Glycogen metabolism

Karoline Hanevik

Overview

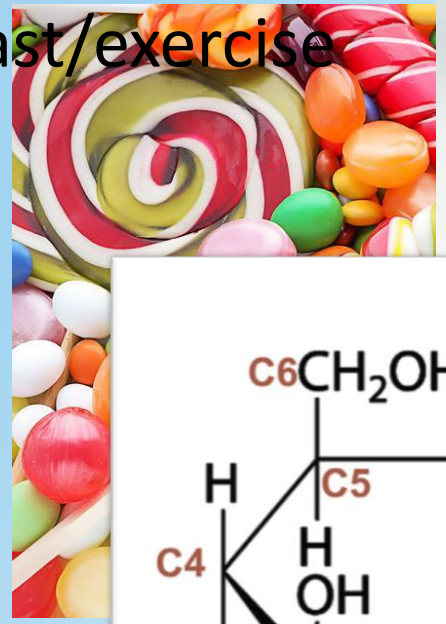
- ❑ Function of glycogen
- ❑ Structure and storage
- ❑ **Synthesis**
- ❑ **Degradation**
- ❑ Glycogen storage diseases

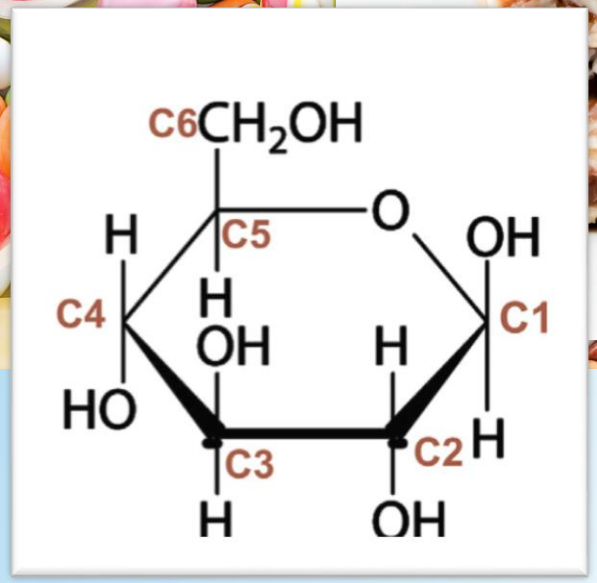
Glycogen

- *Branched polymer* of glucose
  → **storage in cytoplasm**

Initial source of glucose during fast/exercise

The body's granola-bar





Glucose homeostasis

→ Insulin and glucagon

- Liver and skeletal muscle (cardiac muscle and kidneys)

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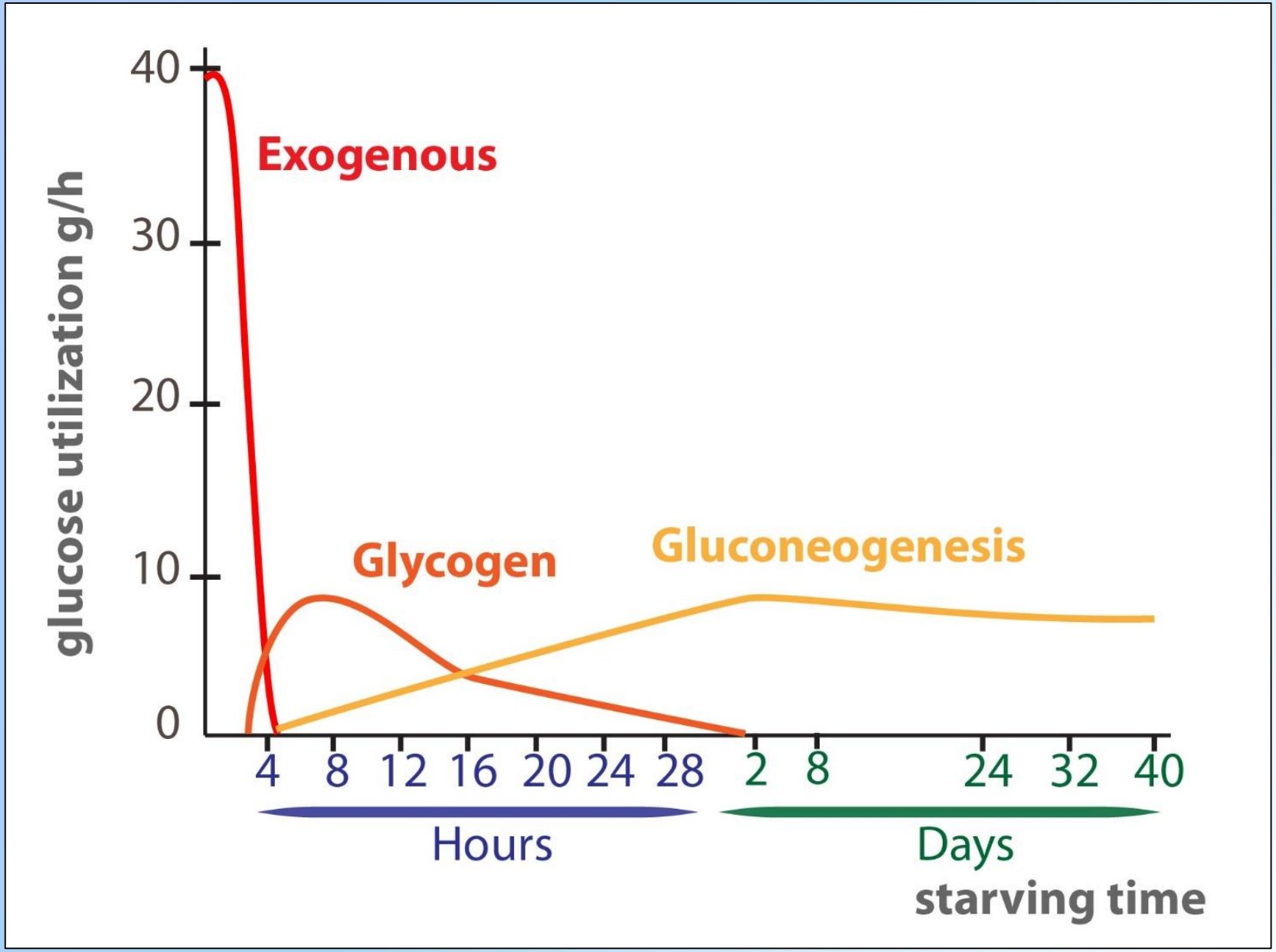

glucose utilization g/h
40
30
20
10
0
Exogenous
Glycogen
Gluconeogenesis
4 8 12 16 20 24 28
2 8 24 32 40
Hours
Days
starving time

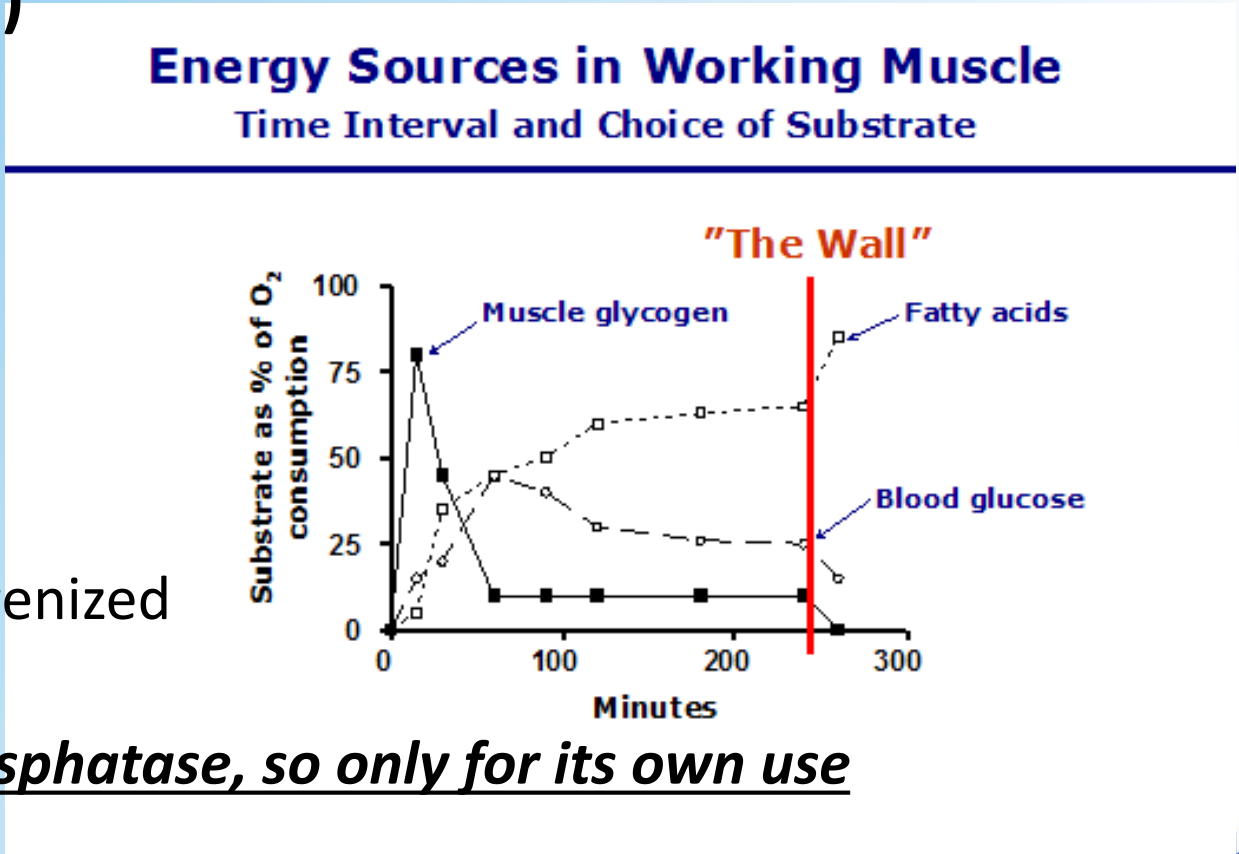
Function

Glucose reserve that can provide energy during fasting or ↑ demand

- Low supplies **(last around 10 hours)**

Stored mainly in liver and muscle

- Liver → hypoglycemia
- Skeletal muscle → energy reserve
  - White muscle fibers → lactate
  - Red muscle fibers → completely oxygenized



- ***<u>Muscle does not have glucose-6-phosphatase, so only for its own use</u>***

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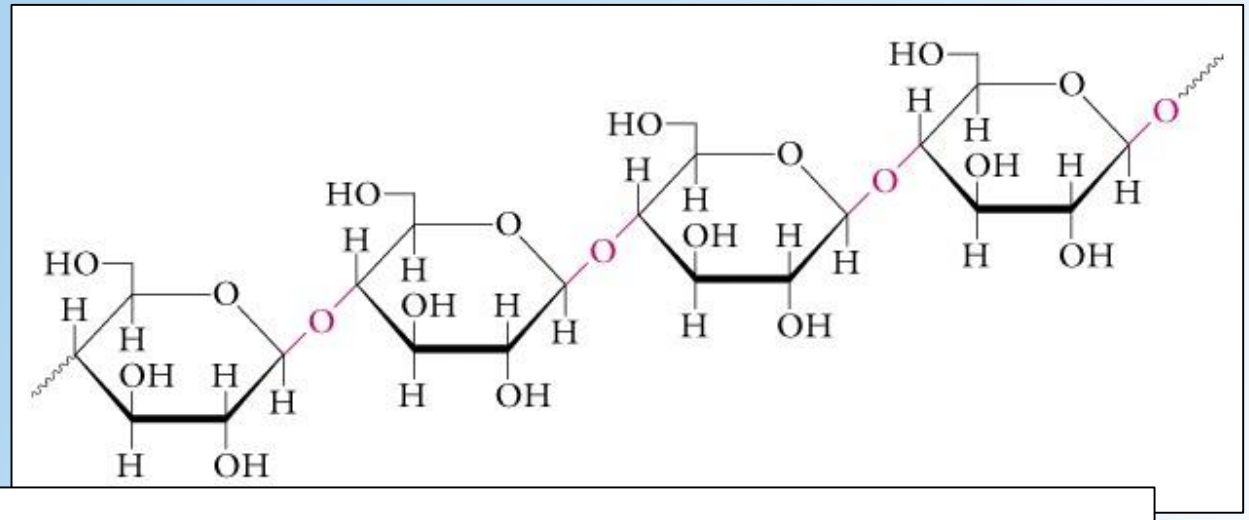
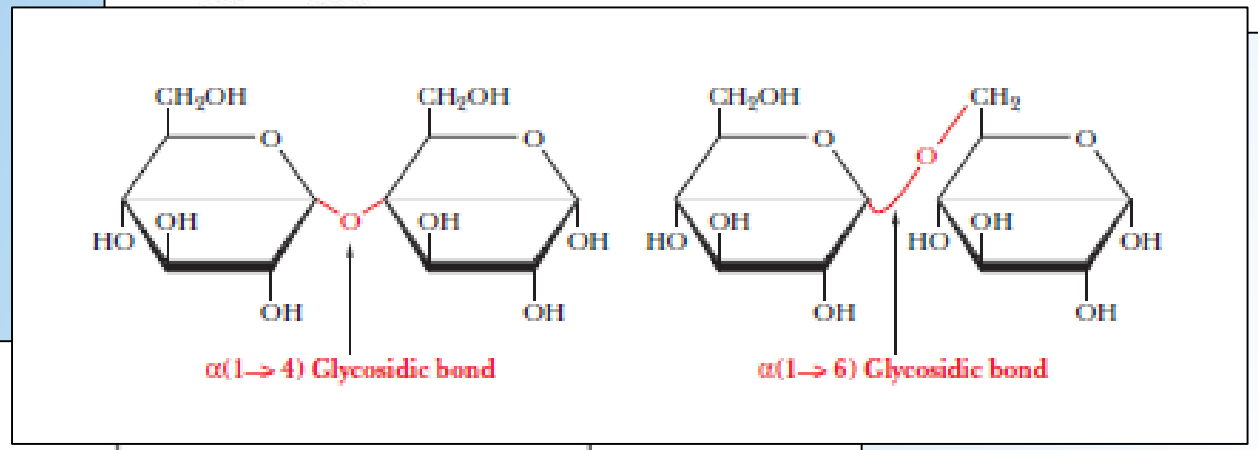
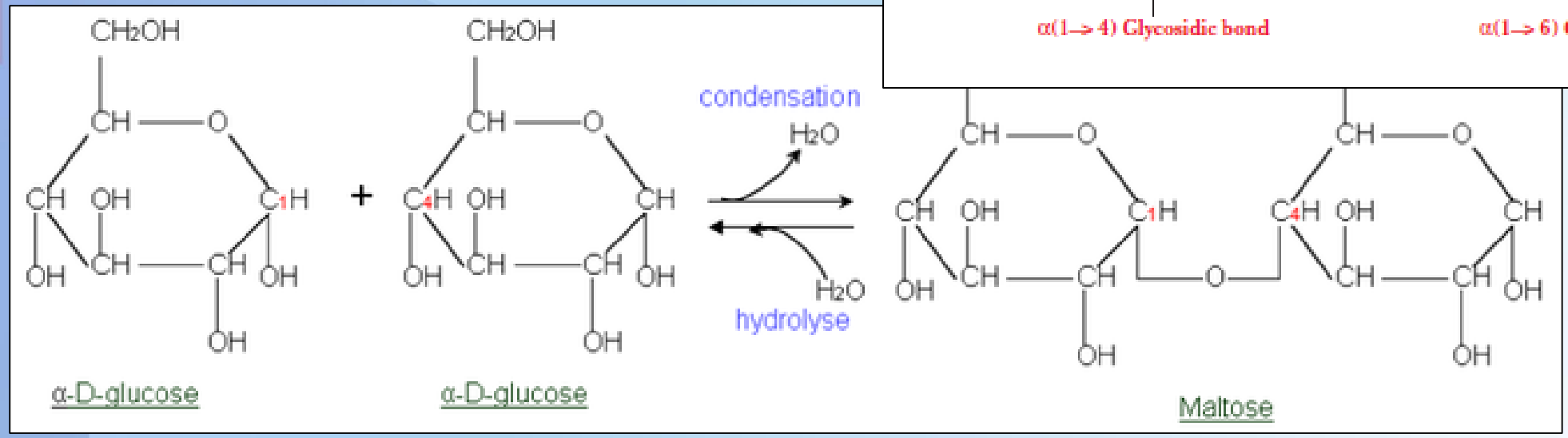
Molecular structure

- Core = **glycogenin**
- Straight chains = **α-1,4-bonds**
- Branch-points = **α-1,6-bonds**



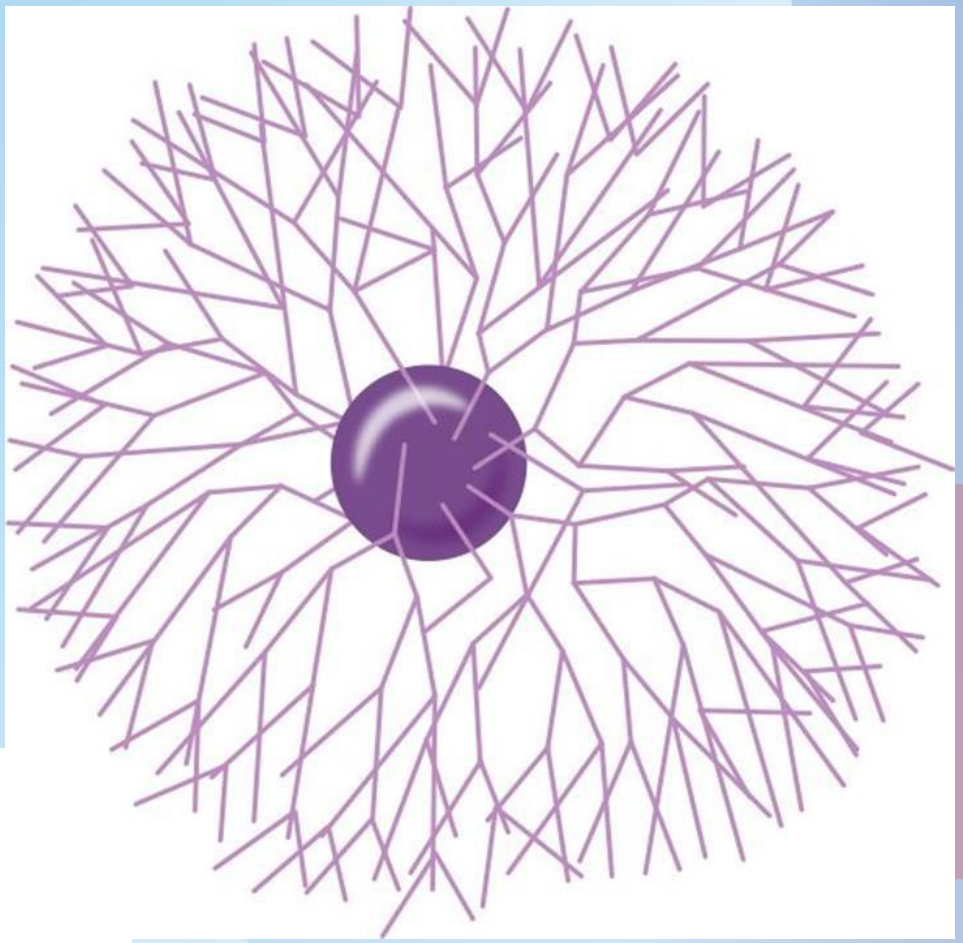
GLYCOSIDIC BONDS!

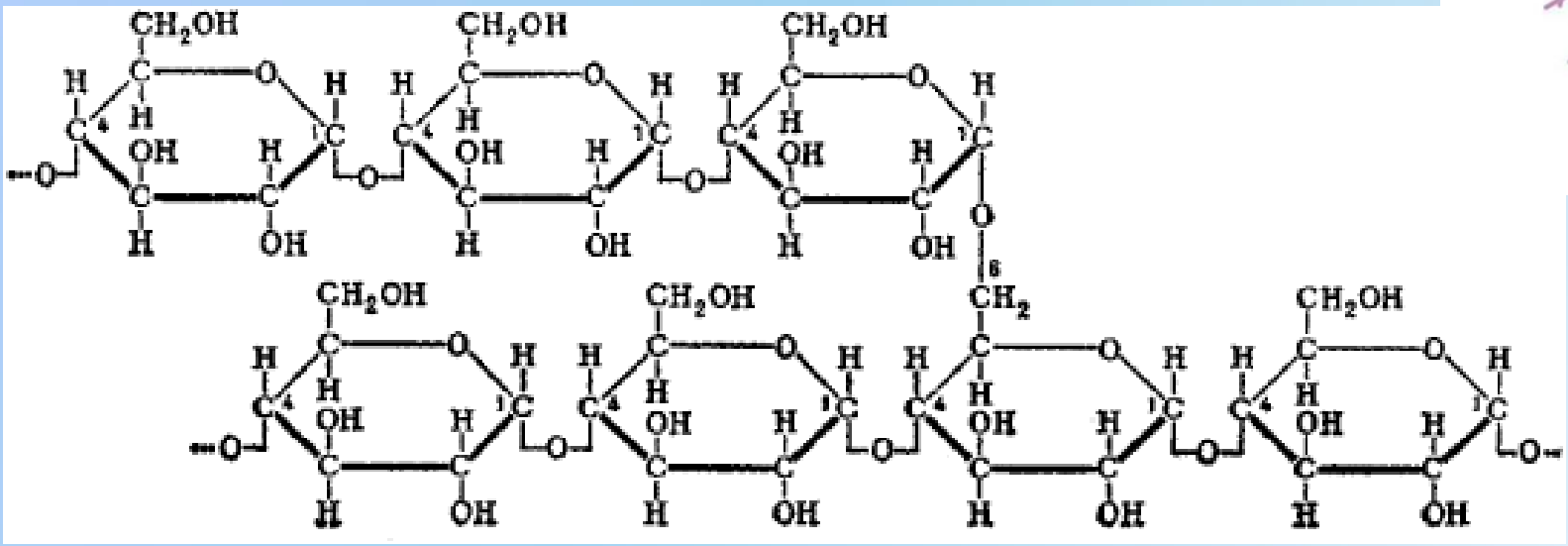




Branched polymer

- Increased water solubility
- More terminal glucose residues
- Less osmotic



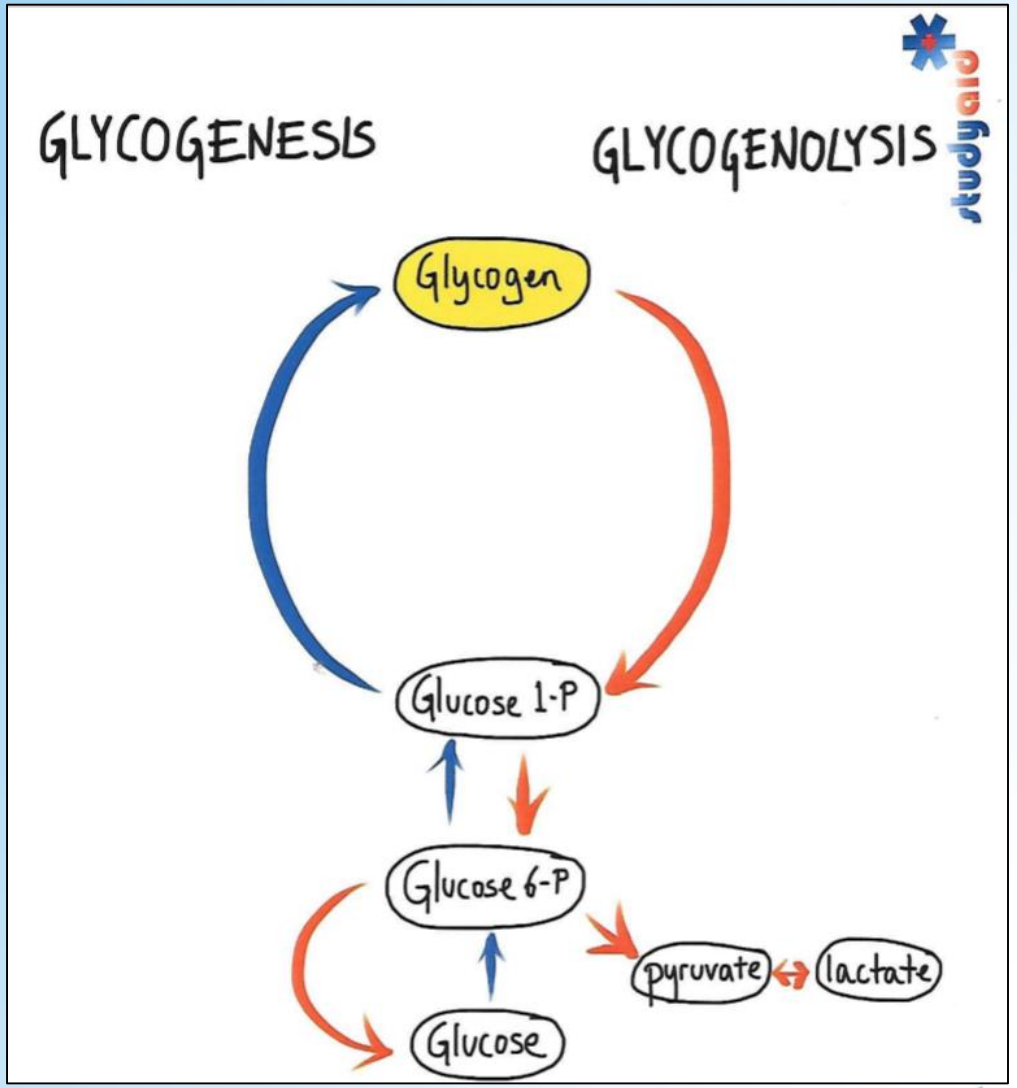


Glycogen synthesis = glycogenesis ≠ gluconeogenesis

Glycogen synthesis =

GLYCOGENESIS *≠ glycolysis ≠*

gluconeogenesis



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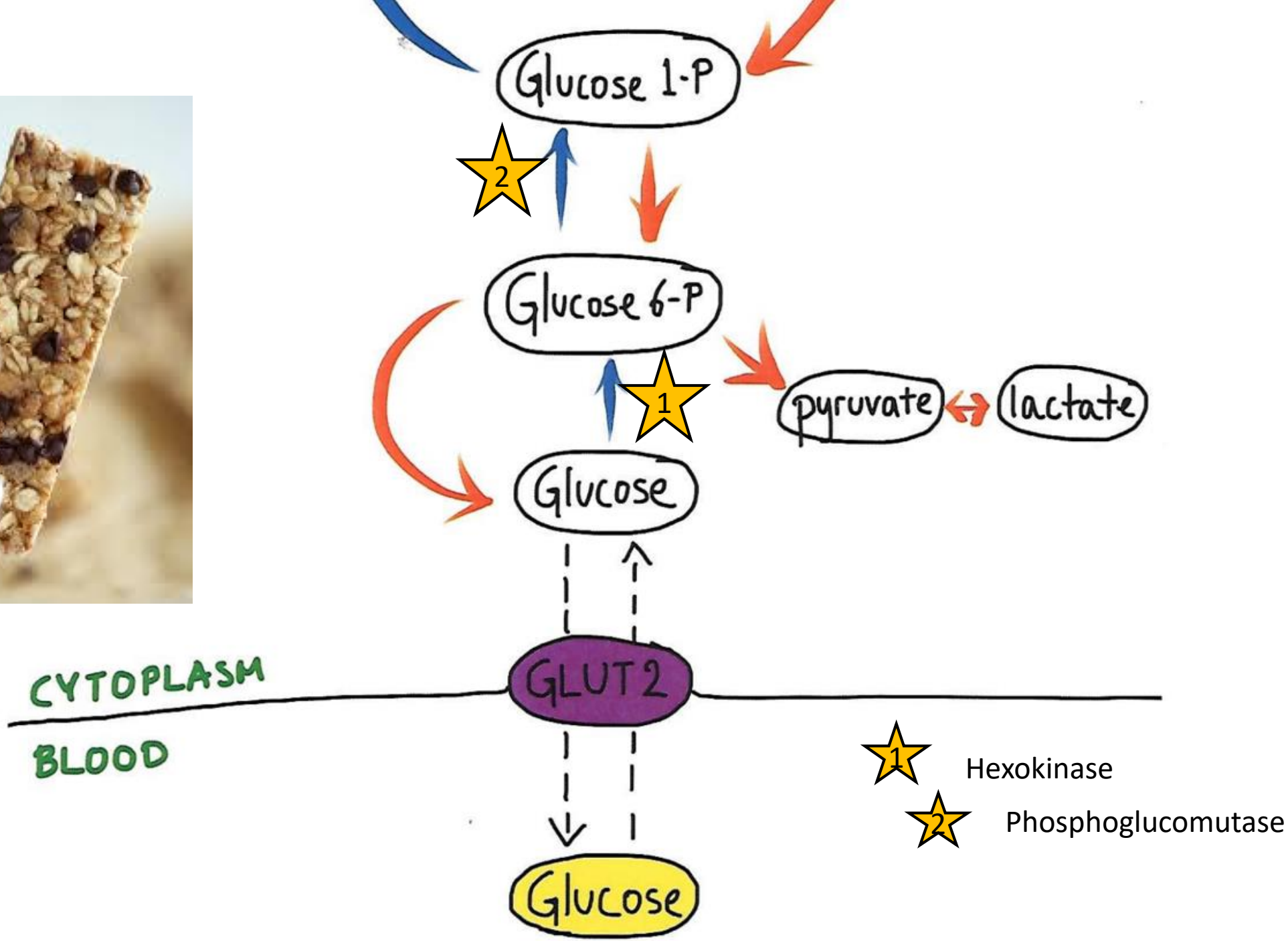
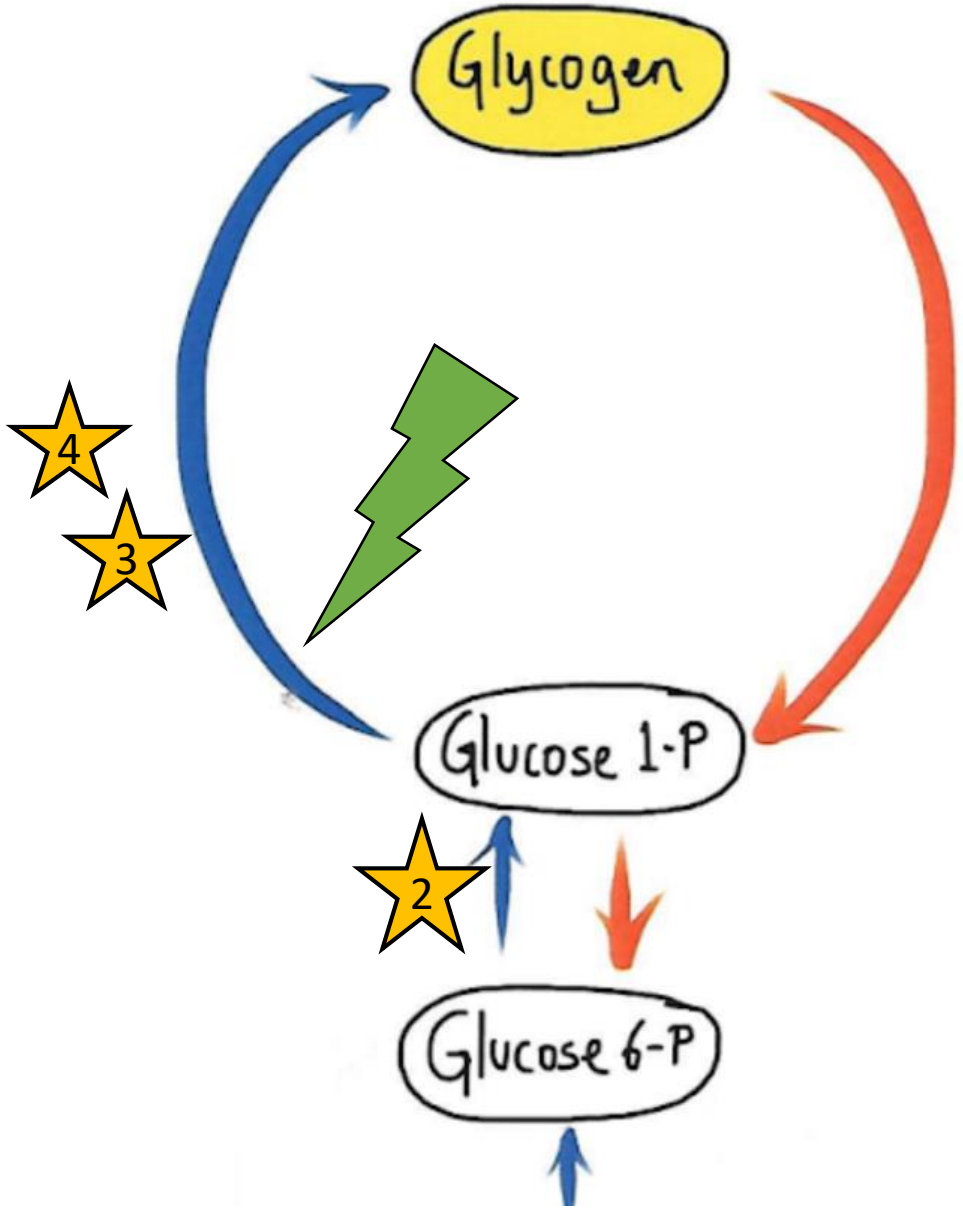

Glucose 1-P
2
Glucose 6-P
1
pyruvate
lactate
Glucose
CYTOPLASM
GLUT 2
BLOOD
Glucose
1 Hexokinase
2 Phosphoglucomutase



UTP—glucose-1-phosphate uridylyltransferase

G-1-P + UTP → **UDP-glucose** + PPi

2 Phosphoglucomutase

3 Glycogen synthase

4 Branching enzyme

Rate-limiting enzyme

- **GLYCOGEN SYNTHASE**
  - **Rate-limiting enzyme**
  - Forms *α-1-4 glycosidic bonds* in linear glucose chains
  - Extends new branches
  - **Active when NOT phosphorylated**

Activated by INSULIN

Inhibited by GLUCAGON (liver) and EPINEPHRINE

- BRANCHING ENZYME
  - Transfers the oligosaccharide unit
  - Forms *α-1-6 glycosidic bonds* to create a new branch

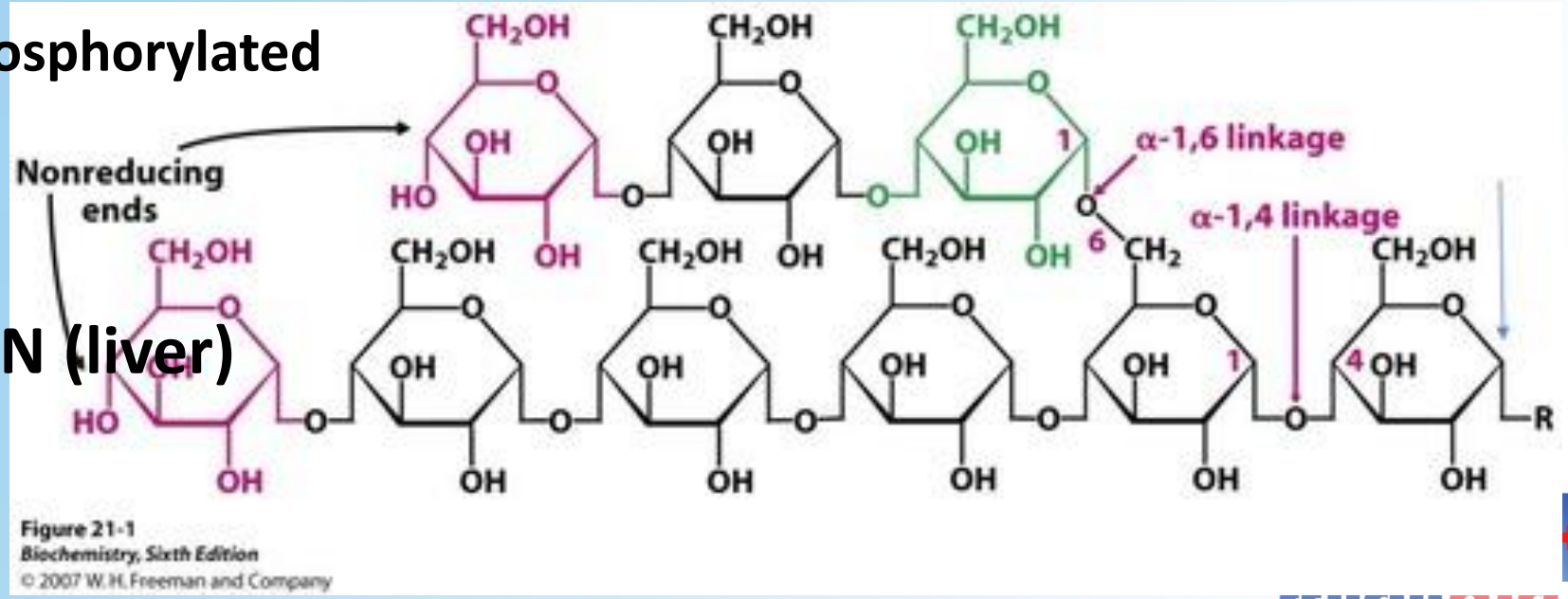


Figure 21-1
Biochemistry, Sixth Edition
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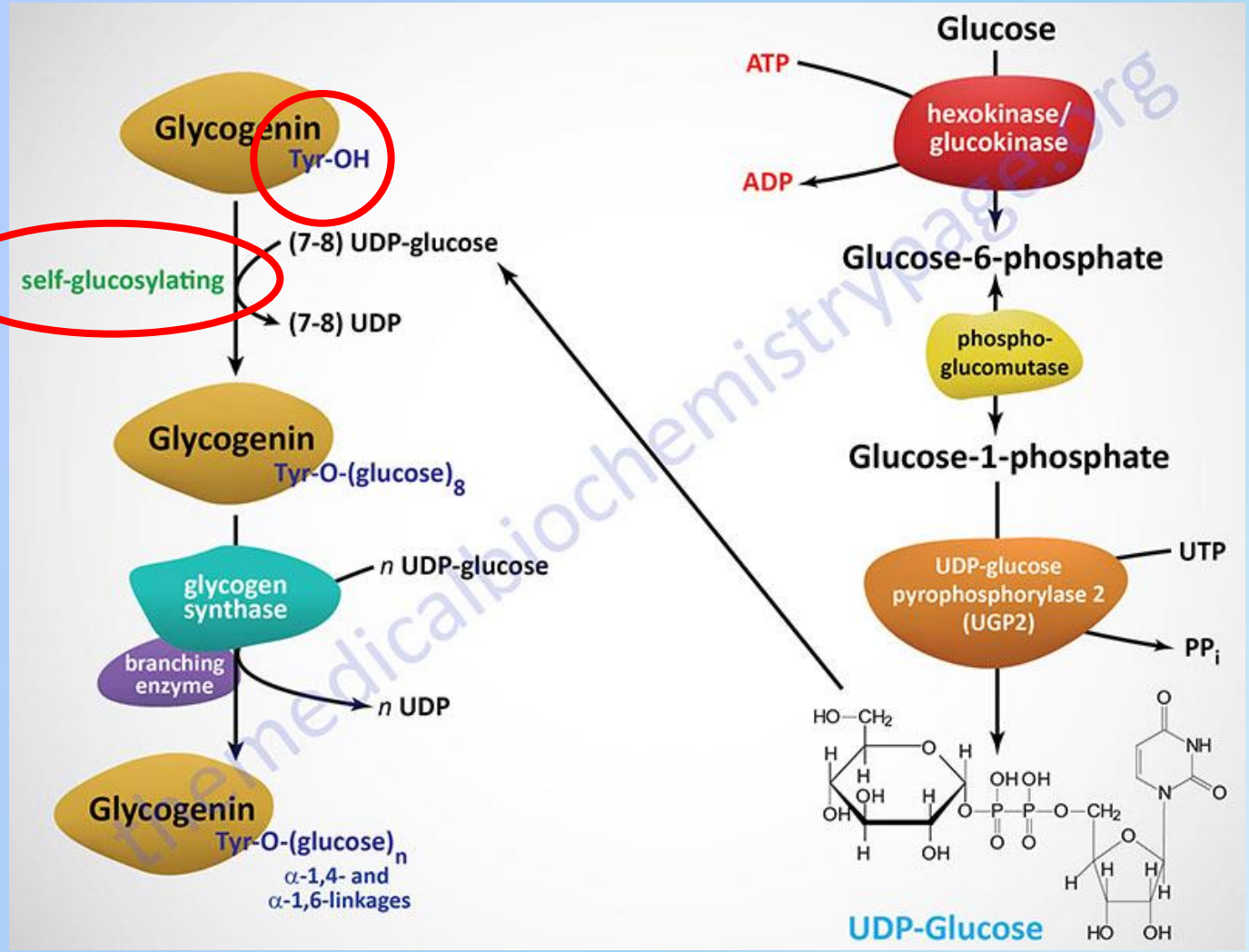
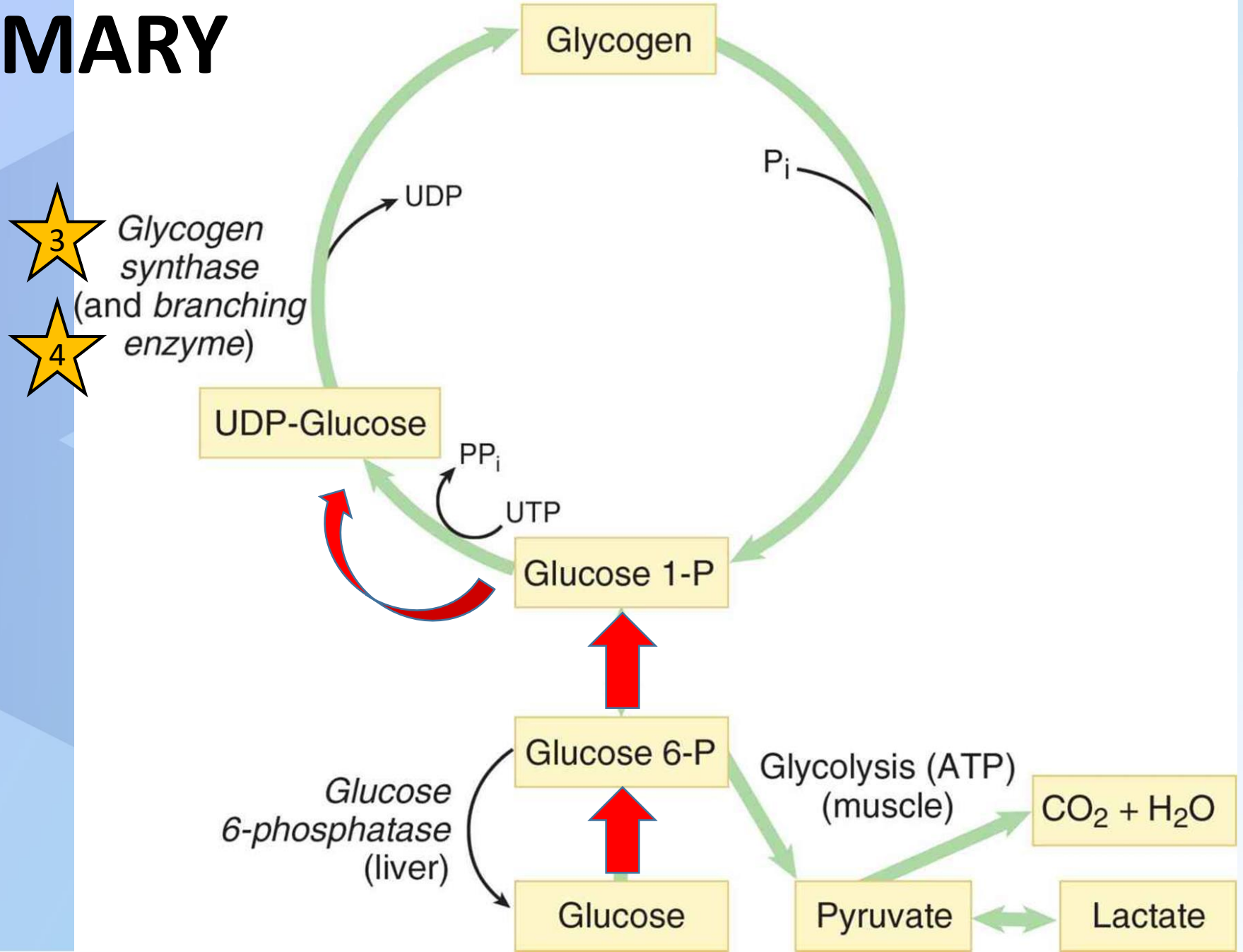
Polysaccharide addition to glycogenin



SUMMARY

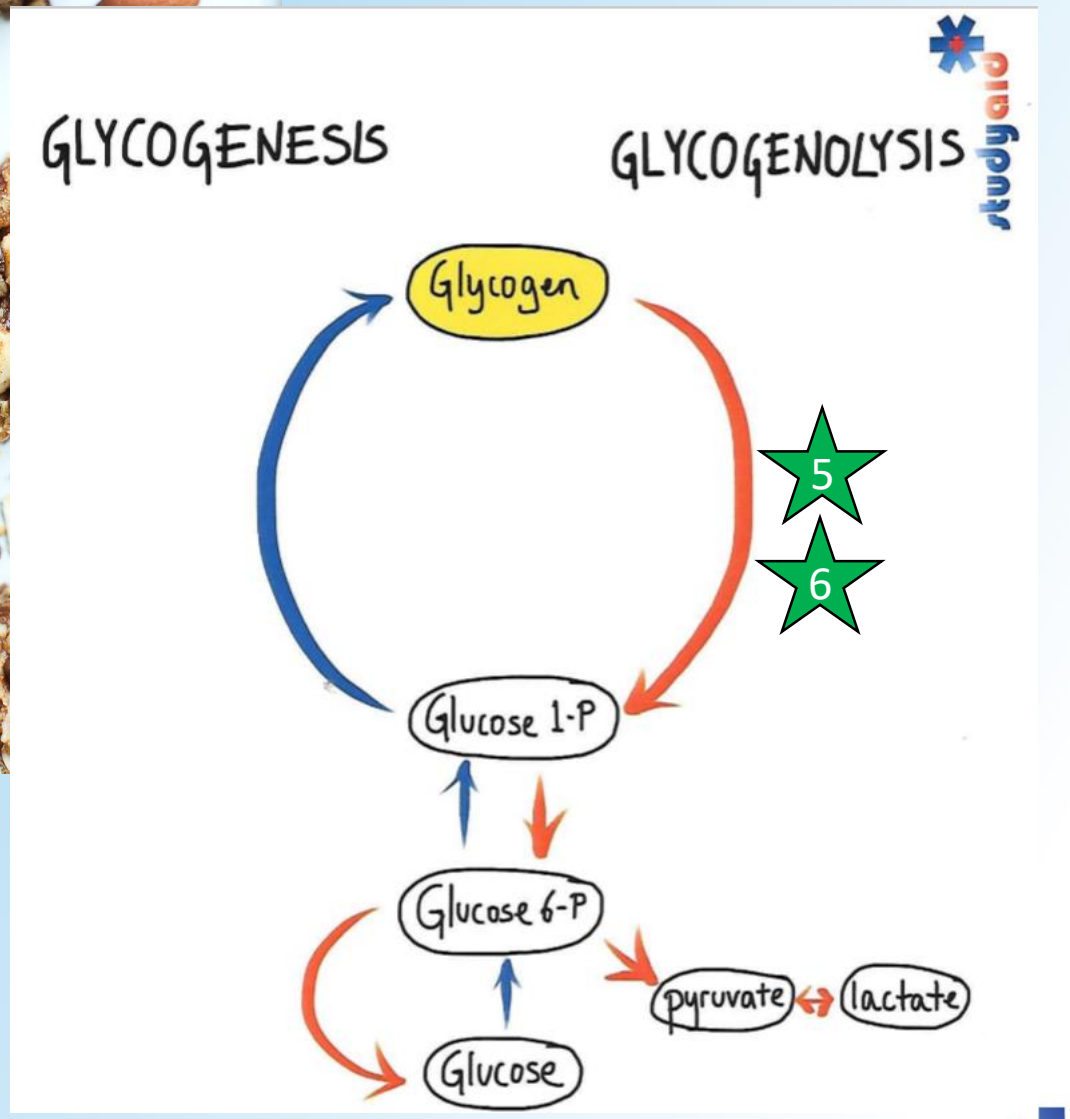

3
Glycogen synthase
4
(and branching enzyme)
Glycogen
UDP
Pi
UDP-Glucose
PPi
UTP
Glucose 1-P
Glucose 6-P
Glycolysis (ATP)
(muscle)
CO2 + H2O
Glucose 6-phosphatase
(liver)
Glucose
Pyruvate
Lactate

Overview

- ✓ Function of glycogen
- ✓ Structure and storage
- ✓ **Synthesis**
- ❑ **Degradation**
- ❑ Glycogen storage diseases

Glycogenolysis

- Glyco**geno**lysis ≠ Glycolysis
- ENERGY RESERVE!
- **Glycogen phosphorylase** (5)
  - Breaks bonds using Pi instead of H2O
  - Breaks α-1-4 glycosidic bonds
  - **Rate-limiting enzyme**
- **Debranching enzyme** (6)



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Hypoglycemia /// high energy demand

- **GLYCOGEN PHOSPHORYLASE**
  - **Rate-limiting enzyme!**
  - Breaks α-1-4 bonds using Pi
  - Works on non-reducing ends
  - **Active when phosphorylated**

Activated by:

In liver: **GLUCAGON**; EPINEPHRINE

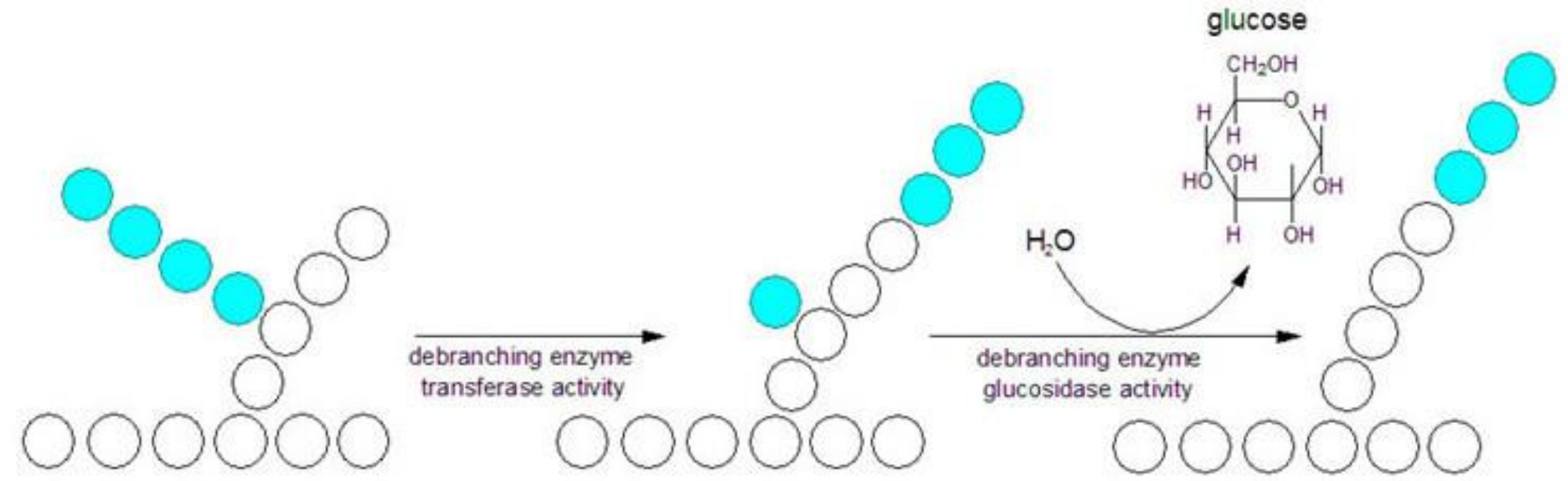
In muscle: EPINEPHRINE; **AMP; calcium**

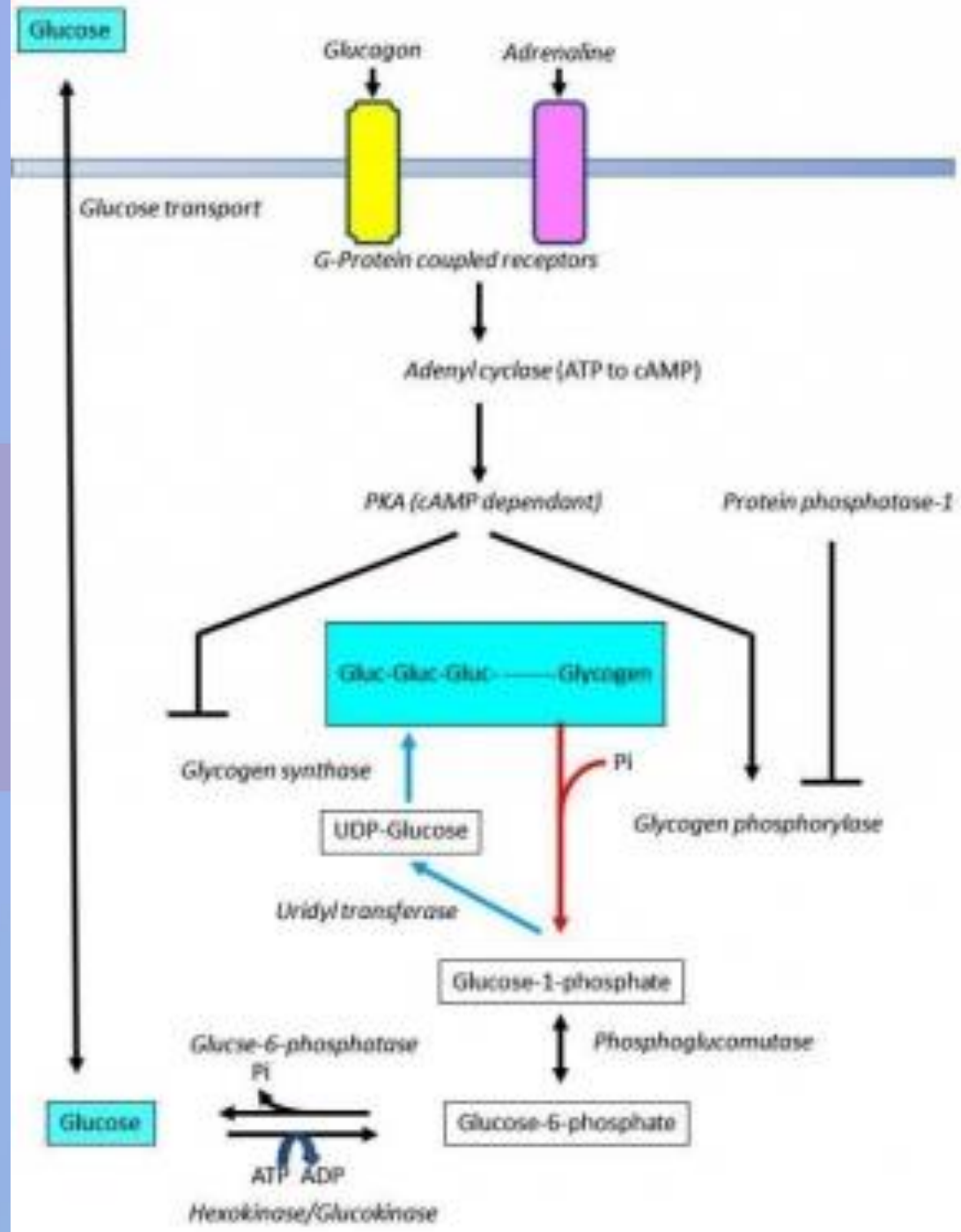
Inhibited by: insulin, ATP in muscle

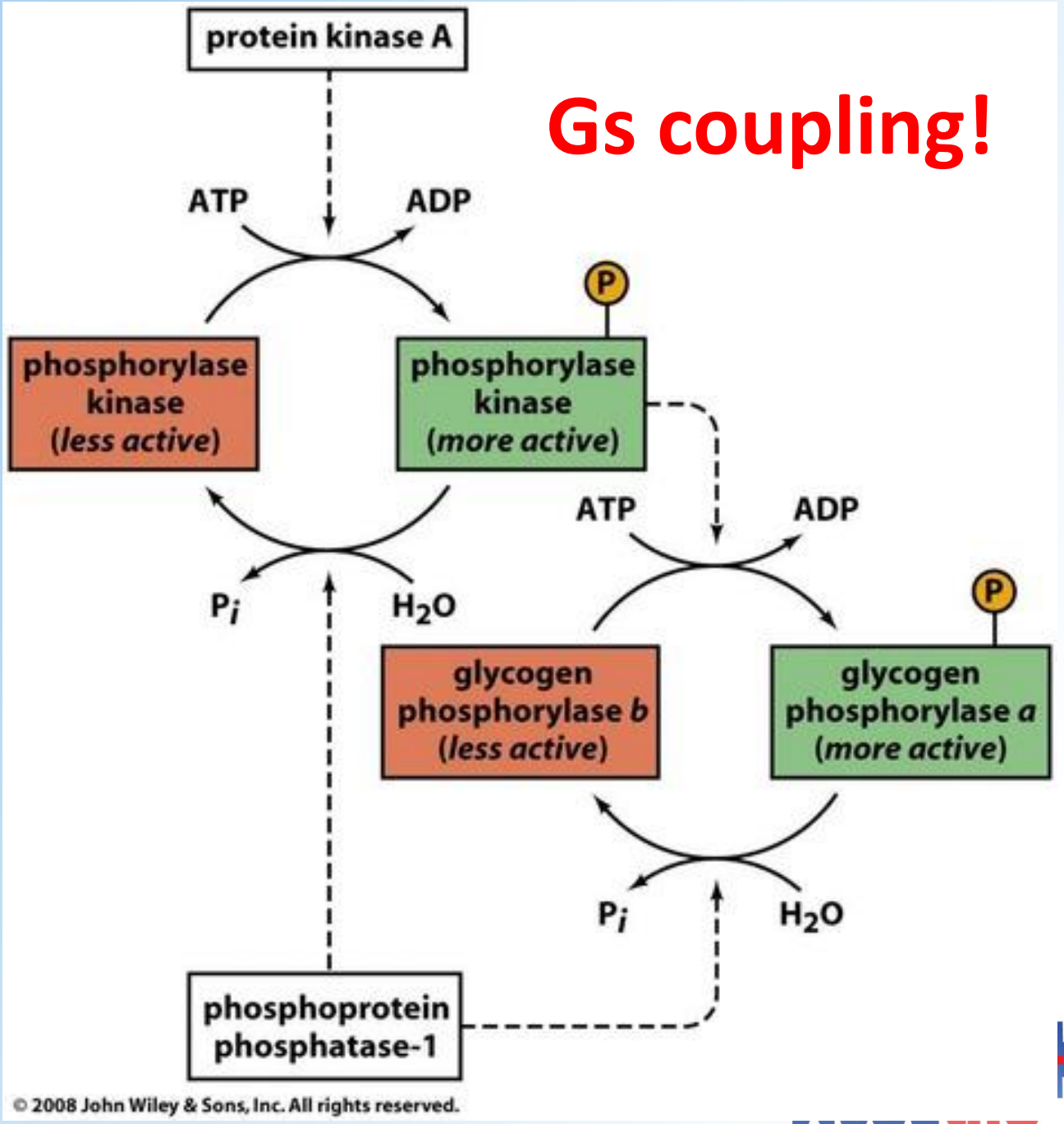
- DEBRANCHING ENZYME
  - Hydrolyzes at **branch points** (α-1-6 bonds)
  - Bifunctional enzyme

Two actions of debranching enzyme

- Moves oligosaccharide unit to end of another chain (*transferase*)
- Hydrolyzes the α-1-6 bond releasing a single glucose *(glucosidase)*




Glucose
Glucagon
Adrenaline
Glucose transport
G-Protein coupled receptors
Adenyl cyclase (ATP to cAMP)
PKA (cAMP dependant)
Protein phosphatase-1
Gluc-Gluc-Gluc-------Glycogen
Glycogen synthase
Pi
UDP-Glucose
Glycogen phosphorylase
Uridyl transferase
Glucose-1-phosphate
Glucose-6-phosphatase
Phosphoglucomutase
Pi
Glucose
Glucose-6-phosphate
ATP ADP
Hexokinase/Glucokinase


protein kinase A
Gs coupling!
ATP
ADP
phosphorylase kinase (less active)
phosphorylase kinase (more active)
P
ATP
ADP
Pi
H2O
glycogen phosphorylase b (less active)
glycogen phosphorylase a (more active)
P
Pi
H2O
phosphoprotein phosphatase-1
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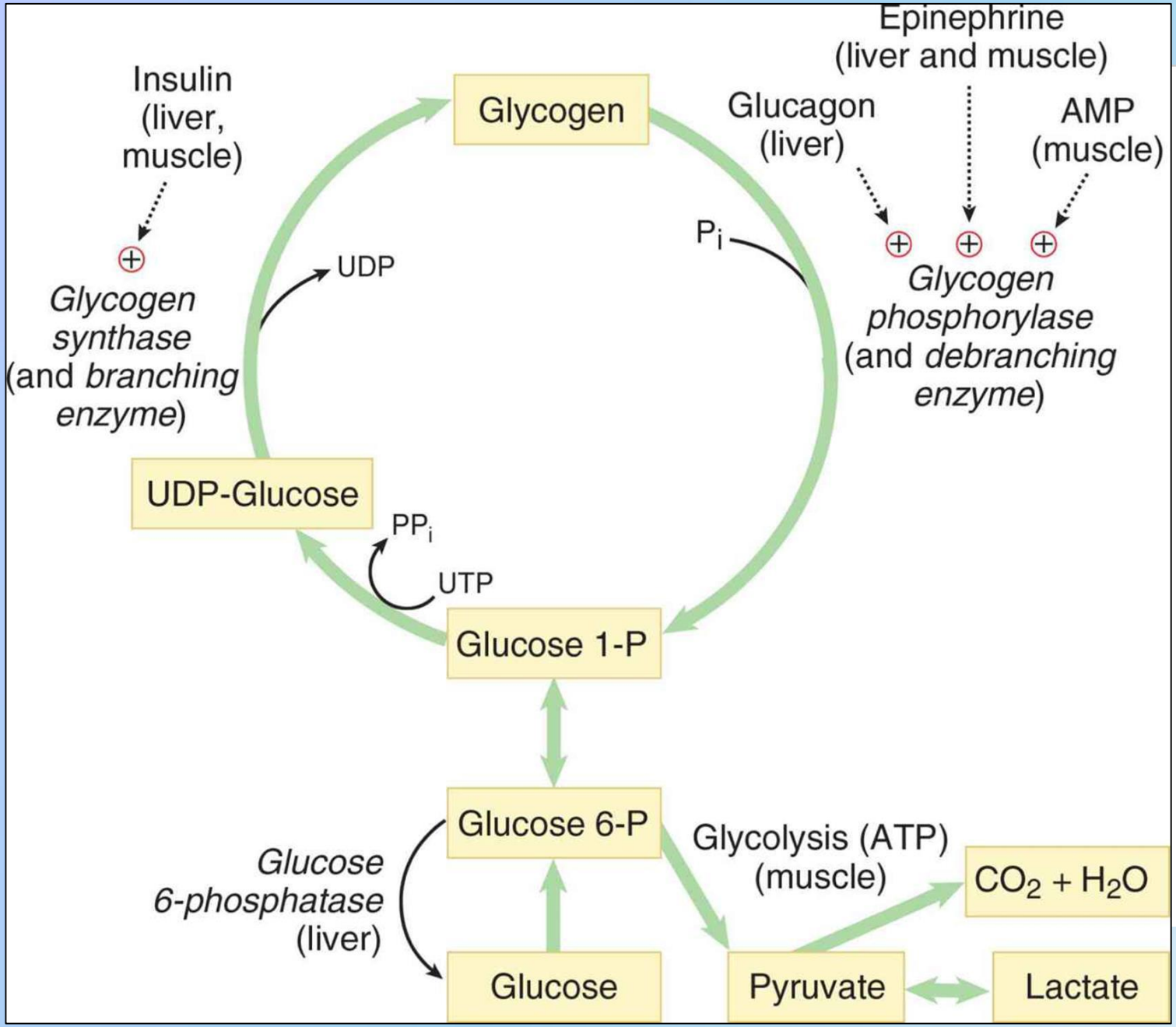
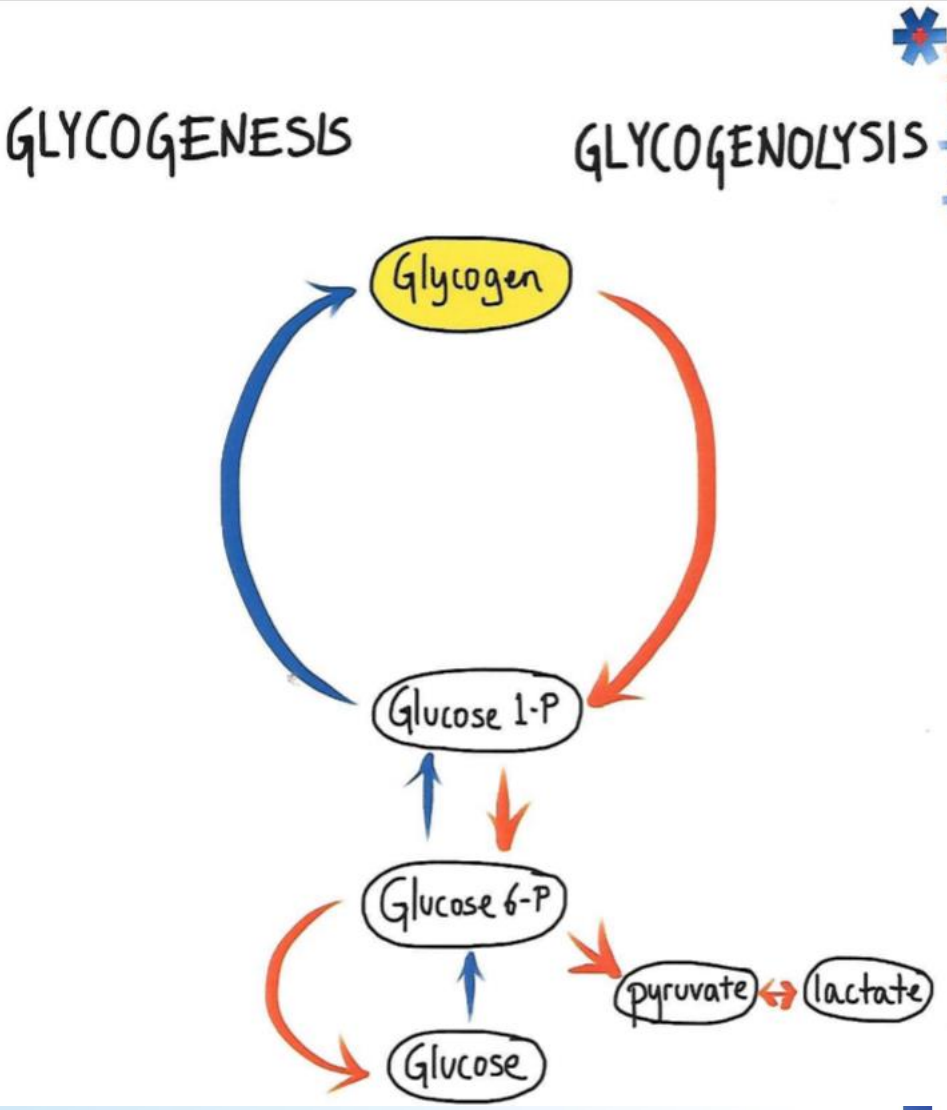
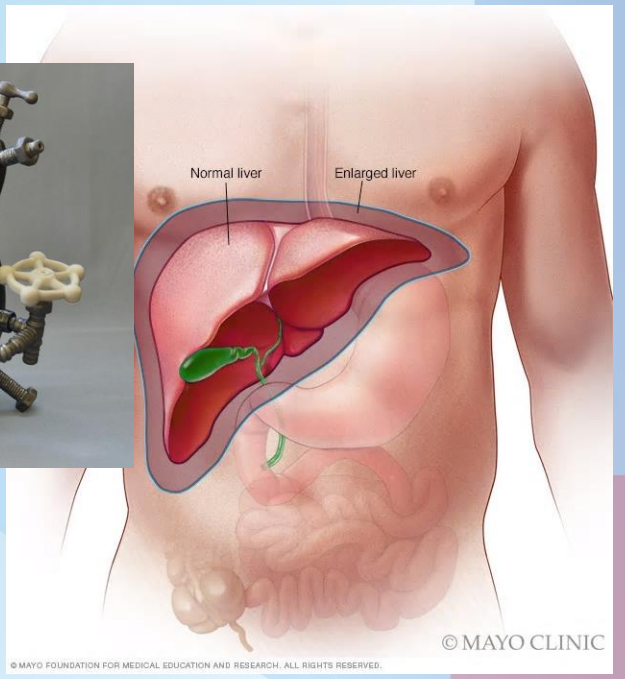

Insulin
(liver,
muscle)
Glycogen
Epinephrine
(liver and muscle)
Glucagon
(liver)
AMP
(muscle)
Pi
UDP
Glycogen
synthase
(and branching
enzyme)
Glycogen
phosphorylase
(and debranching
enzyme)
UDP-Glucose
PPi
UTP
Glucose 1-P
Glucose 6-P
Glycolysis (ATP)
(muscle)
Glucose
6-phosphatase
(liver)
CO2 + H2O
Glucose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


GLYCOGENESIS
GLYCOGENOLYSIS
Glycogen
Glucose 1-P
Glucose 6-P
pyruvate
lactate
Glucose

Glycogen Storage Disorders

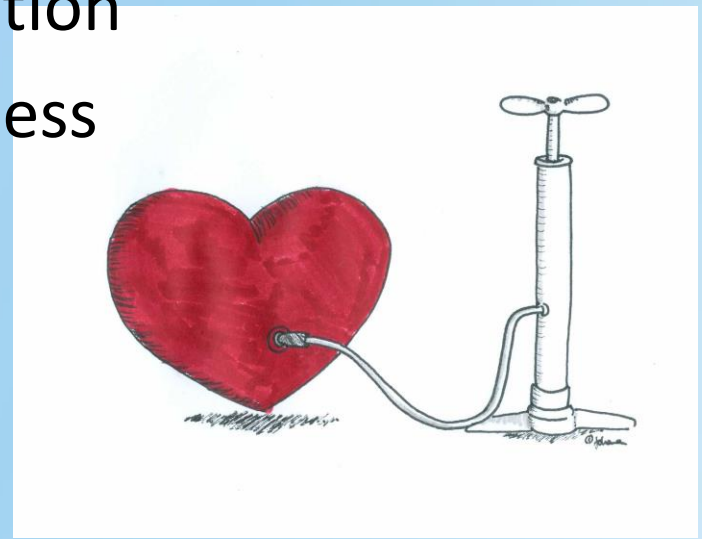


Very Poor Carbohydrate Metabolism

Rare diseases with abnormal glycogen metabolism.

Signs and symptoms:

- Organ dysfunction
- Muscle weakness
- 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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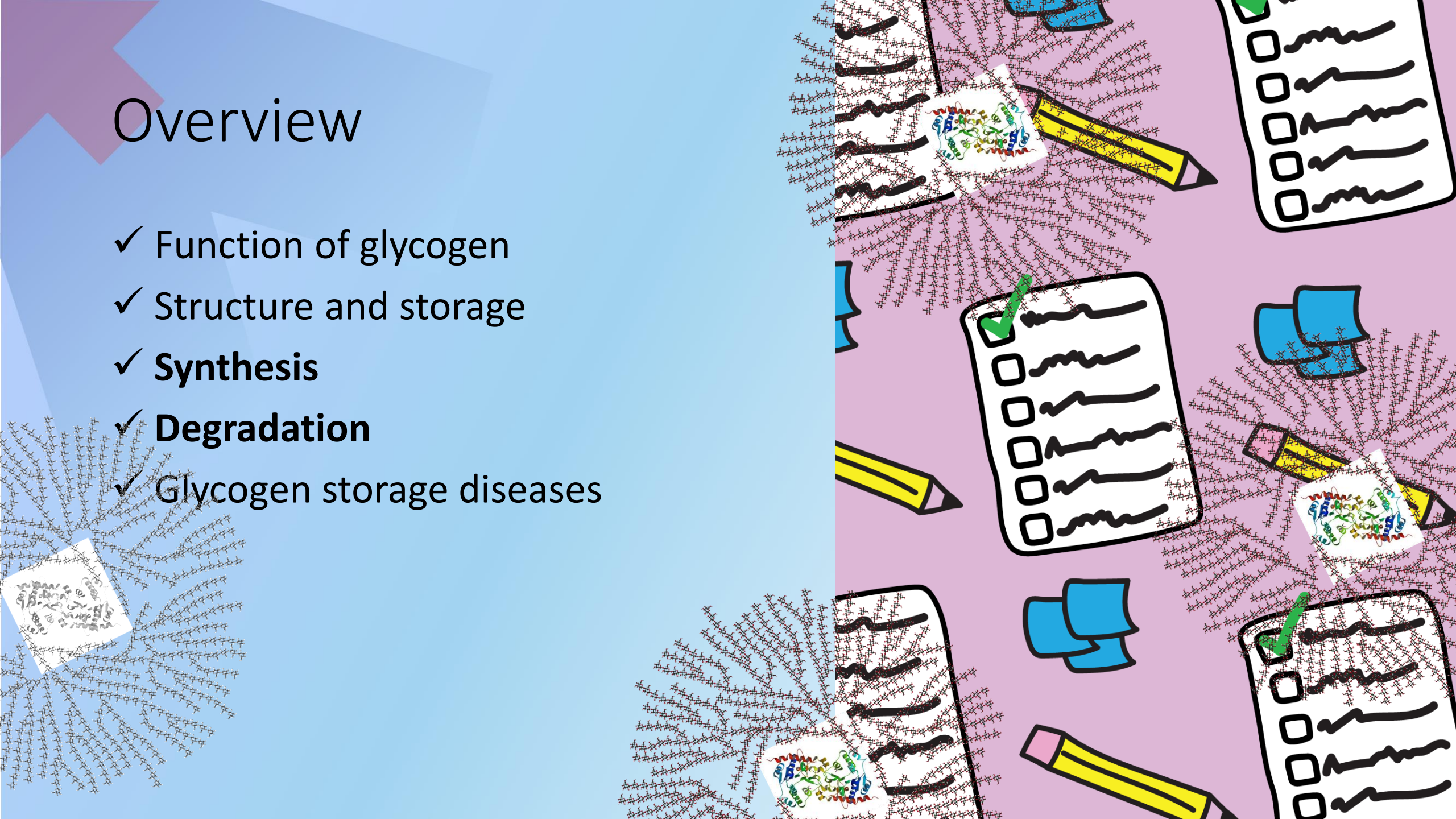

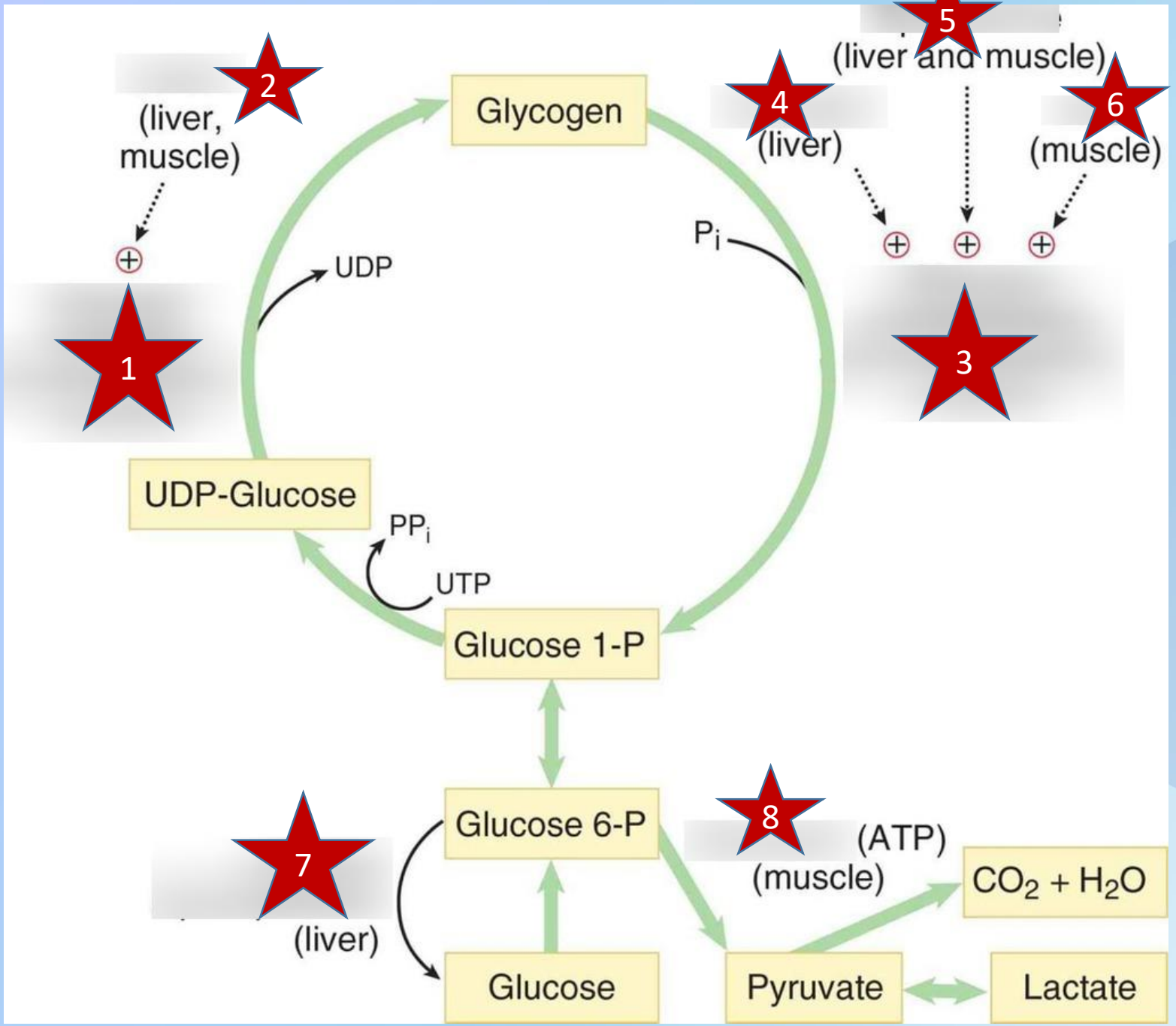

QUIZ

1. Glycogen synthase and branching enzyme
2. Insulin
3. Glycogen phosphorylase and debranching enzyme
4. Glucagon
5. Epinephrine
6. AMP
7. Glucose-6-phosphatase
8. Glycolysis

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Essential summary:

https://www.ncbi.nlm.nih.gov/books/NBK539802/

- *Glycogen is implicated in glucose homeostasis.*
- *Glycogen is highly concentrated in the liver although skeletal muscle contains the most glycogen by weight. Glycogen does not exist in plant tissue.*
- *Skeletal muscle is unable to release glycogen into the bloodstream due to lack of glucose-6-phosphatase (G6Pase)*
- *Glycogen is composed of two major bonds, which are alpha-1,4 and alpha-1,6 glycosidic bonds - these bonds give rise to linear chains and branching points, respectively*
- *Glycogen branching is essential because it allows for increased water solubility and a number of sites to break it down; this allows for easy and quick utilization of glycogen when it is broken down*
- *Glycogen synthesis and breakdown correlate with high and low energy states, respectively*
- *Insulin and glucagon are peptide hormones that orchestrate glycogen metabolic regulation as they signal high and low energy states, respectively*

Fill in the blank. Linear chains of muscle glycogen are linked by _____ glycosidic bonds, and branch-points are similarly formed through _____ bonds. Glycogen phosphorylase is activated through a cascade involving _____. It's end-product is _____.

a) α(1→6), α(1→4), protein kinase A, glucose-6-phosphate
b) α(1→6), α(1→4), protein kinase C, glucose
c) α(1→4), α(1→6), protein kinase C, glucose-1-phosphate
d) α(1→4), α(1→6), protein kinase A, glucose-1-phosphate
e) α(1→4), α(1→6), protein kinase A, glucose-6-phosphate

Answer: d

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Why can muscle glycogen not contribute to maintain blood glucose during a fast?

Answer: Glucose-6-phosphatase is not present in muscle

A 25 year old man visits the doctor due to exercise intolerance during the first 15-20 minutes of a work-out. His muscles stiffen and he feels weak. When he drinks Gatorade before the work-out he is able to prevent severe weakness. His urine appears reddish-brown after exercise, urinalysis is 1+ positive for blood. Ischemic forearm test indicates suggests absent lactate production. Which is the most likely enzyme defect?

a) Muscle glycogen phosphorylase
b) Hepatic glycogen phosphorylase
c) Branching enzyme
d) Debranching enzyme
e) Glucose-6-phosphatase

Answer: a