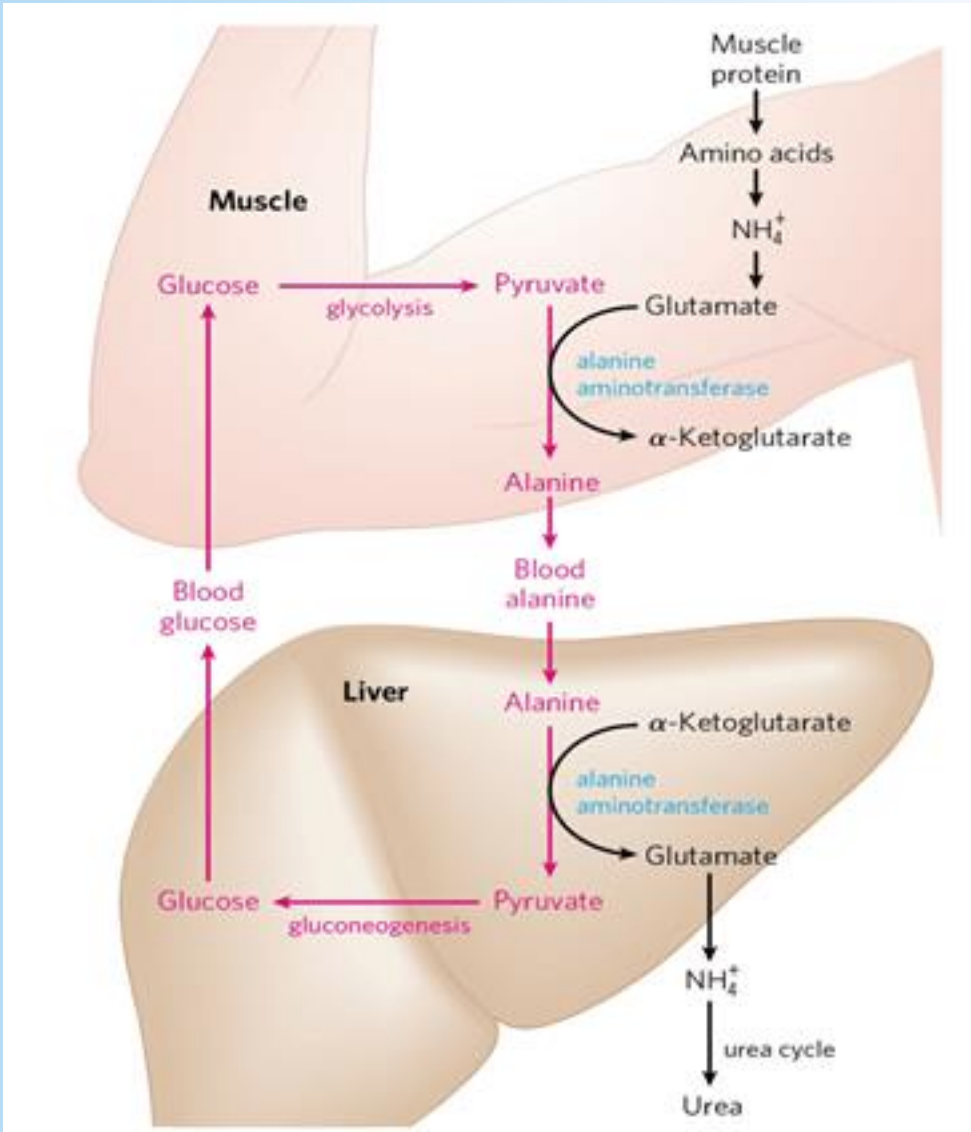
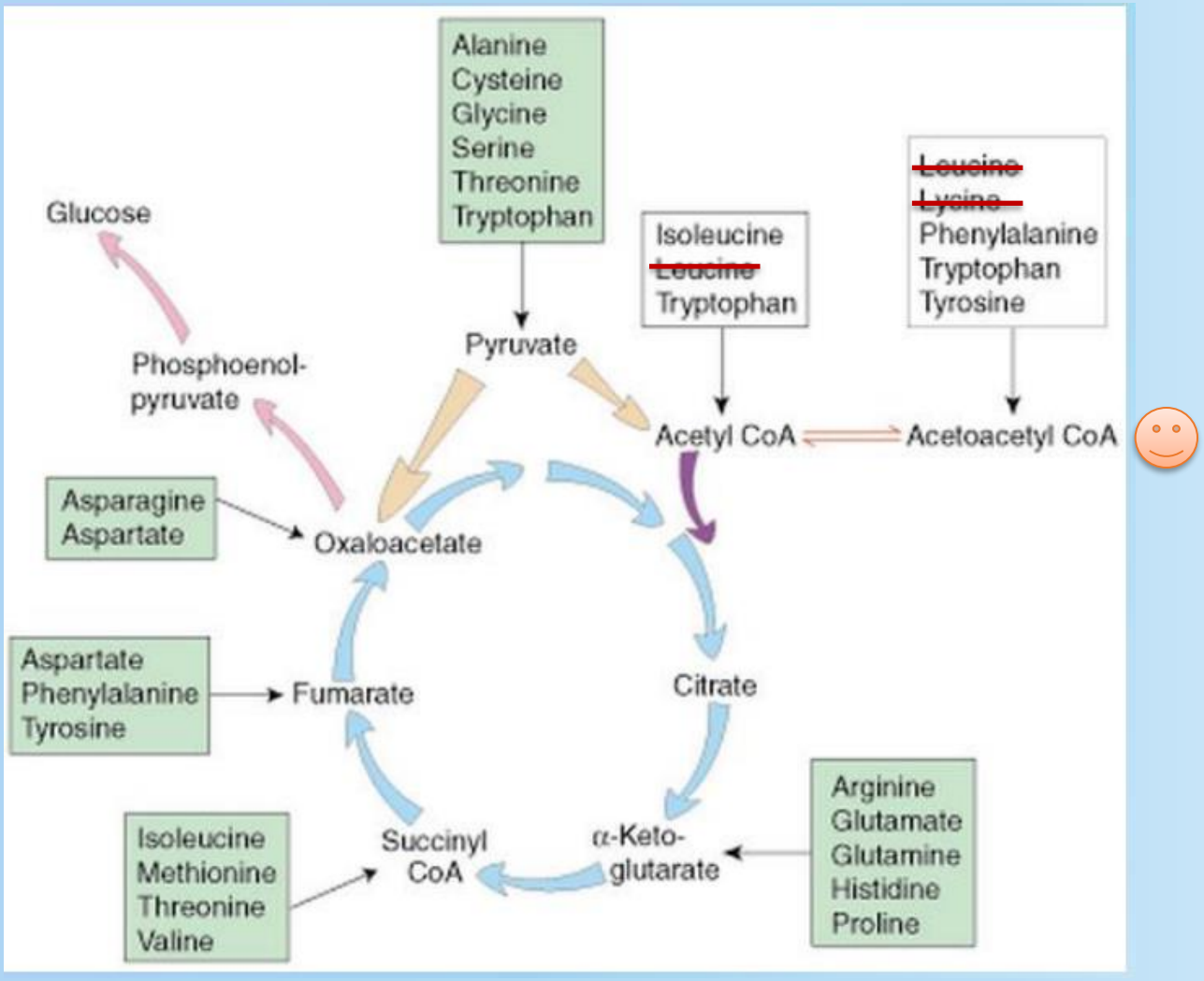
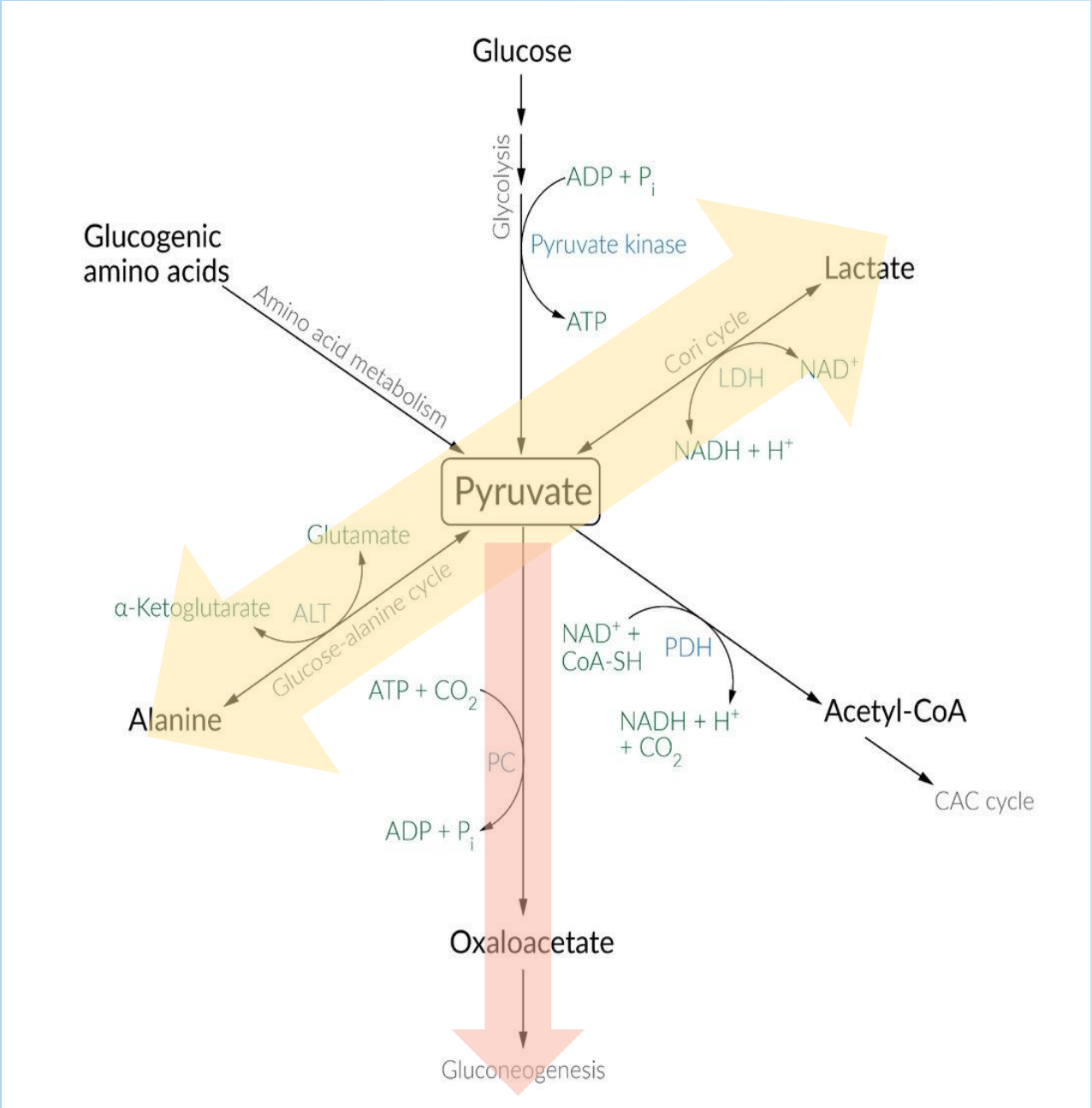


Other glucogenic amino acids




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

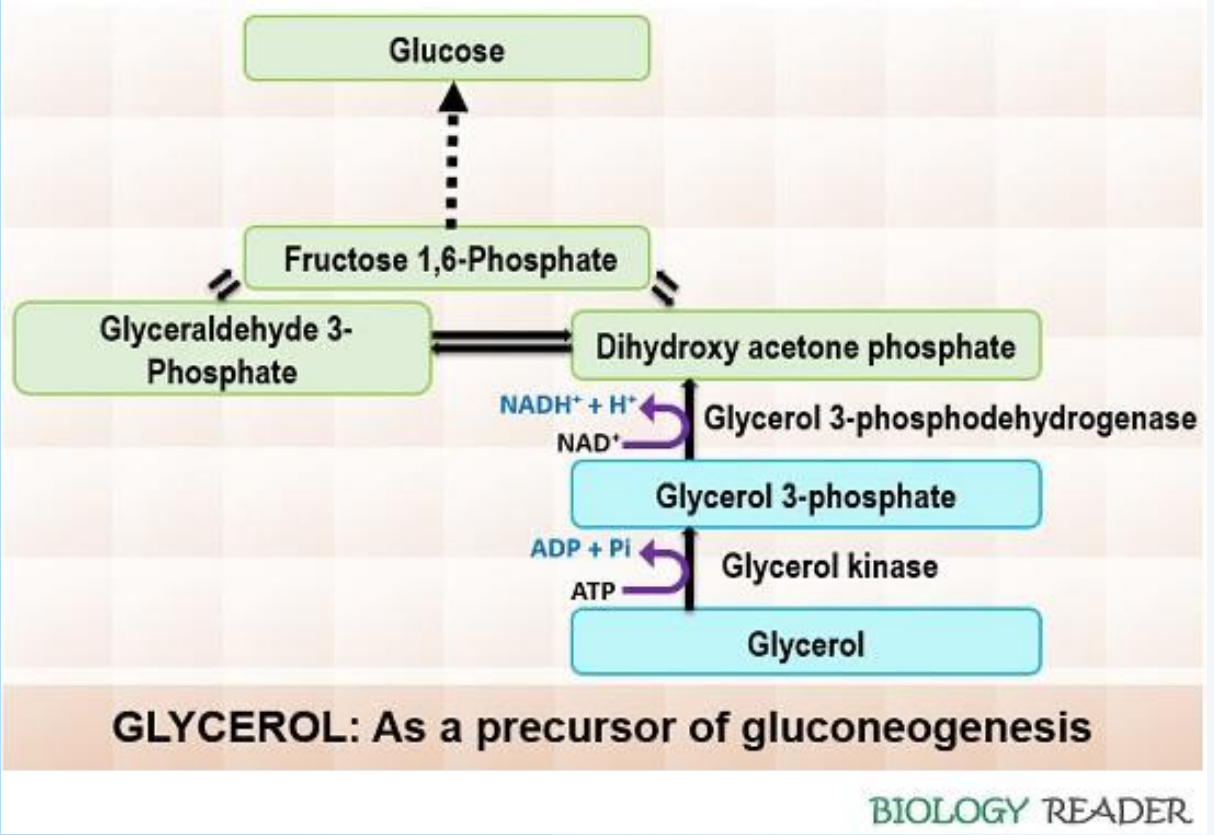
Glycerol precursor

Triglycerides undergo lipolysis providing glycerol

Glycerol kinase phosphorylates glycerol to glycerol-3-phosphate

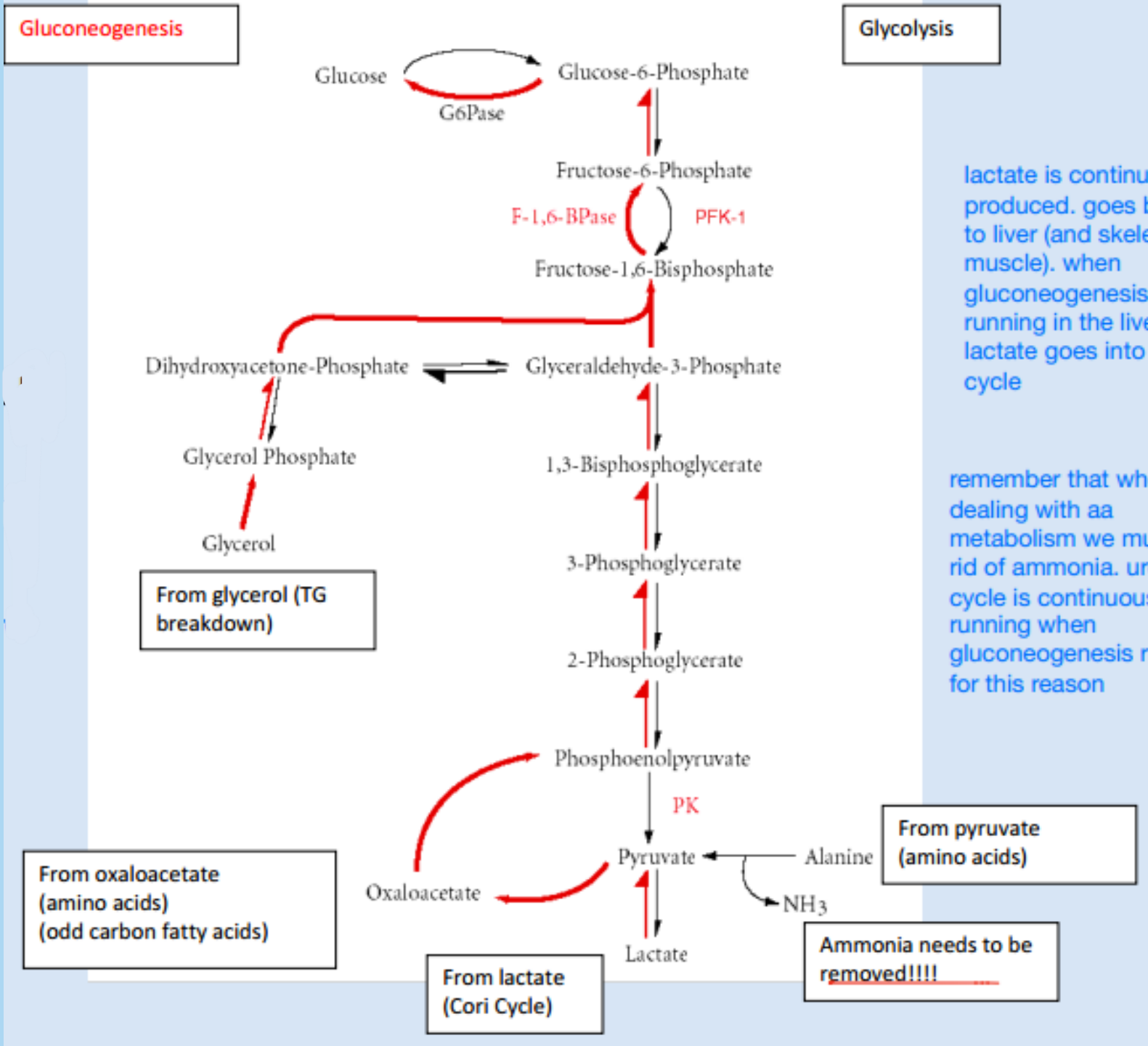
G3P gets converted to DHAP

DHAP gets converted to Fructose 1,6-bisphosphate



LIVER
(kidney)

↓ Insulin
↑ Glucagon
↑ Epinephrin



lactate is continuously produced. goes back to liver (and skeletal muscle). when gluconeogenesis is running in the liver lactate goes into this cycle

remember that when dealing with aa metabolism we must rid of ammonia. urea cycle is continuously running when gluconeogenesis runs for this reason

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FNIZPF

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BREAK

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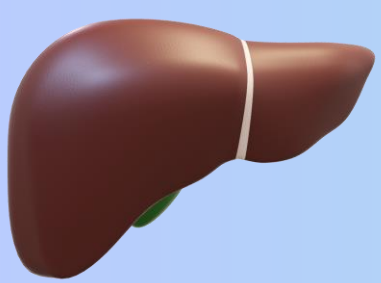
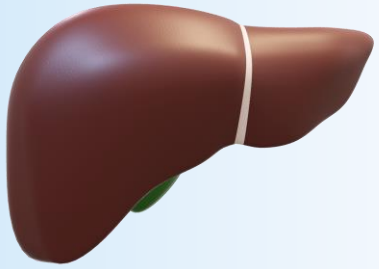
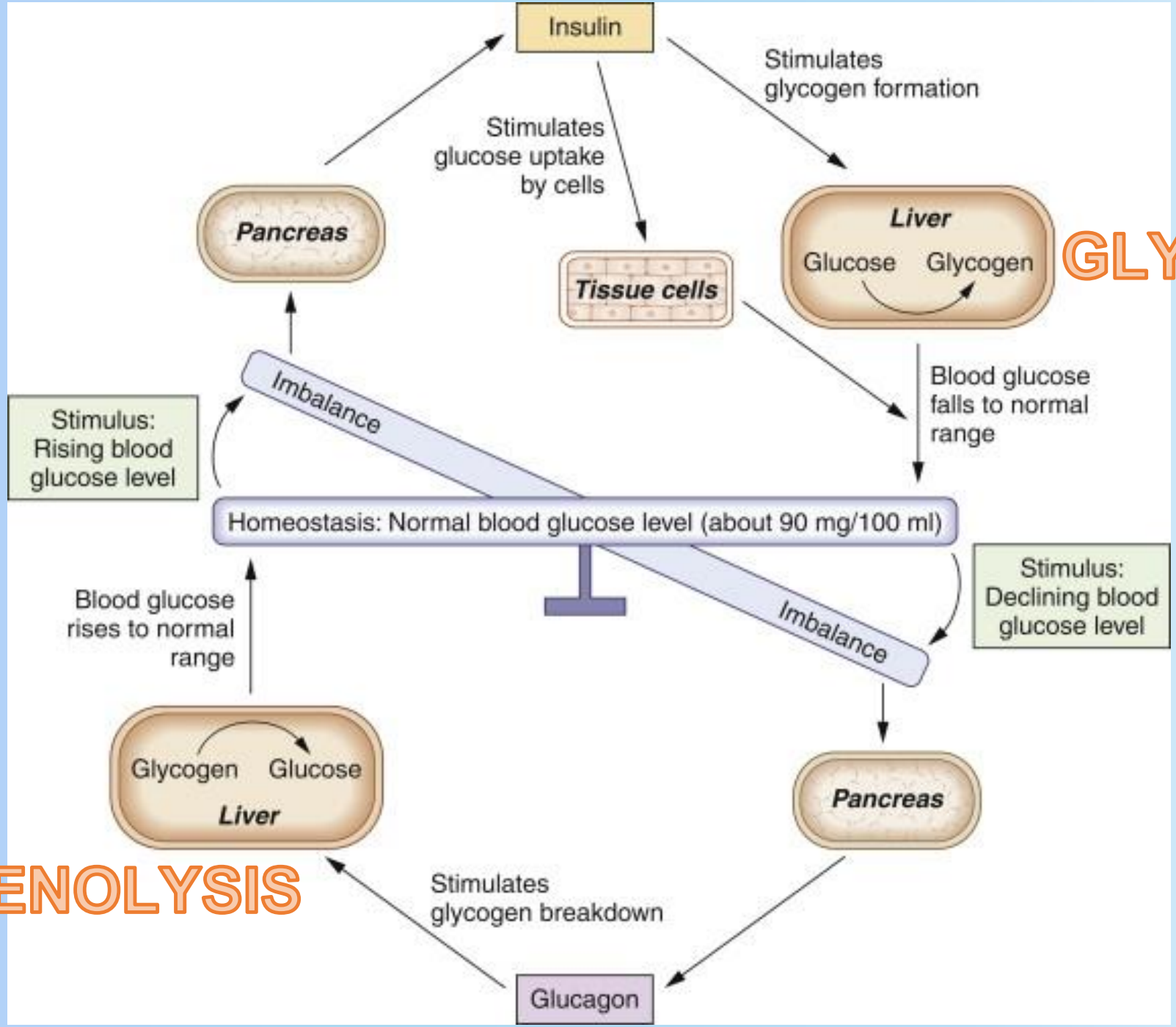
Glycogenolysis

Glycogen → Glucose





GLYCOGENESIS



GLYCOGENOLYSIS

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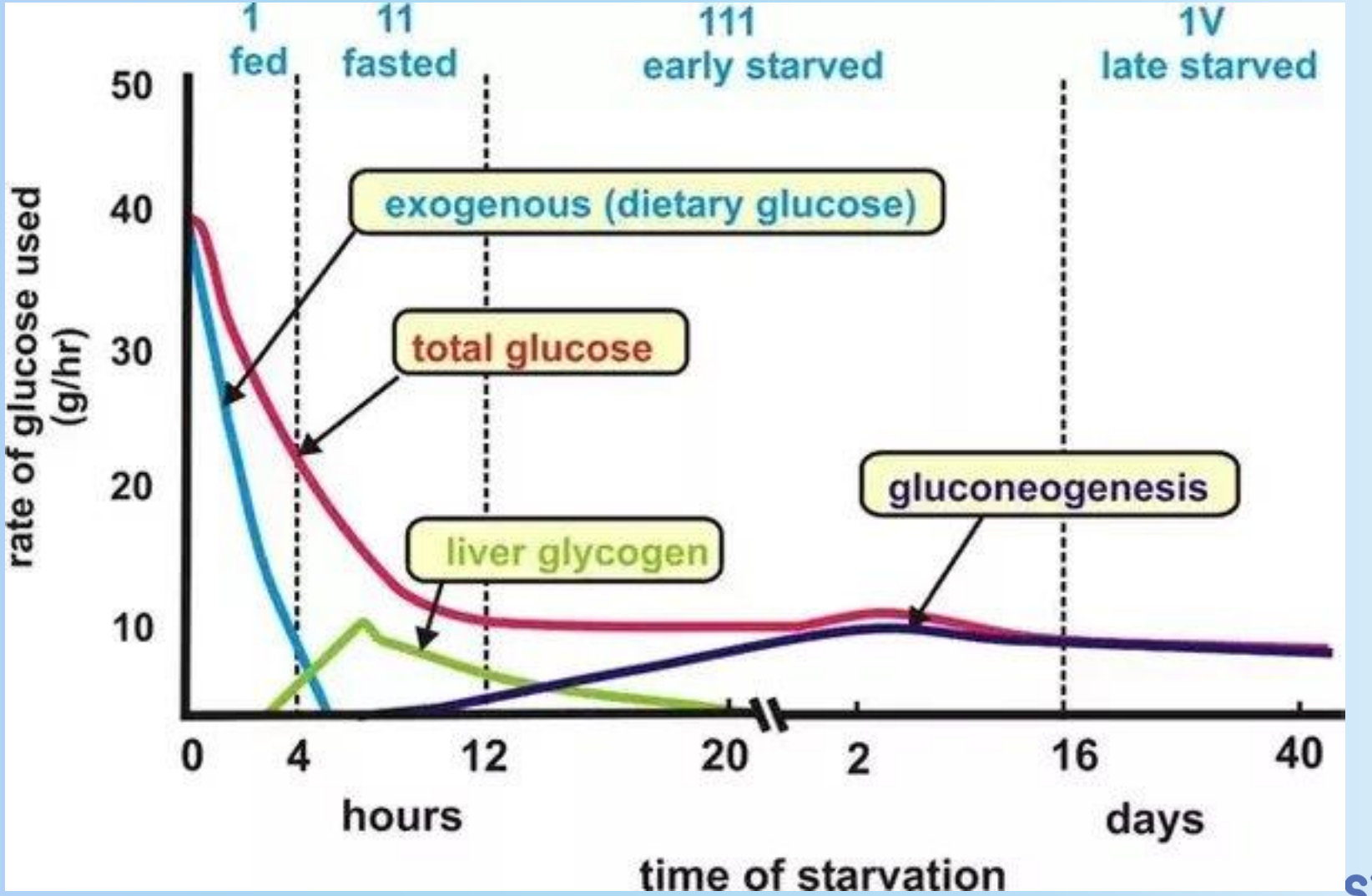
1
fed
11
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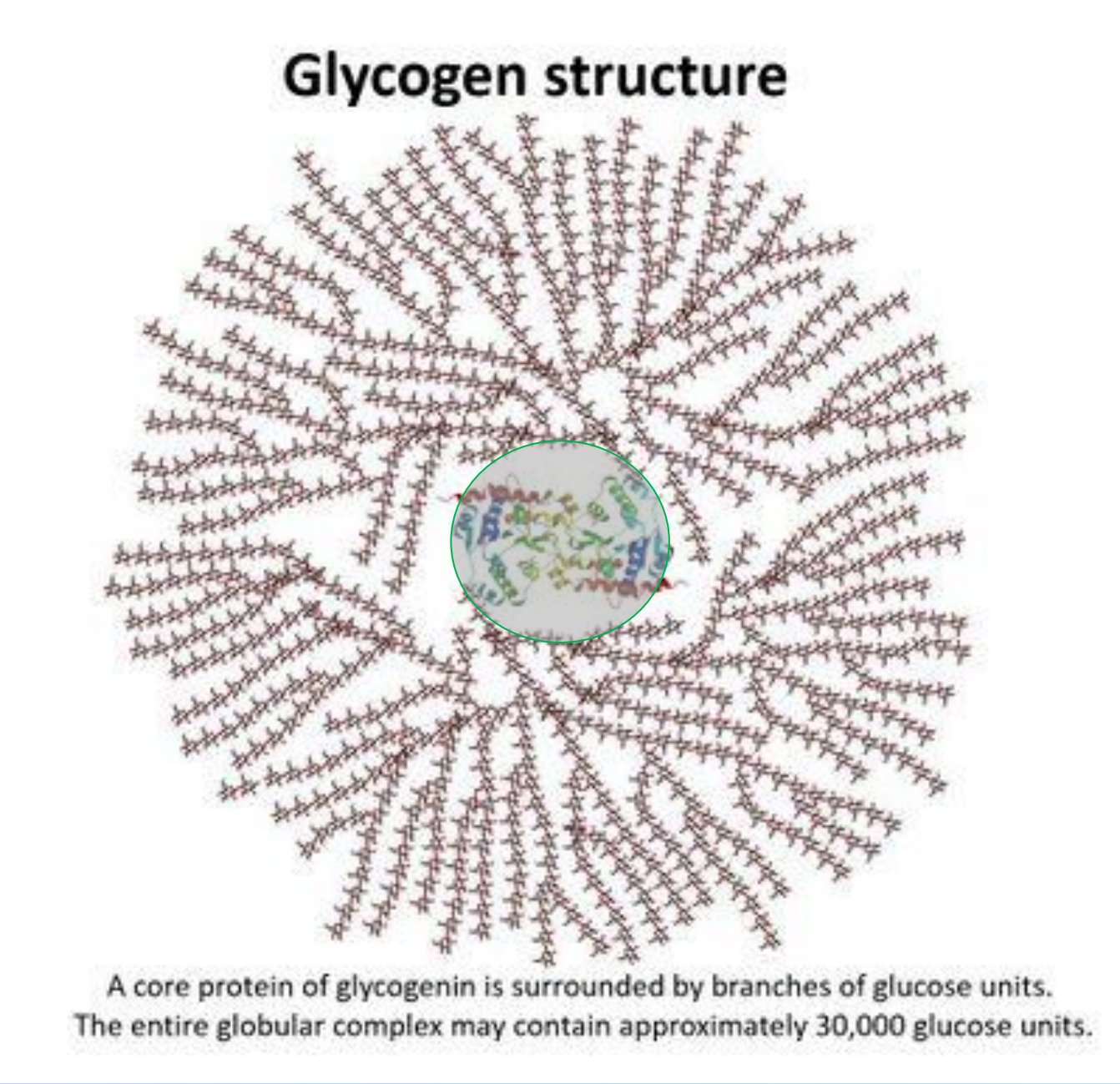
111
early starved
1V
late starved
50
40
30
20
10
rate of glucose used
(g/hr)
exogenous (dietary glucose)
total glucose
liver glycogen
gluconeogenesis
0
4
12
20
2
16
40
hours
days
time of starvation



Glycogen is smaller and more efficient to store
Higher concentration of glycogen in liver but total muscle mass is greater so 75% of total body glycogen is in muscle
Glycogen exists as granules in cell cytoplasm with enzymes for both glycogenesis and glycogenolysis.

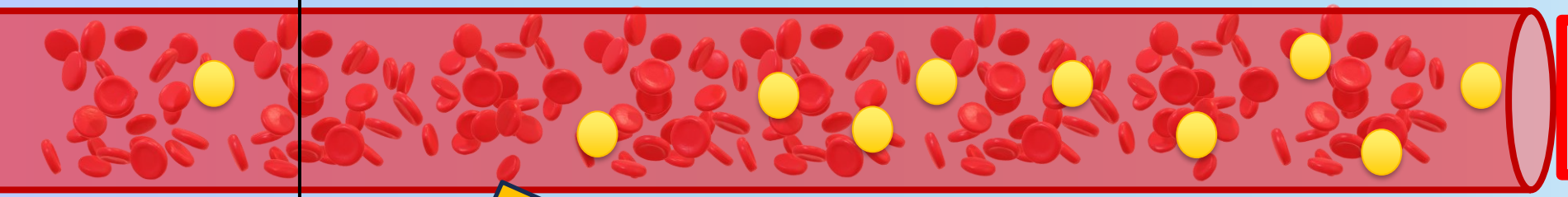
Glucose around glycogenin in
- linear α1,4 bonds
- branched α1,6 bonds

<u>Glycogen in Muscles</u>
- Provides a readily available source of G1P for glycolysis within the muscle
- Lack of **Glucose-6-phosphatase** does <u>not</u> allow for muscle glycogen to yield free glucose directly

Remember the Cori and glucose-alanine Cycles

Fasting/Starved

Make



Blood Glucose Range
70-100 mg/dL

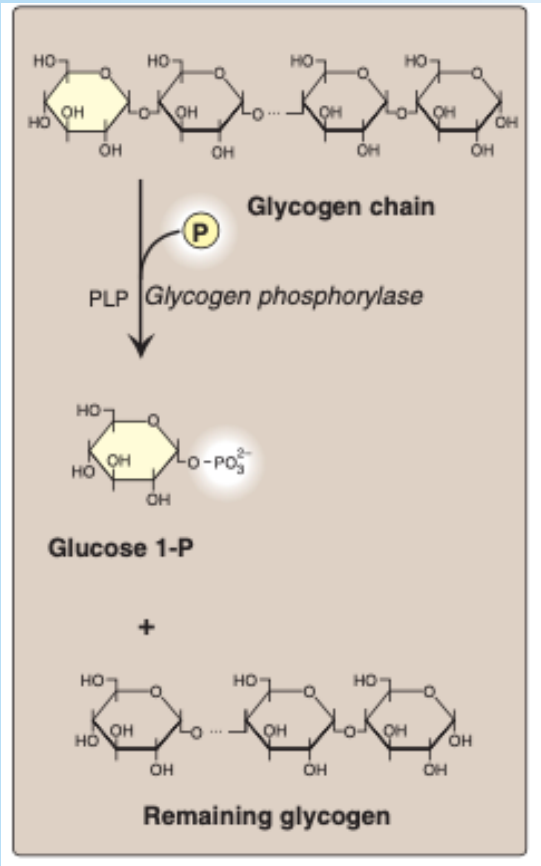
⊖ Insulin
⊕ Glucagon
⊕ Epinephrin

Glycogenolysis

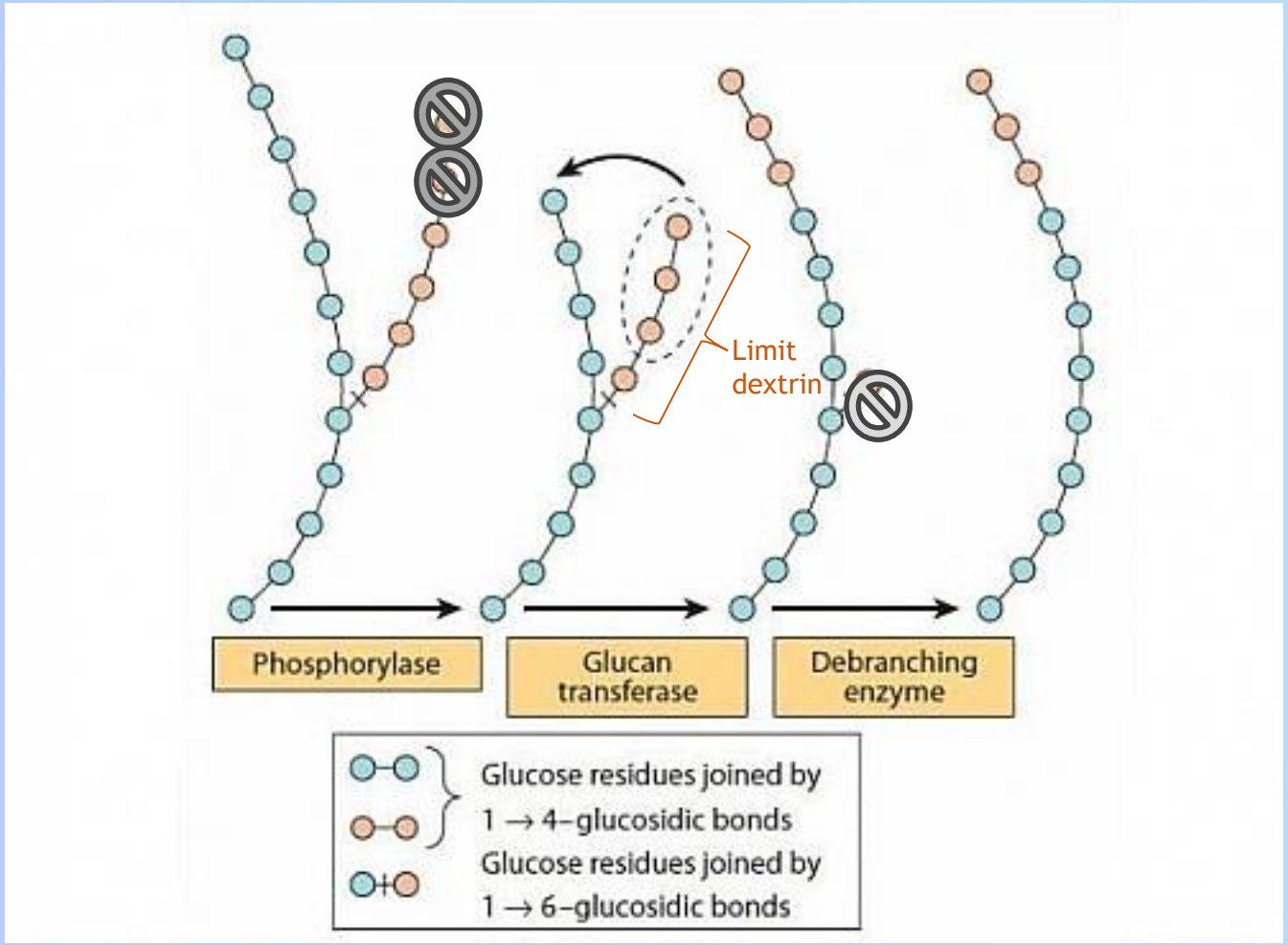
Break down glycogen → glucose

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

2. Convert G1P → Glucose



Glycogenolysis step simplified



Cleave glucose residues until 4 are left

→ Transfer over a group of 3

→ Cleave the final glucose

→ Repeat

Glycogen Phosphorylase

Type 5: McArdle's Disease
MUSCLE

Type 6: Her's Disease
HEPATIC

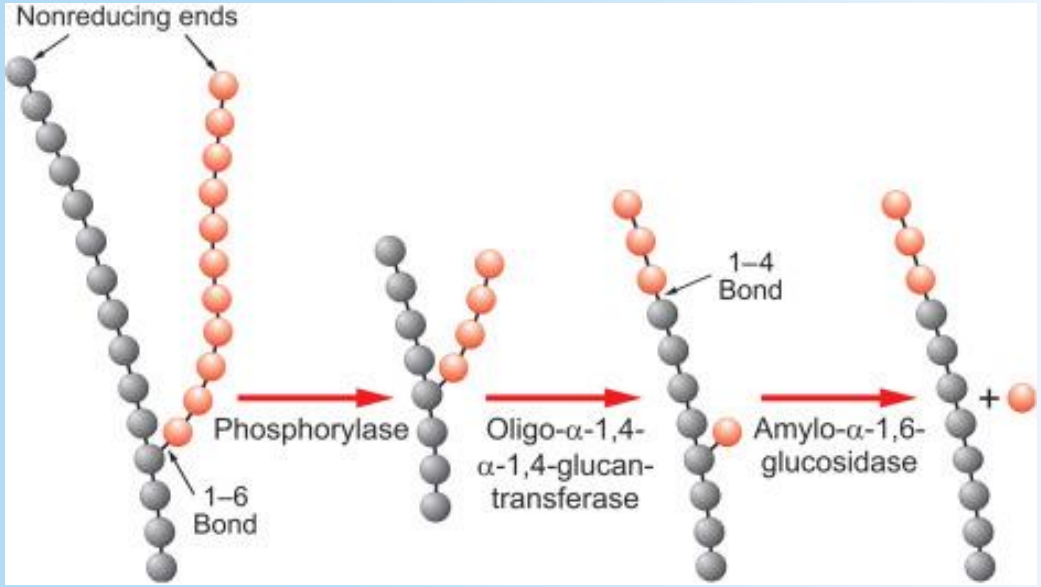
Breaks α1,4 bonds

Yields G1P

Requires a coenzyme: Pyridoxal phosphate
(derivative of B6)

Phosphate form is active

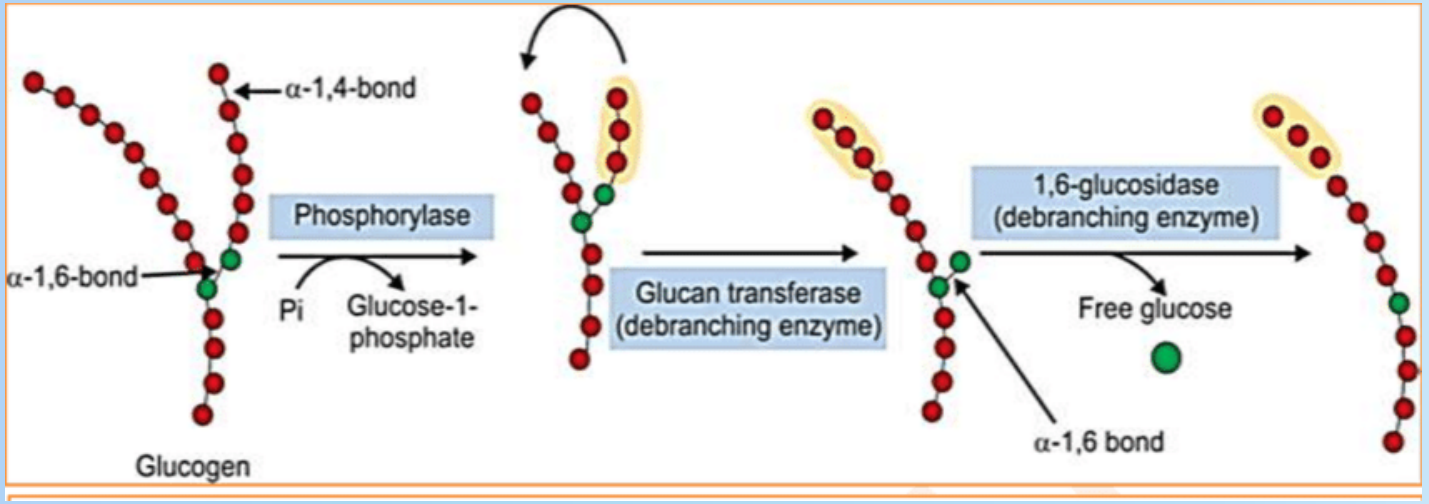
Rate limiting enzyme



Debranching enzyme

Type 3: Cori Disease

Enzyme with 2 catalytic sites

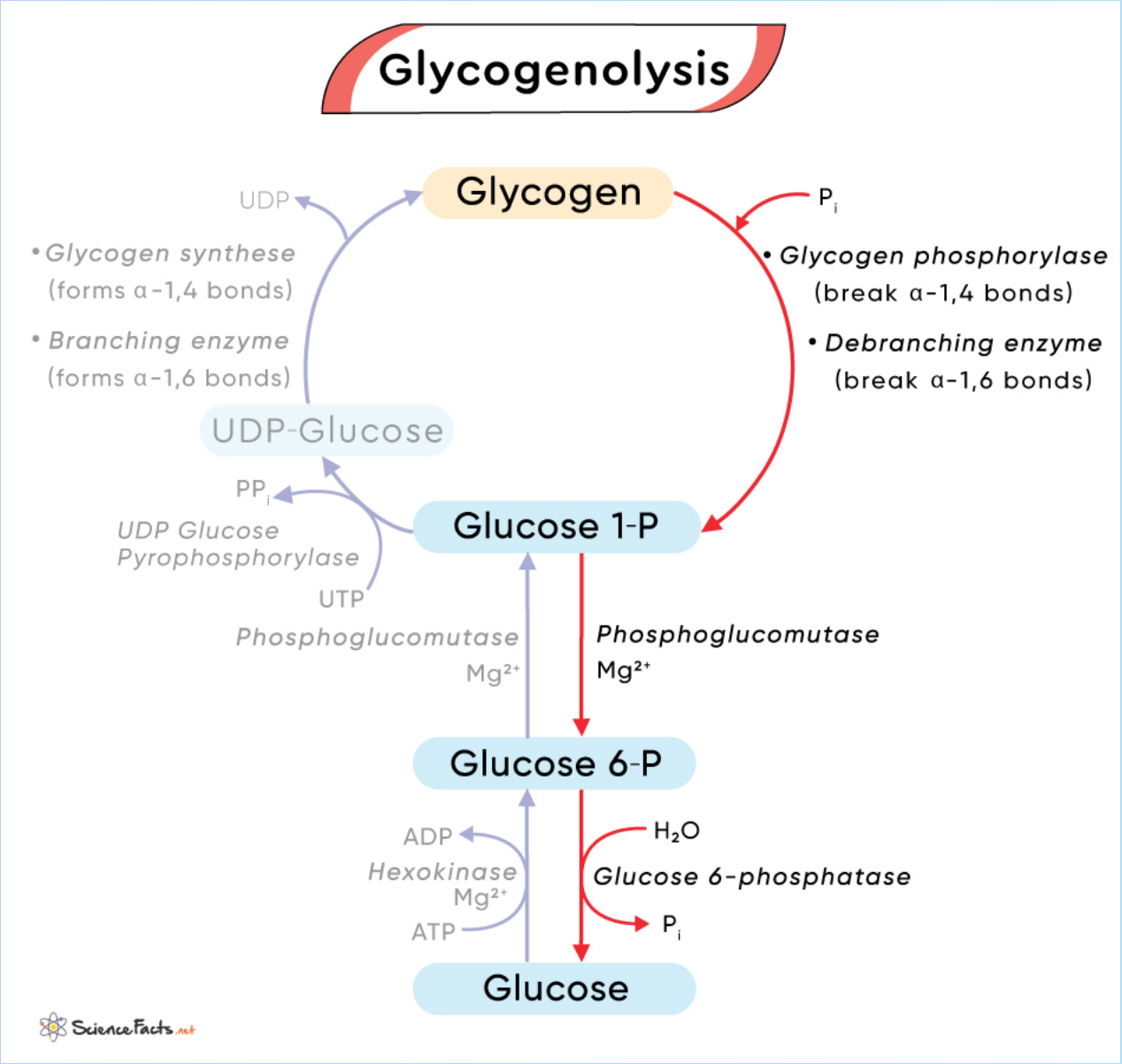


4-α-glucanotransferase Activity

- Moves trisaccharide unit

Amylo-1,6-glucosidase Activity

- Cleaves branch and leaves free glucose



Phosphoglucomutase: isomerization reaction transforming G1P → G6P

In liver, but not muscle, **glucose-6-phosphatase** catalyzes hydrolysis of G6P, yielding glucose that is exported → increase in the blood glucose concentration

Type 1: von Gierke Disease

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Glycogenesis

Glucose → Glycogen

After meal/ Fed state

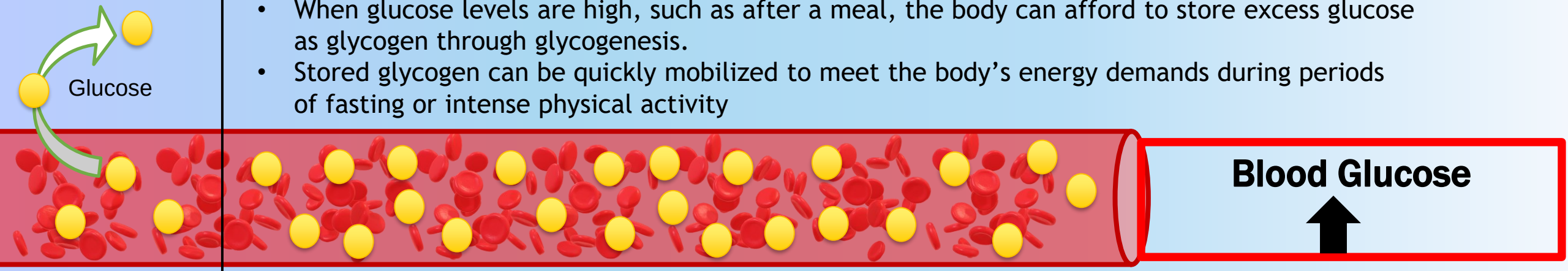
TAKE

Glycolysis (just learned)

- *the body prioritizes glycolysis to meet immediate energy demands and only engages in glycogenesis when there is an excess of glucose*

Glycogenesis

- Occurs in the liver (makes reserve for blood glucose) & muscles (for energy*)
- When glucose levels are high, such as after a meal, the body can afford to store excess glucose as glycogen through glycogenesis.
- Stored glycogen can be quickly mobilized to meet the body's energy demands during periods of fasting or intense physical activity



↑ Insulin
↓ Glucagon
↓ Epinephrin

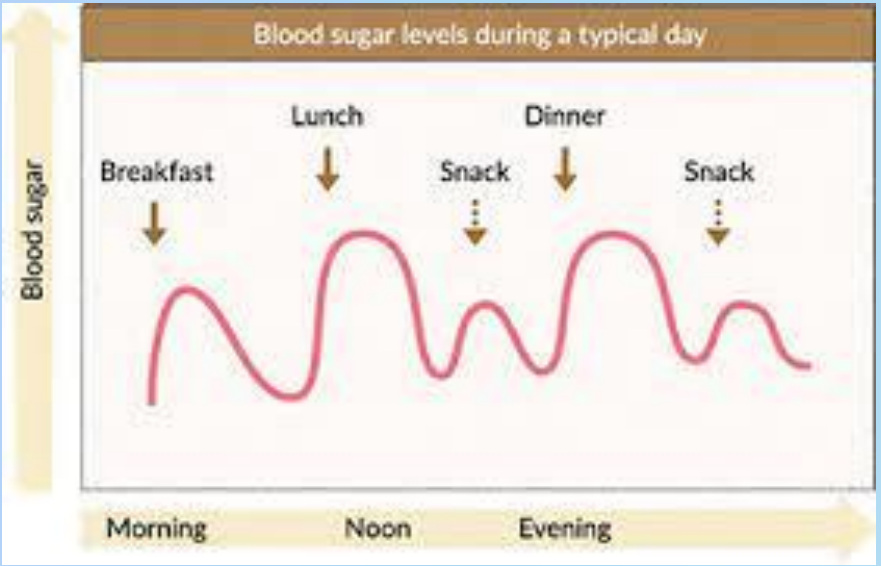


TABLE 18–1 Storage of Carbohydrate in a 70-kg Person

	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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Preparing glucose

Glucose

LIVER	MUSCLE
glucokinase	*hexokinase*

ATP

Glucose-6-Phosphate

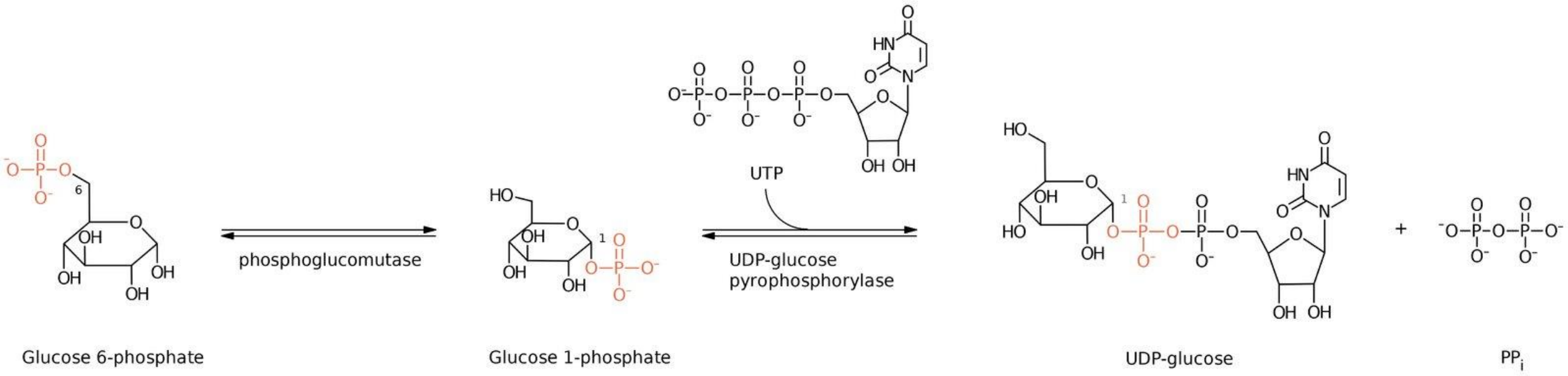
phosphoglucomutase

Moves the phosphate group

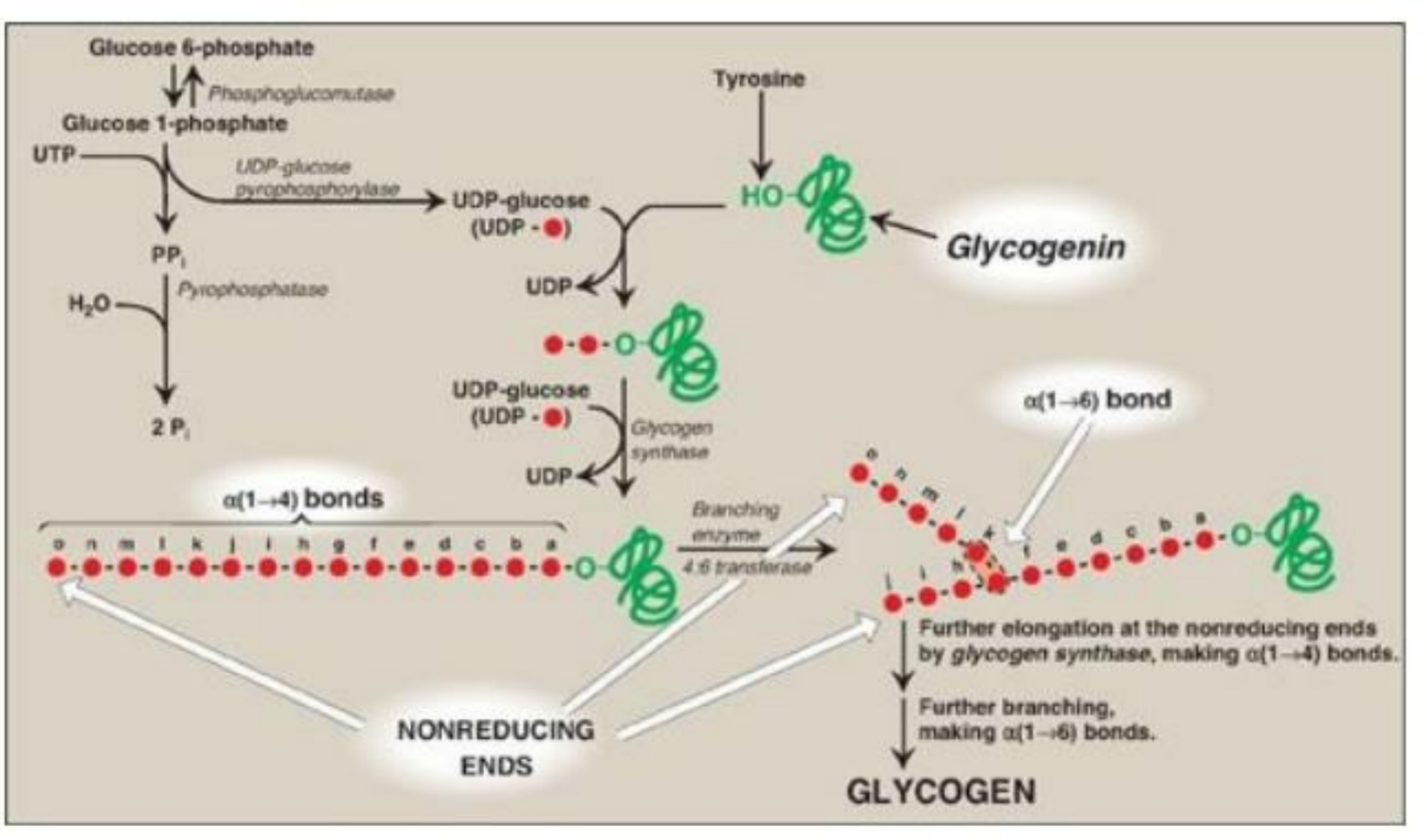
Glucose-1-Phosphate

UDP Glucose pyrophosphorylase

Glucose-1-phosphate reacts with uridine triphosphate (UTP) to form the active nucleotide **uridine diphosphate glucose (UDPGlc)** and pyrophosphate



Glycogenin



Protein and enzyme

Autoglucosylation: adds glucose onto itself

Forms a <u>glycogen primer</u> to which **glycogen synthase** can now continue adding glucose

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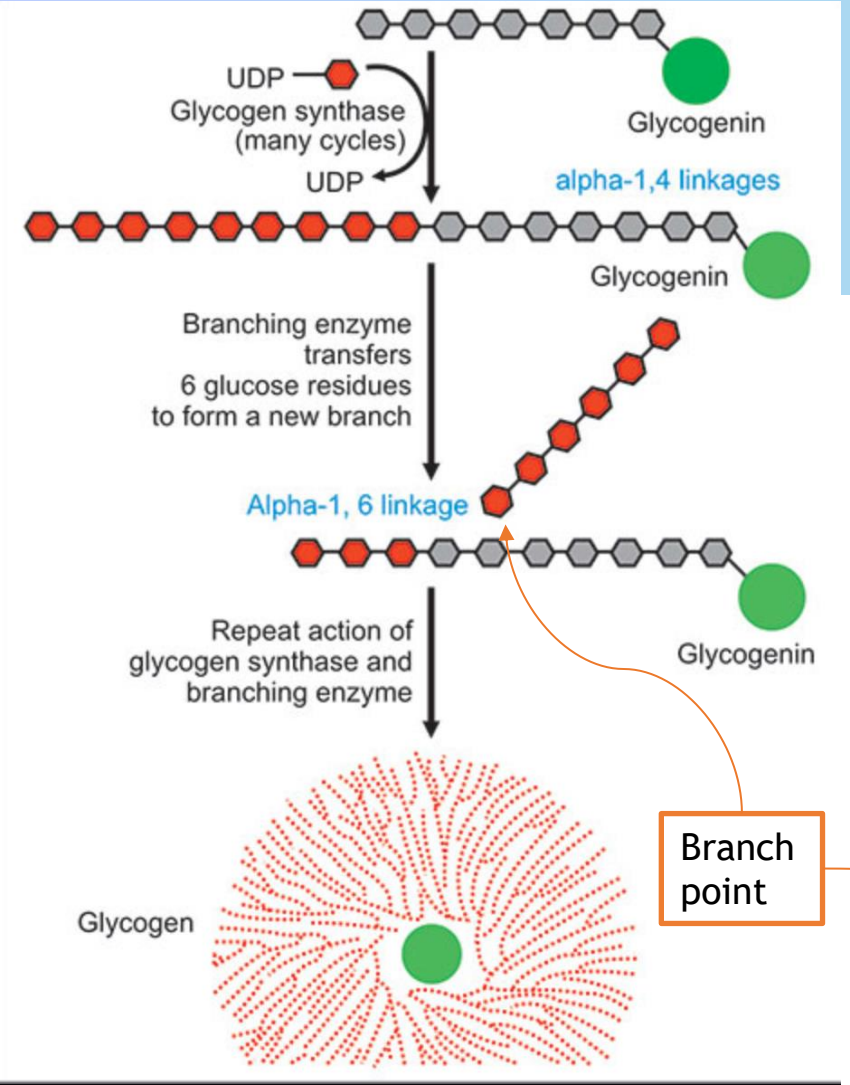
Building Glycogen

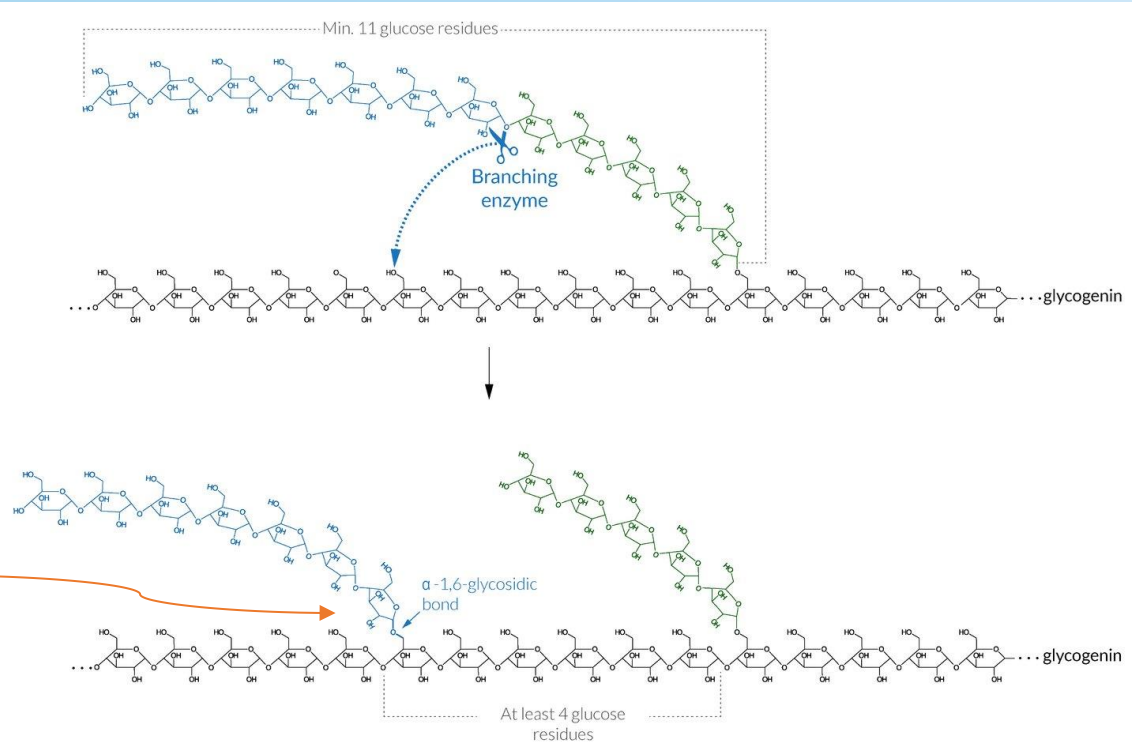
Type 0: Lewis' Disease

Glycogen synthase: glycoside bond between C-1 of UDP glucose and C-4 of the terminal glucose residue of glycogen, releasing UDP in the process

Branching enzyme: transfers a portion of the α1,4 chain (at least 6 residues) to a neighboring chain form an α1,6 linkage called a branch point
The growing chain needs to be at least 11 residues long before branching enzyme initiates this transfer.

Type 4: Anderson Disease





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 ENZYME

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

Regulation of Glycogen Metabolism

Glycogen Phosphorylase

Phosphorylation: increases activity

Epinephrine, NE, glucagon: increases formation of cyclic AMP → increased phosphorylation

Allosterically inhibited by ATP and G6P

Only in liver: free glucose is an inhibitor

Only in muscle: AMP is activator

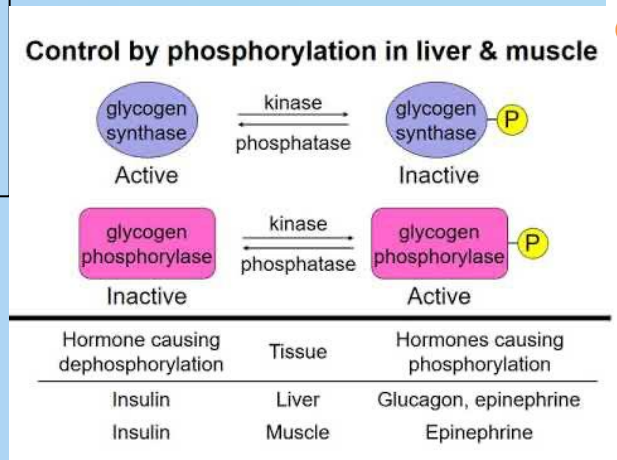
In short Ca2+ is an activator
- related to increased release of epinephrine

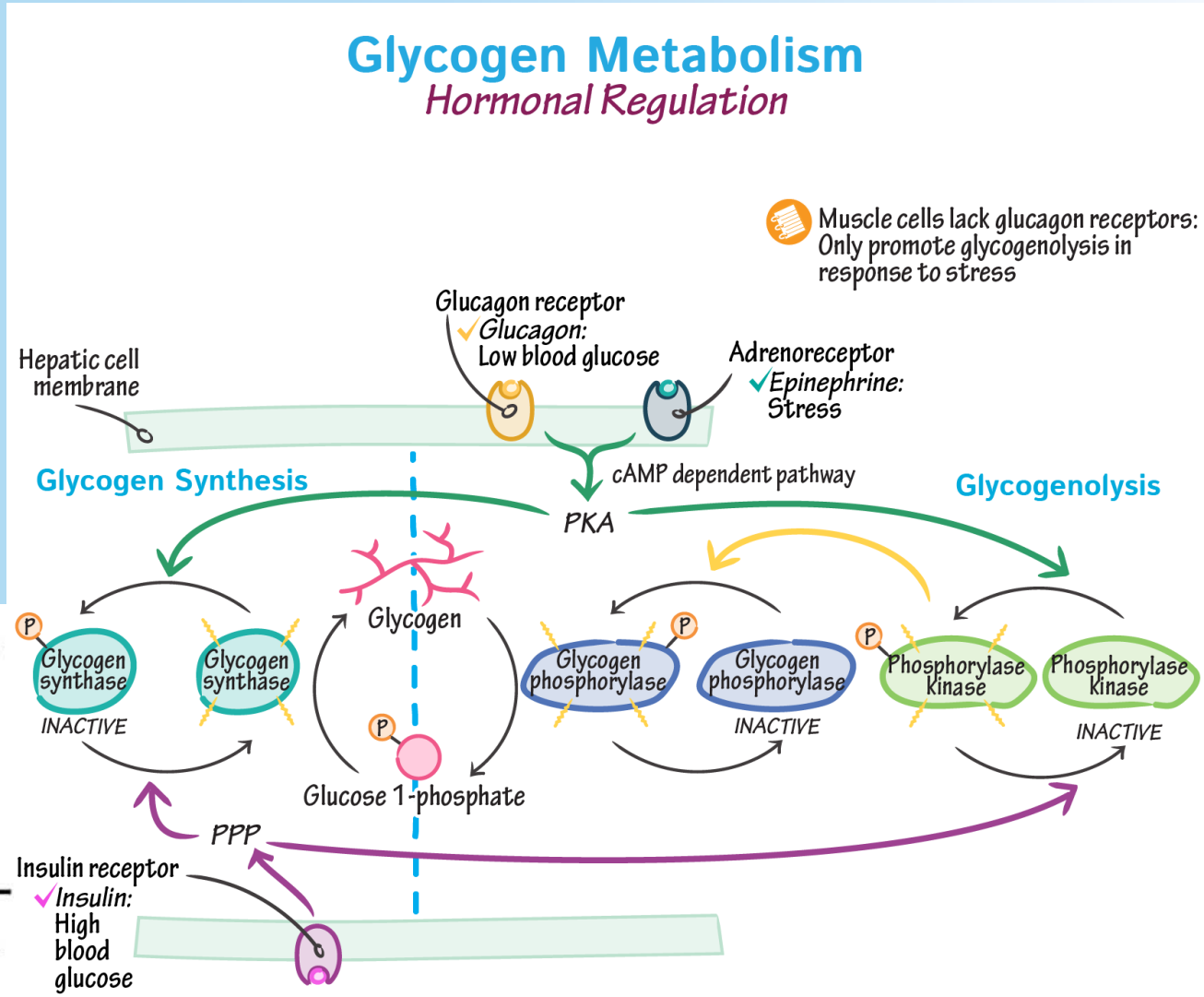
Glycogen Synthase

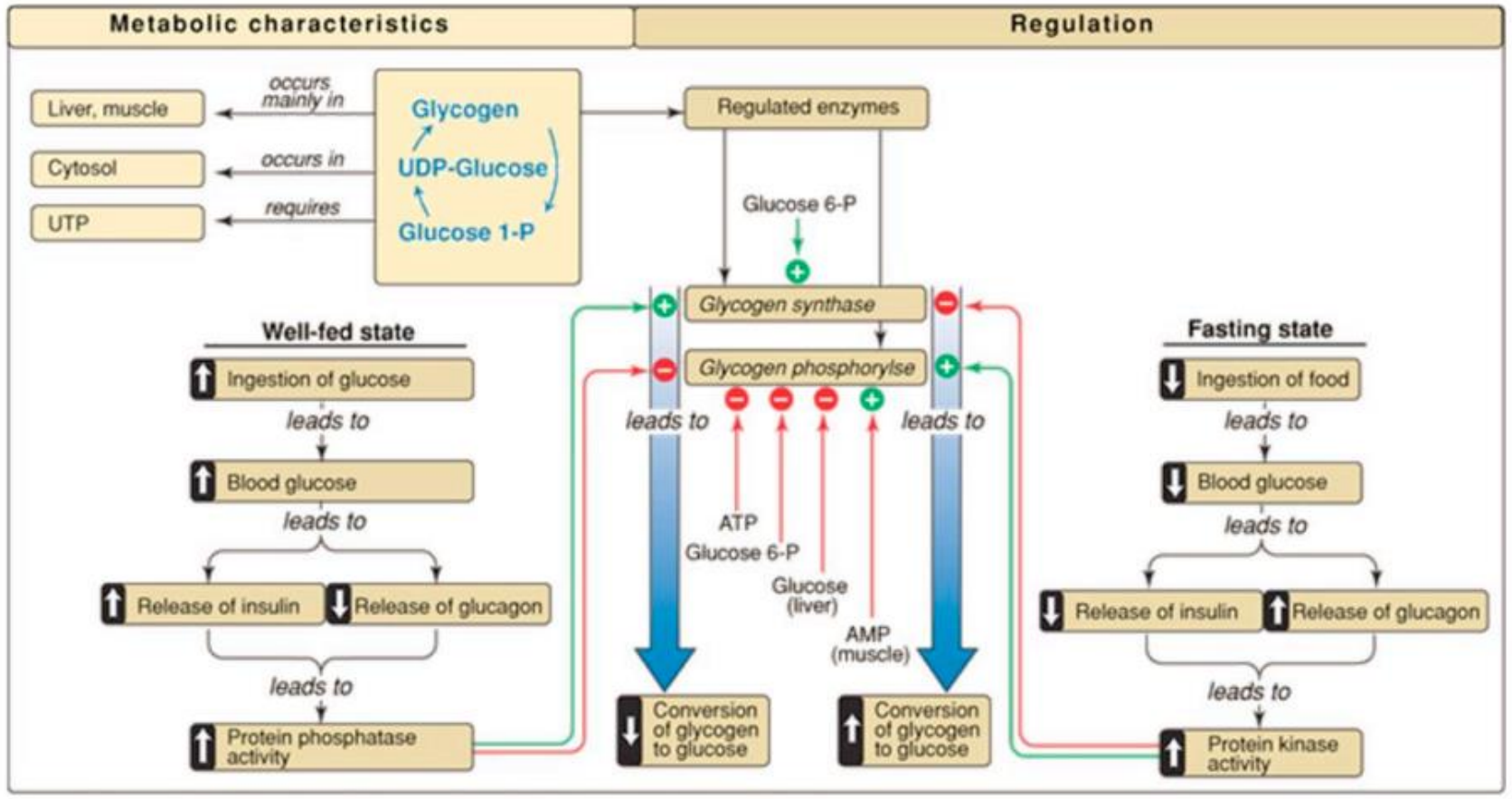
Phosphorylation reduces activity

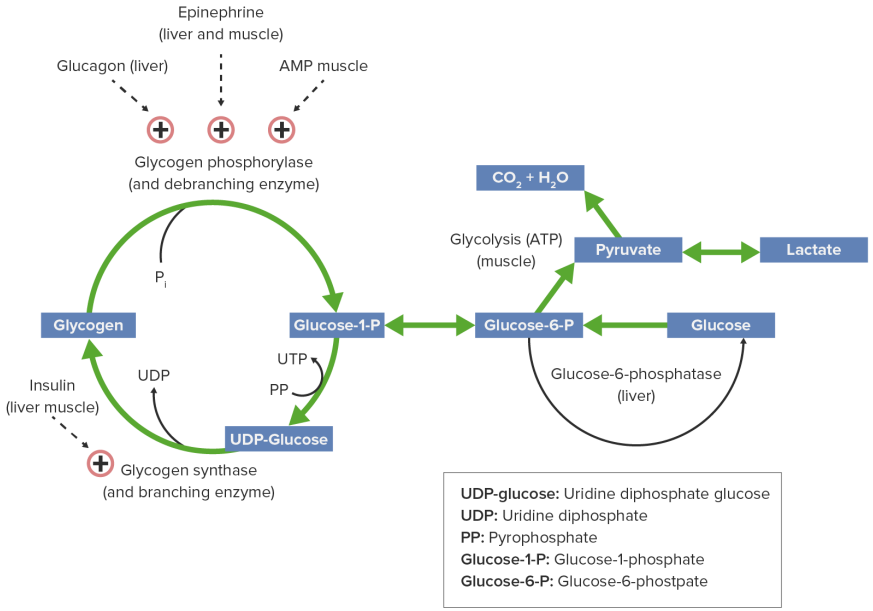
Insulin increases activity of phosphodiesterase, terminating hormone action, decreasing phosphorylation

(by decreasing phosphorylation we are **INCREASING activity**)






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
leads to
ATP
Glucose 6-P
Glucose (liver)
AMP (muscle)
Well-fed state
Ingestion of glucose
Blood glucose
Release of insulin
Release of glucagon
Protein phosphatase activity
Conversion of glycogen to glucose
Fasting state
Ingestion of food
Protein kinase activity


Epinephrine (liver and muscle)
Glucagon (liver)
AMP muscle
Glycogen phosphorylase (and debranching enzyme)
Glycogen
Glucose-1-P
Glucose-6-P
Glucose
UDP-Glucose
Insulin (liver muscle)
Glycogen synthase (and branching enzyme)
Glycolysis (ATP) (muscle)
Pyruvate
Lactate
Glucose-6-phosphatase (liver)
UDP-glucose: Uridine diphosphate glucose
UDP: Uridine diphosphate
PP: Pyrophosphate
Glucose-1-P: Glucose-1-phosphate
Glucose-6-P: Glucose-6-phostpate

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Glycogen Storage Diseases

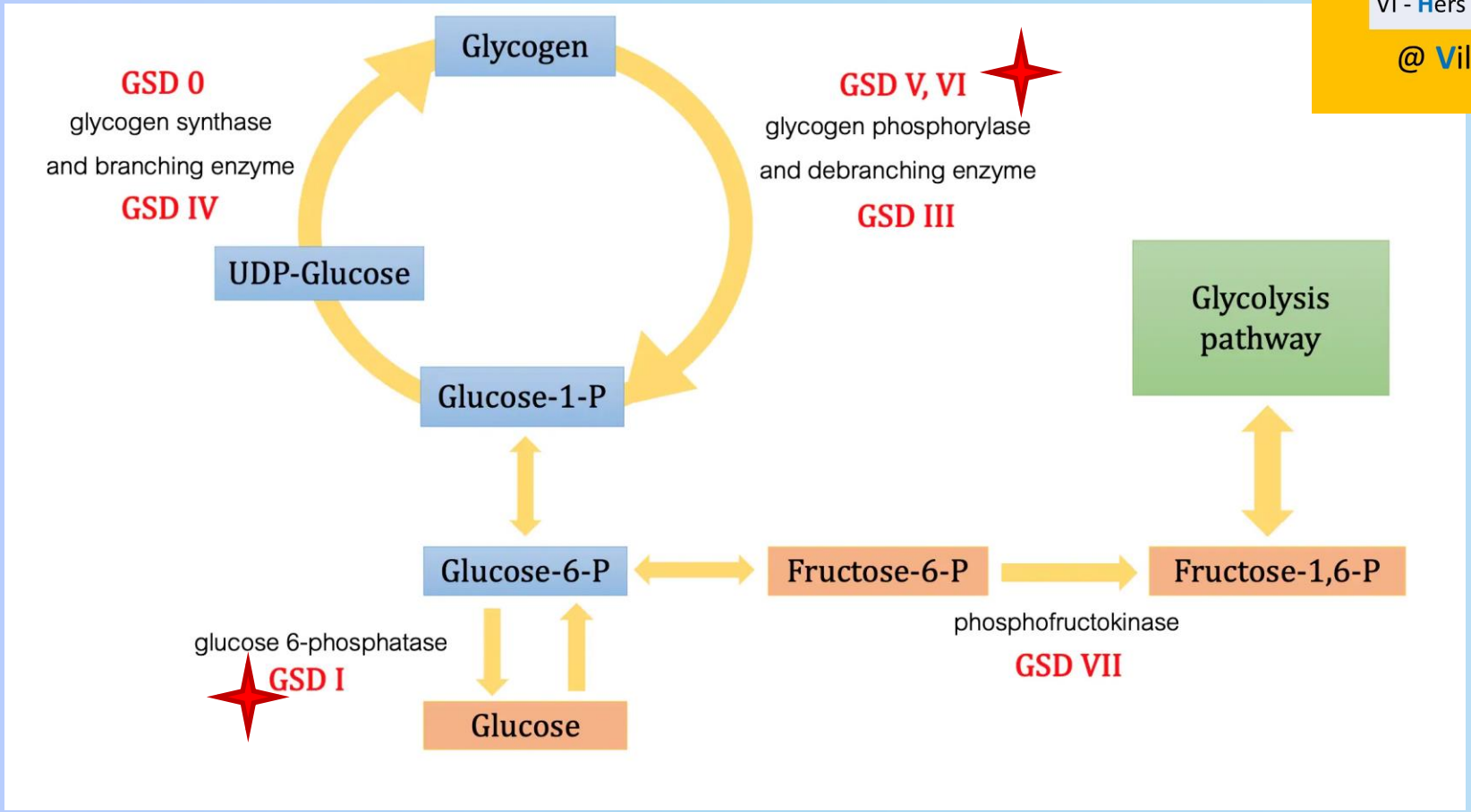
Glycogen Storage Disorders

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 0: Lewis' disease

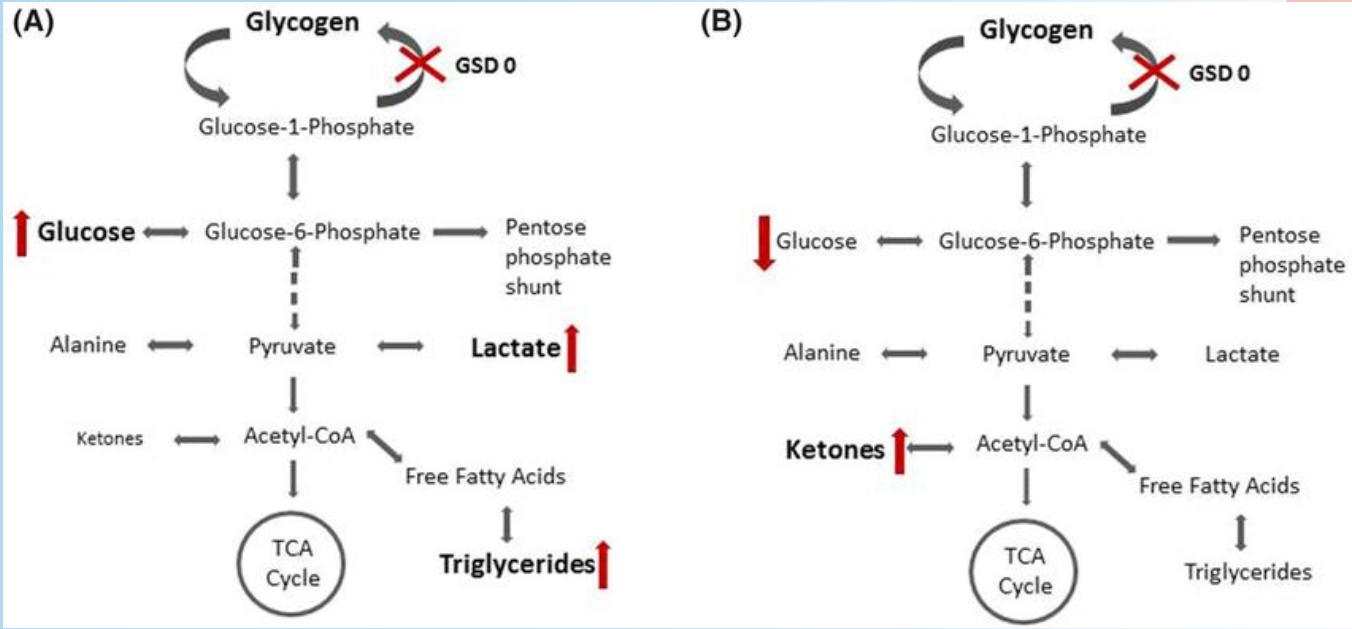
Glycogen synthase deficiency

Muscle: GYS1 Liver: GYS2

Genetic defect causing decreased or absent activity of the enzyme and moderately decreased amounts of structurally normal glycogen in the liver

Causes: fasting hypoglycemia, high blood ketones, and increased fatty acids and lactate, and low levels of alanine.

- Limited glycogen stores and inadequate gluconeogenesis
- Excess glucose is converted to lactate via glycolytic pathway



Type I: Von Gierke Disease

Glucose-6-phosphatase deficiency

Glucose can't be made; buildup of G6P

Autosomal recessive (both parents have to be carriers)

Deficient in liver, kidney and intestinal mucosa

Ia: deficiency of glucose-6-phosphatase

Ib: deficiency in a translocase

- Glycogen and fat accumulate in liver → hepatomegaly
- No glucose = hypoglycemia
- Hyperuricemia, hyperlipidemia (fat/protein catabolism)

Type II: Pompe Disease

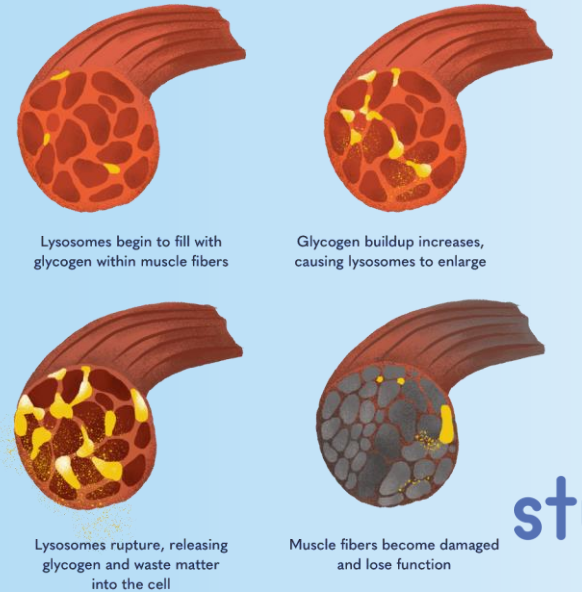
Lysosomal α-glucosidase (debranching enzyme) deficiency

Most severe disease

Autosomal recessive

Affects muscle and nerve cells

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



Pompe = Pump

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Type III: Cori's disease

Glycogen debranching enzyme deficiency

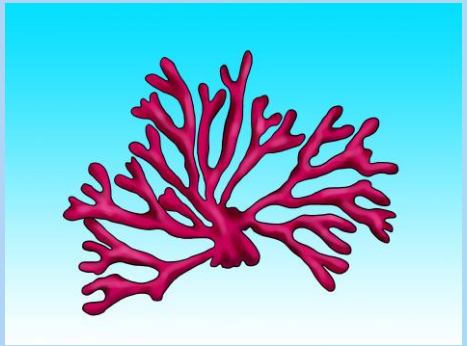
Unable to convert branched glycogen polymers to glucose

Limit dextrose accumulates in cytoplasm

Excess amounts of **abnormal glycogen structures** deposited in liver, muscles, sometimes heart

Presents during infancy as failure to thrive with hypoglycemia

Hepatomegaly and muscular disease



Cori = Coral

Type IV: Andersen's disease

Glycogen branching enzyme defect

Autosomal recessive

Long unbranched glucose chains = low solubility → glycogen precipitation in the liver → CIRRHOSIS

Deposits can build up in muscle and cardiac cells as well

McArdle = Muscle

Type V: McArdle's Disease

Myophosphorylase Deficiency

Autosomal recessive

Can't break down glycogen to G1P

Accumulation of intramuscular glycogen and lack of G1P for cellular fuel

Muscle cramps + hypoglycemia on exertion, myoglobinuria

Her = Hepatic

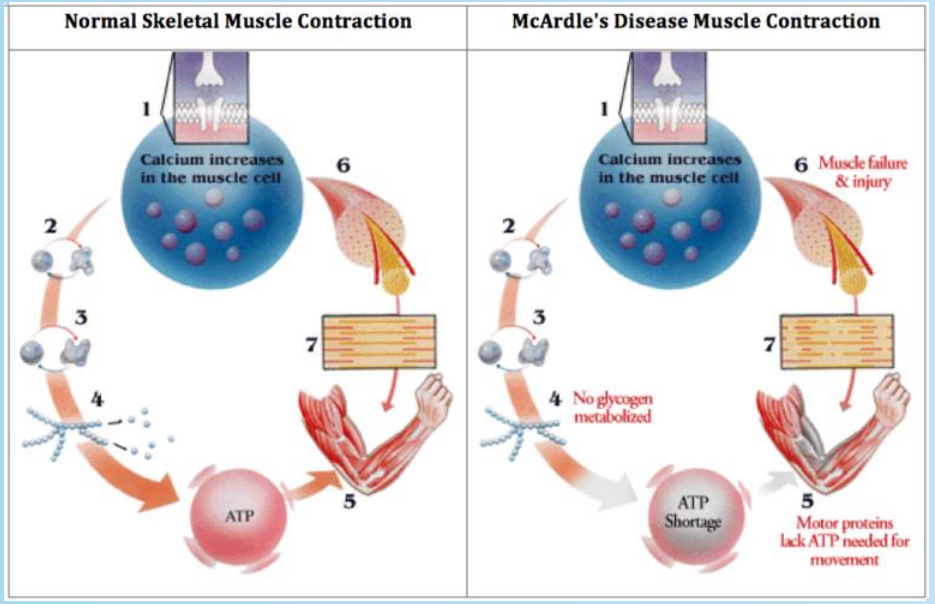
Type VI: Hers Disease

Liver Glycogen Phosphorylase Deficiency

Autosomal recessive (most) OR X-linked recessive

Can't break down glycogen

Hepatomegaly, fasting hypoglycemia



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

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THANK YOU!!

Good luck on your exam! 😄



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