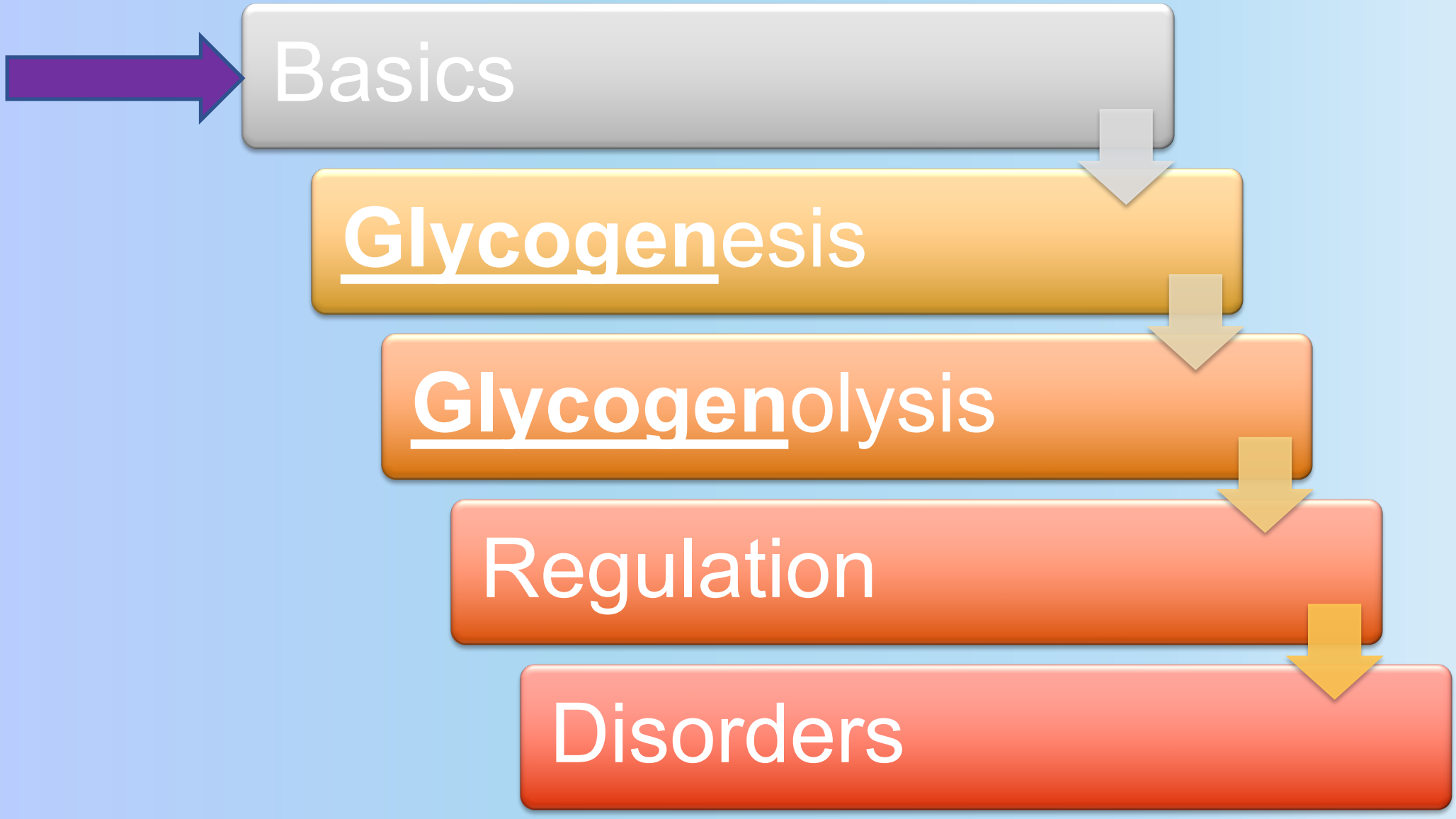
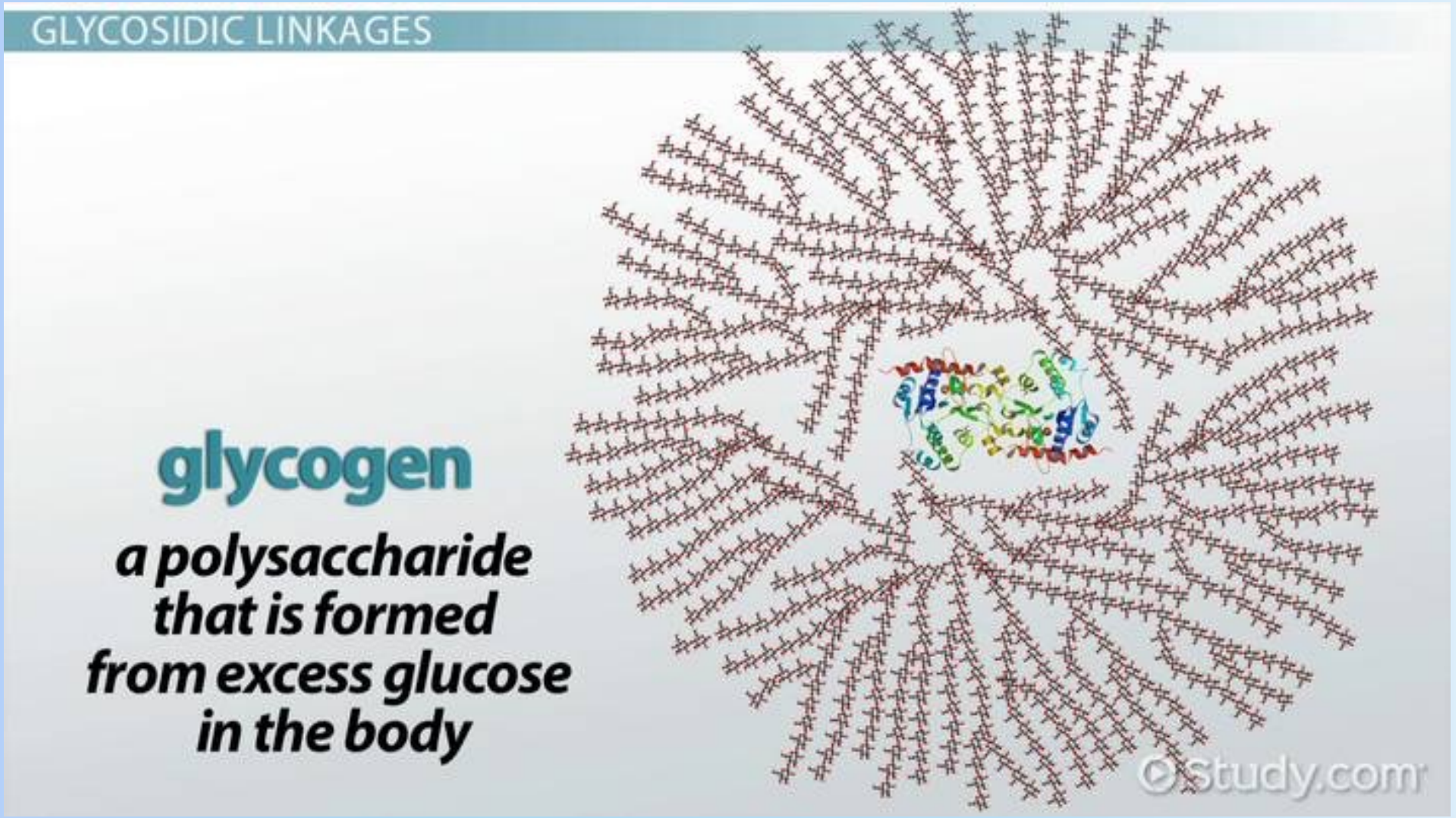
Glycogen Metabolism

By Niki Brzezinski


Basics
Glycogenesis
Glycogenolysis
Regulation
Disorders

Basics



Basics

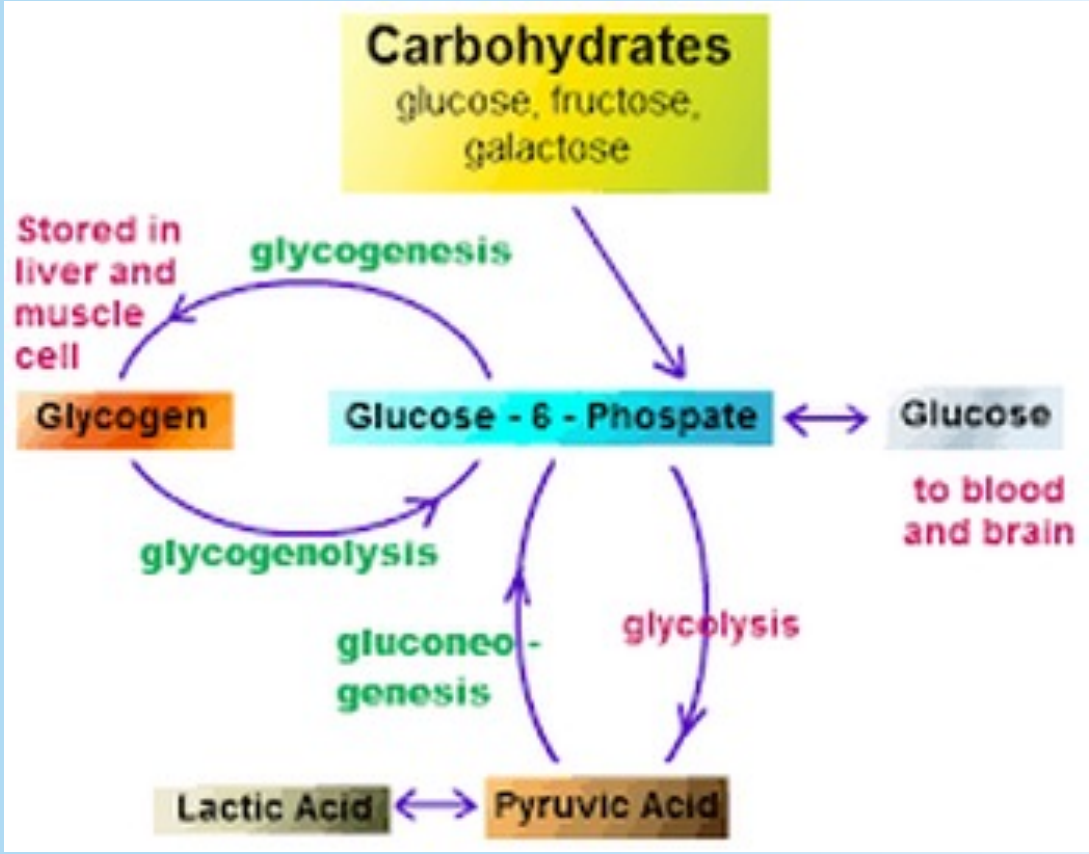
Why glycogen?

Glycogen uses 40x LESS energy to store than glucose

Cells physically can't store the same amount of glucose as glycogen; they would burst from the osmotic pressure

Gluconeogenesis is multistep process, requires time

Fats aren't an adequate source – Ketone bodies – drop pH → ketoacidosis



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Chemical Structure

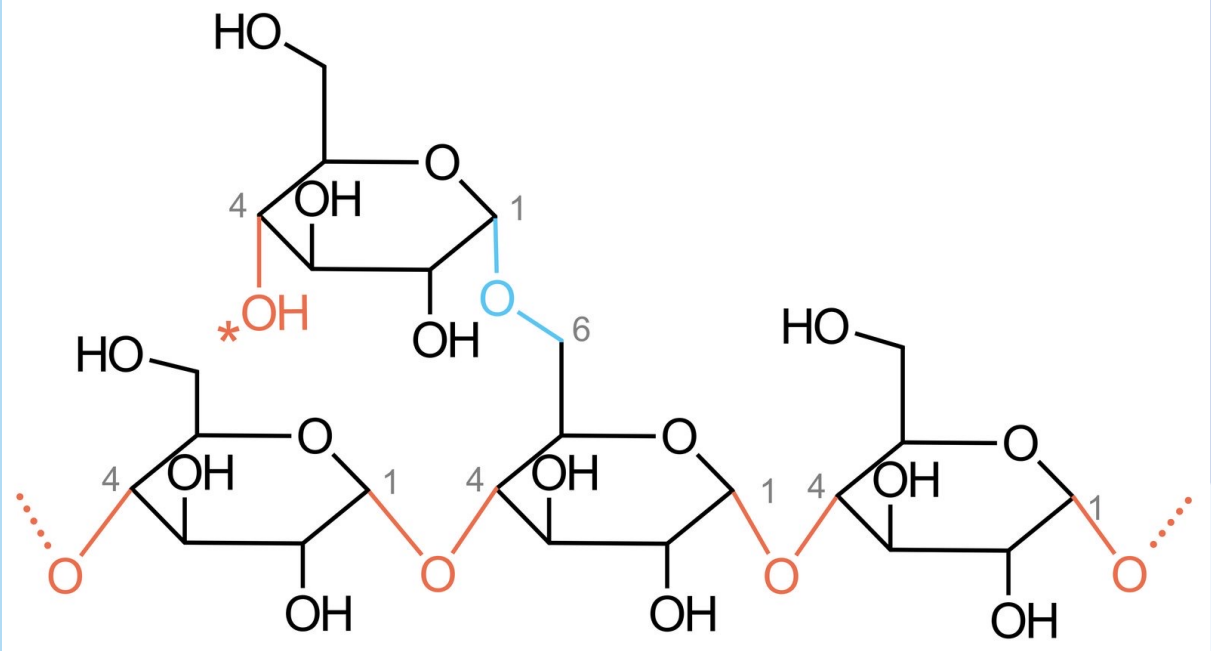
Basics

Straight chain: α 1,4 bonds

Branch chain: α 1,6 bonds
occur every 8-10 units

Exists as granules in cell cytoplasm with enzymes for both glycogenesis and glycogenolysis.

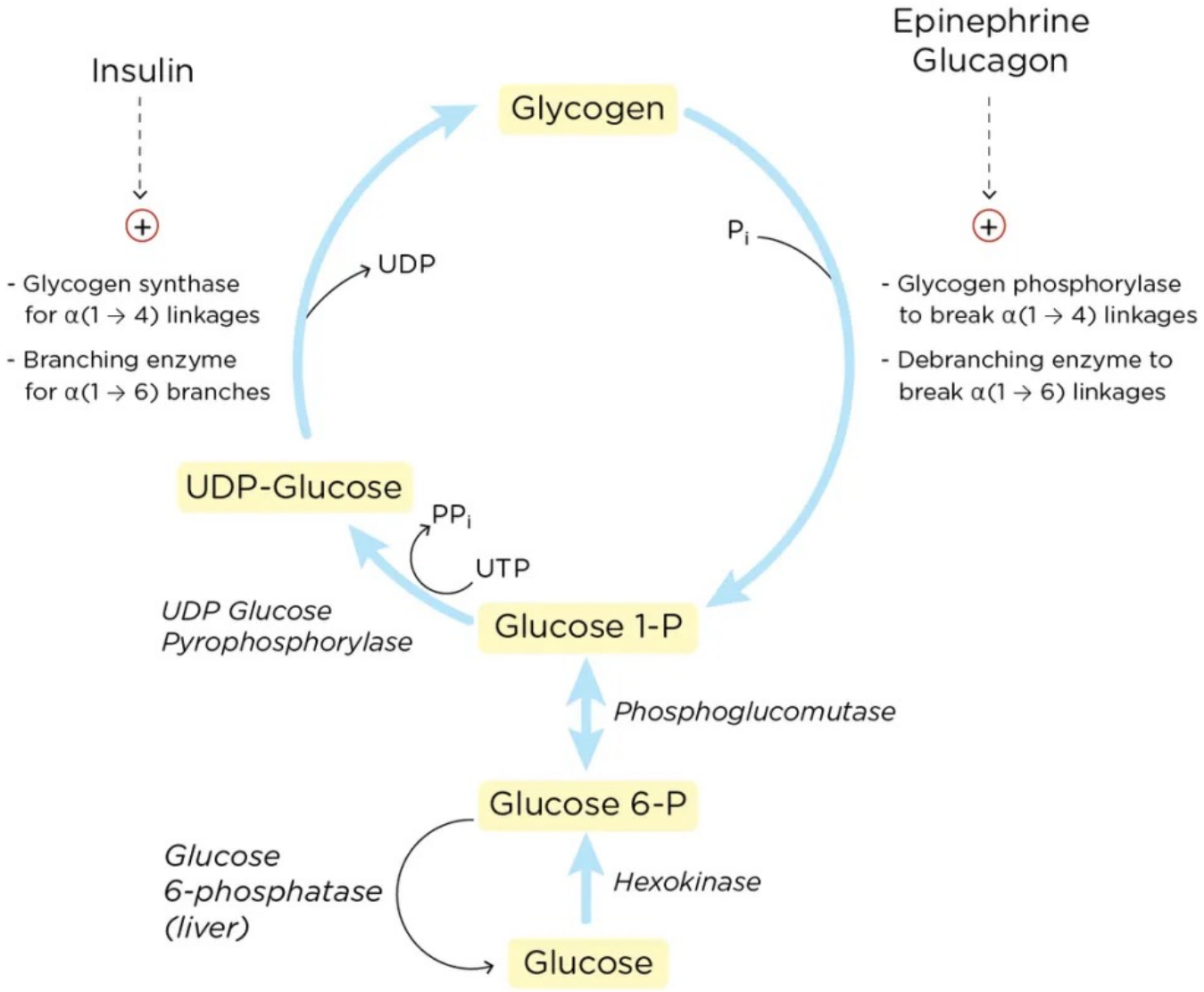
Main chain plus branches allows to compact the molecule and makes it easy to break down.



Basics

Glycogenesis and Glycogenolysis

Occurs in Liver and Skeletal Muscle



Jack Westin

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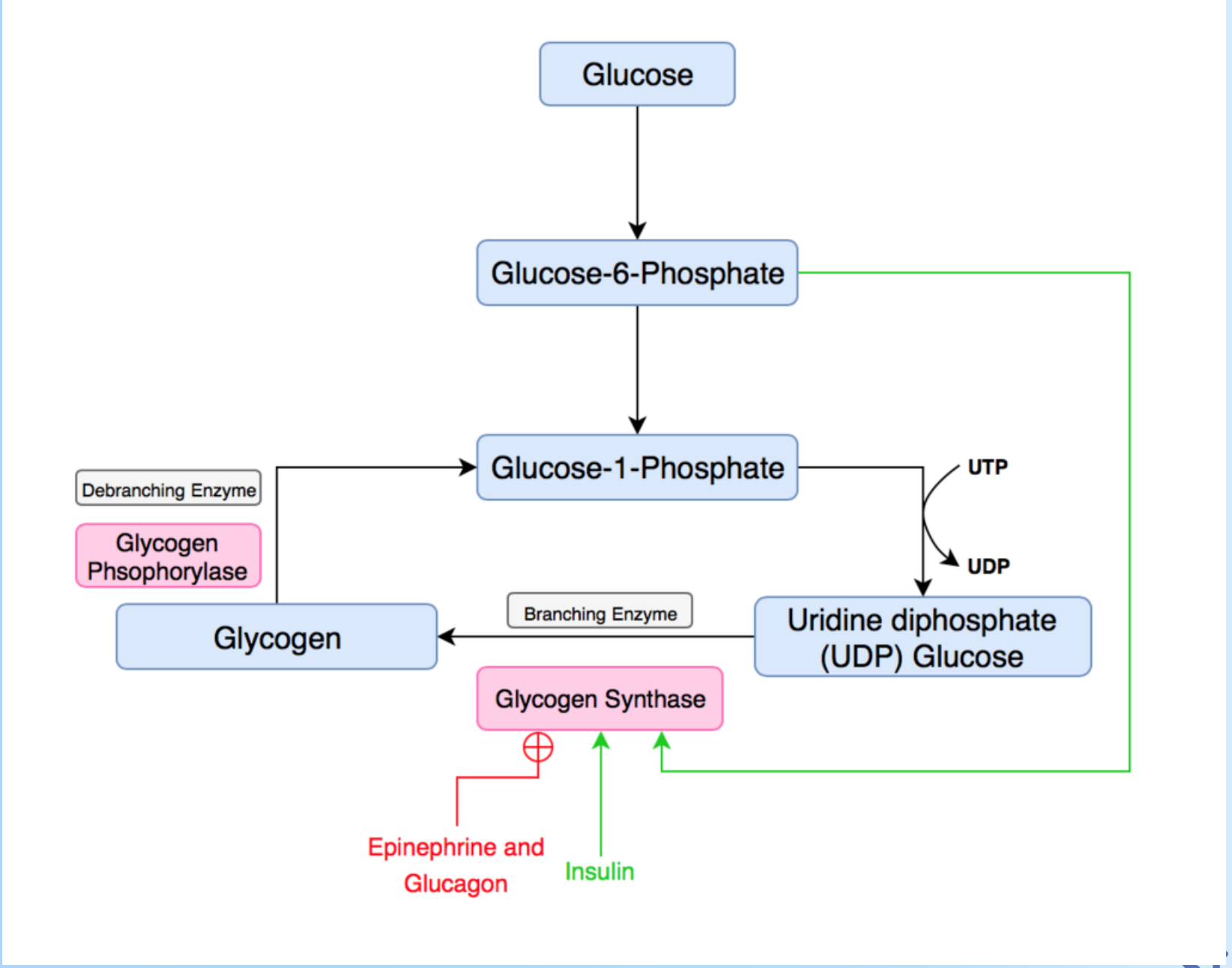
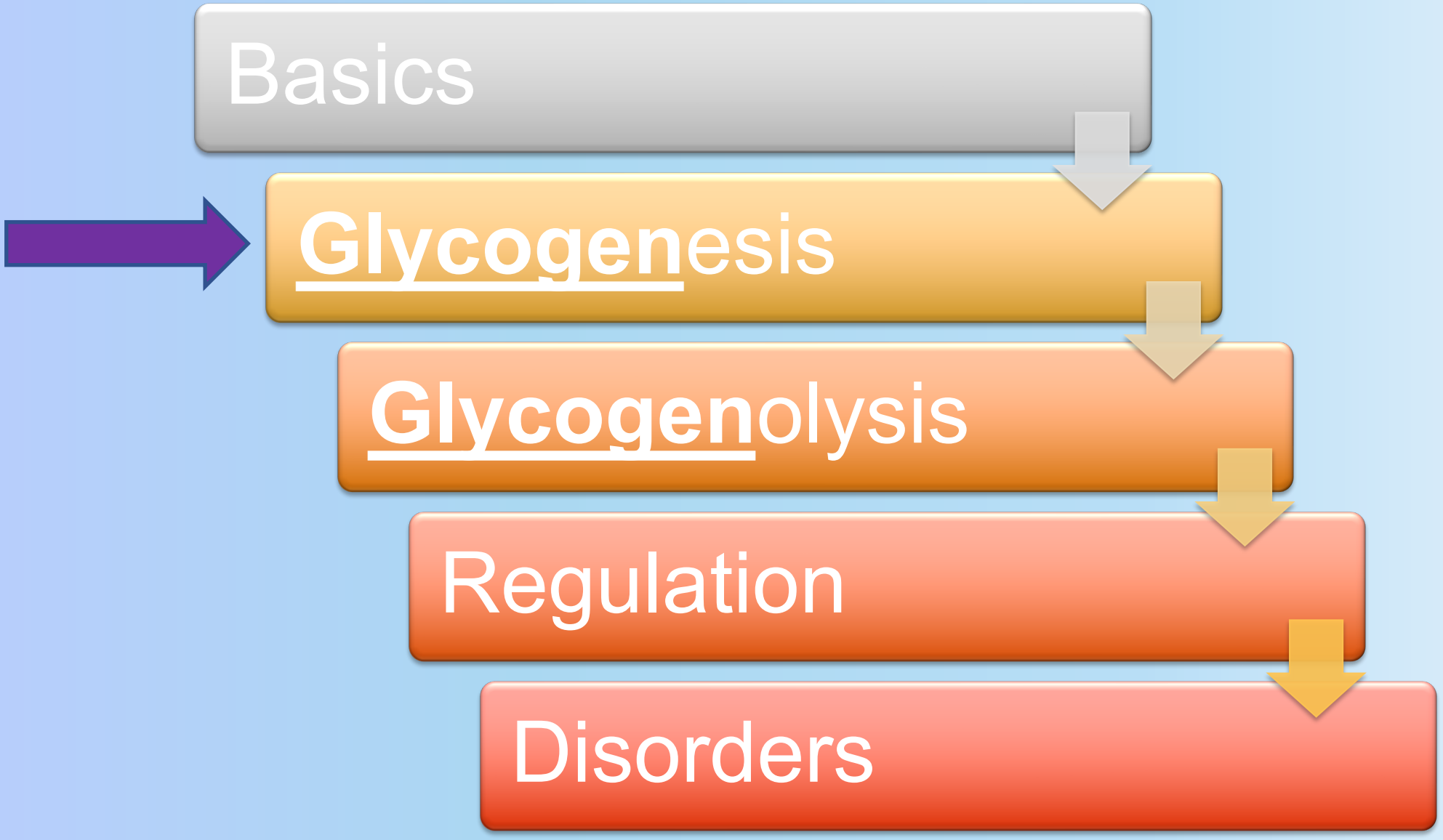
Basics




Basics
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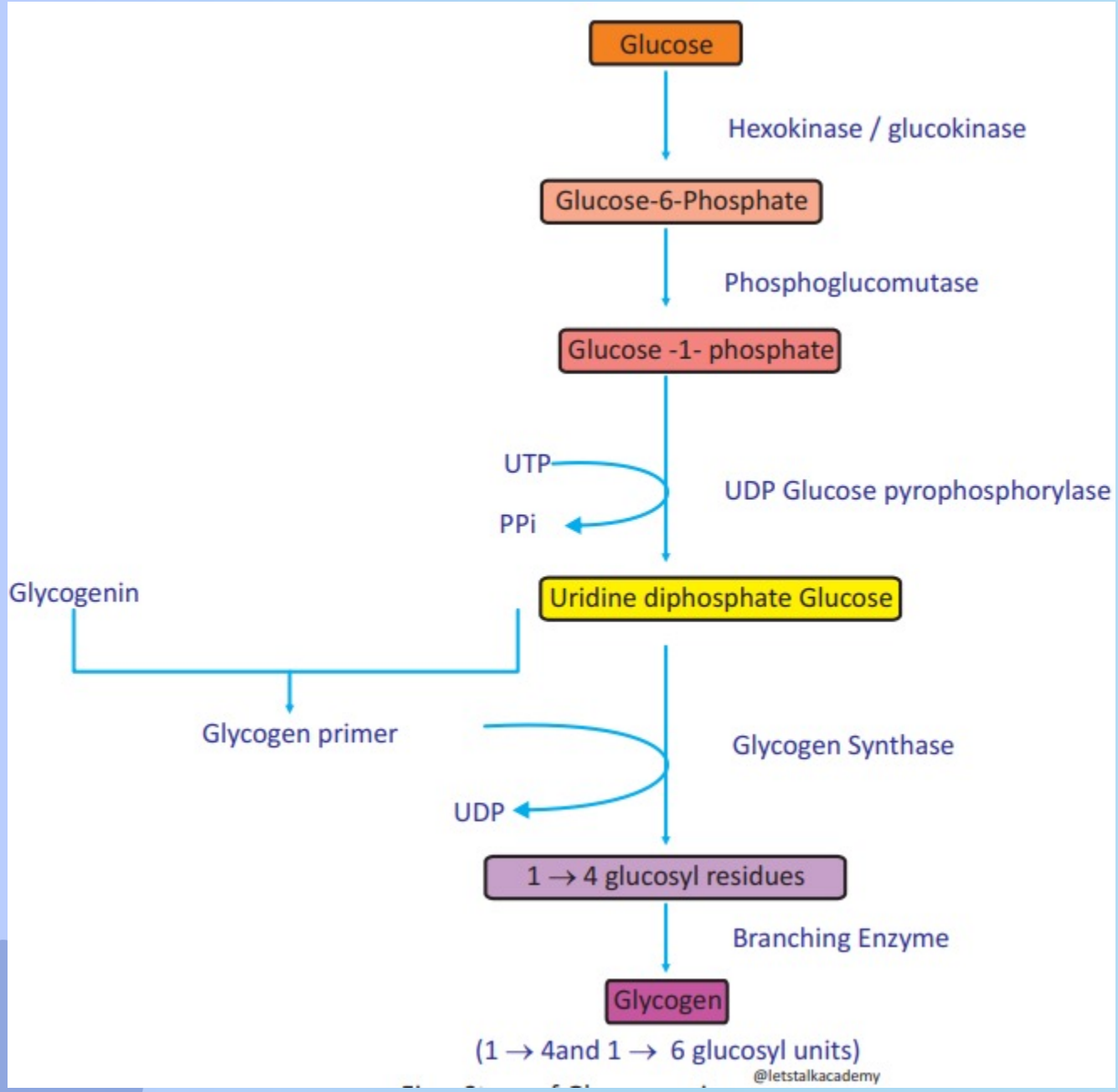

Glycogenesis

The big picture steps:

- Glycolysis rxn (hexokinase)
- Move the phosphate group (phophoglucomutase)
- Add UDP to glucose (UDP glucose pyrophosphorylase)
- Attach the glucose to the ‘primer’ glycogenin
- Add more glucose molecules
- Add branches (branching enzyme)

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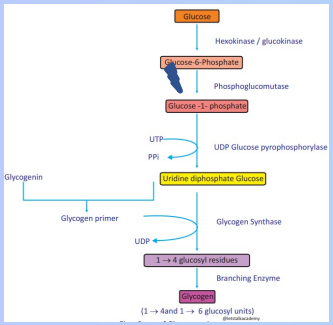
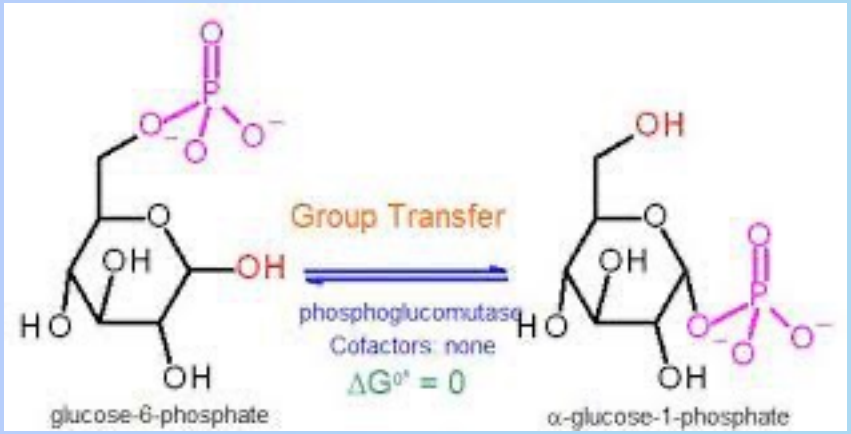
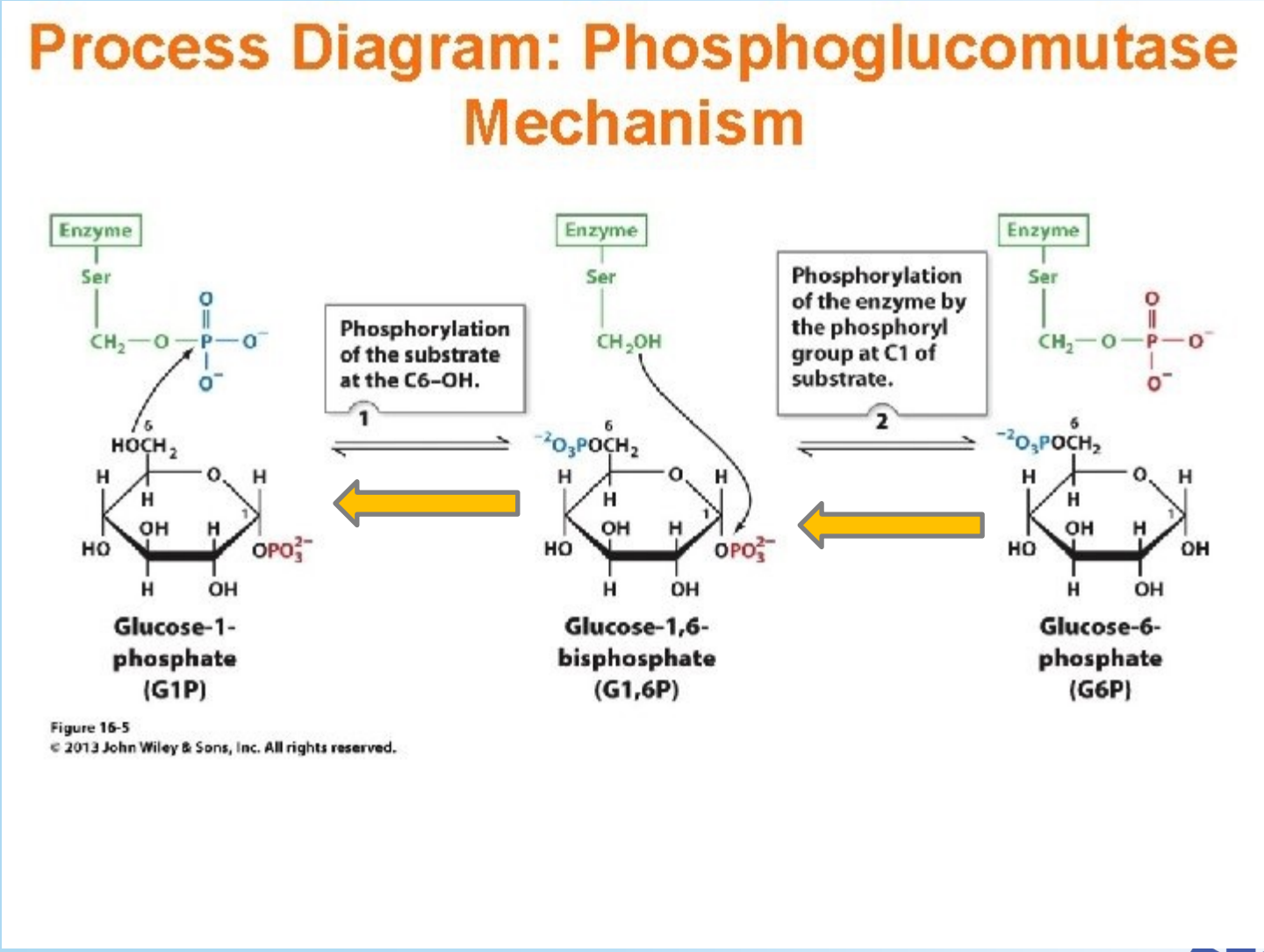
Move the phosphate group



Big picture



The details:



Glycogenesis

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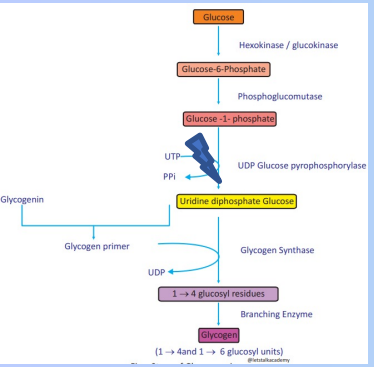
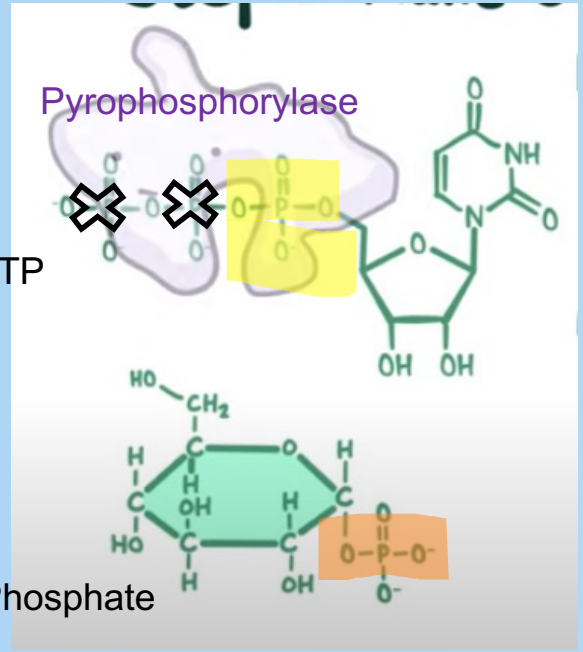


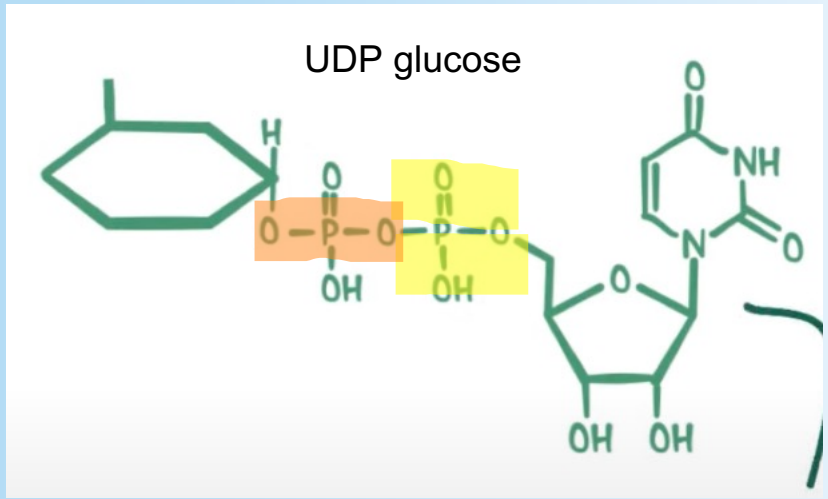
Pyrophosphorylase: Add the UDP to glucose

Adding the UDP "activates" the glucose. Glucose is stable as it is, need to transform it to a more reactive/high energy form.

Glycogenesis

UDP-glucose pyrophosphorylase removes 2 phosphates of UTP (gives the energy)





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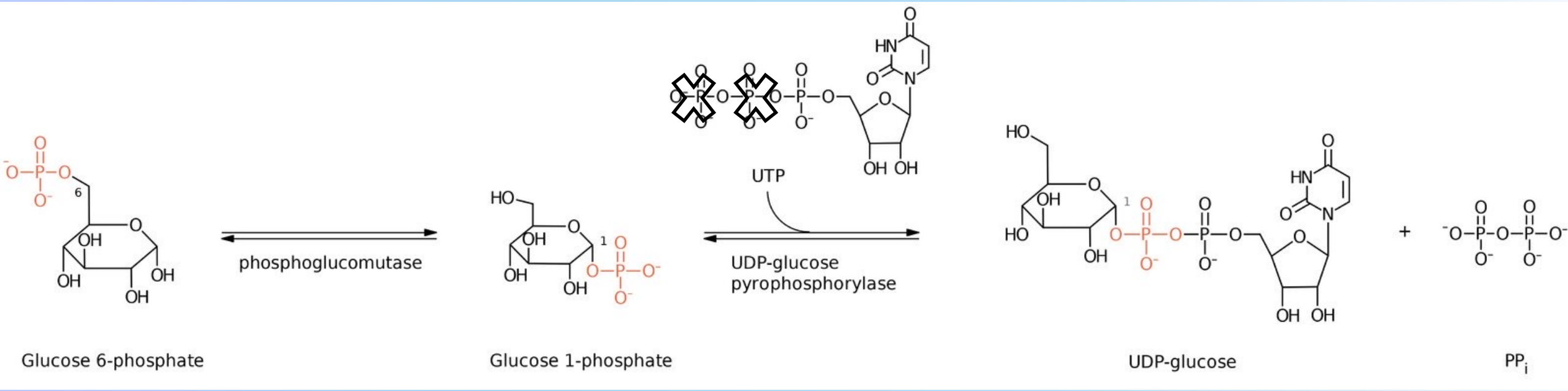
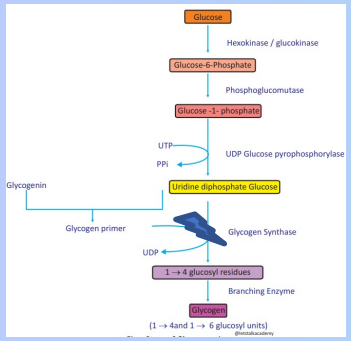
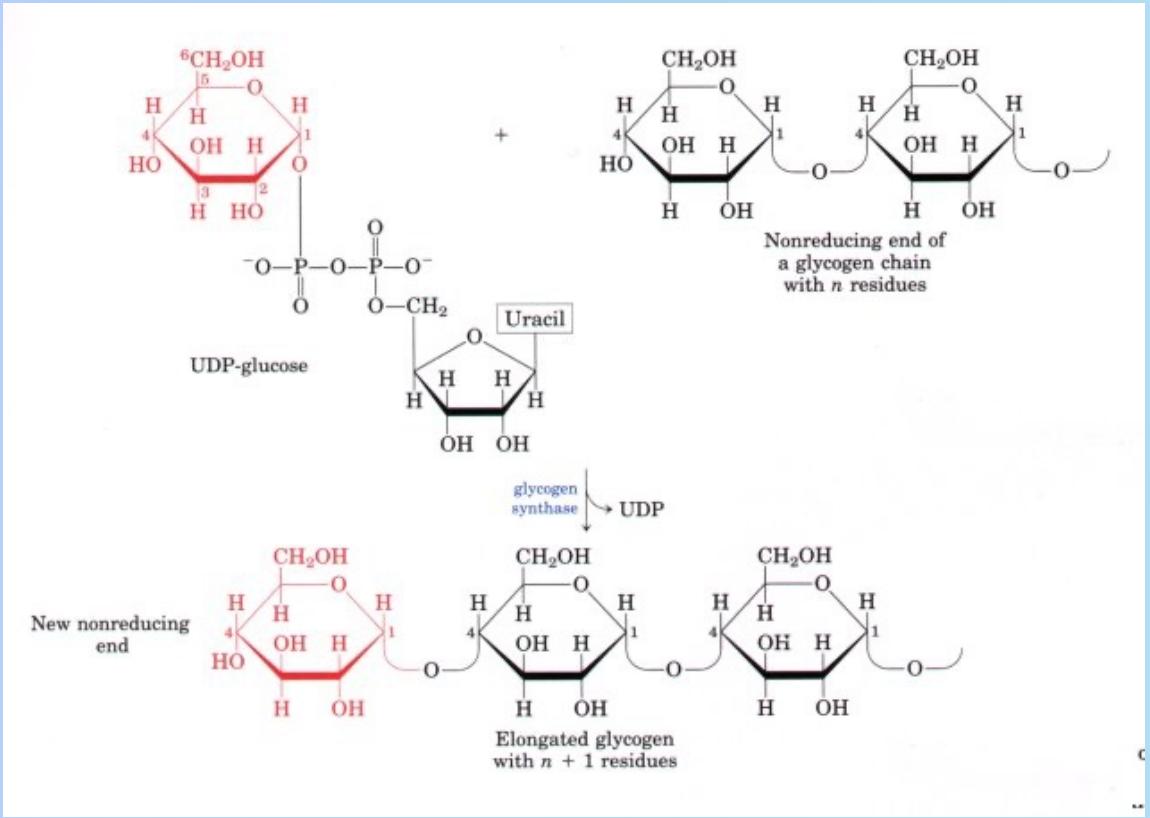

phosphoglucomutase
UTP
UDP-glucose
pyrophosphorylase
+
Glucose 6-phosphate
Glucose 1-phosphate
UDP-glucose
PPi



Glycogen Synthase

Glycogenesis



Makes α1,4 glycosidic bonds

- Hydroxyl group of carbon 1 of activated glucose to the C4 of the accepting glucose chain

Can only elongate an existing chain

RATE LIMITING STEP

ACTIVE WITHOUT phosphate

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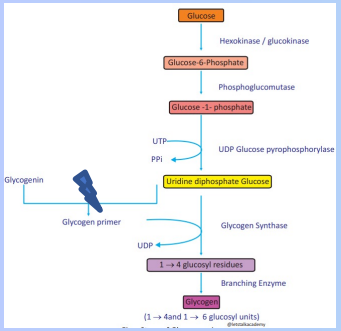
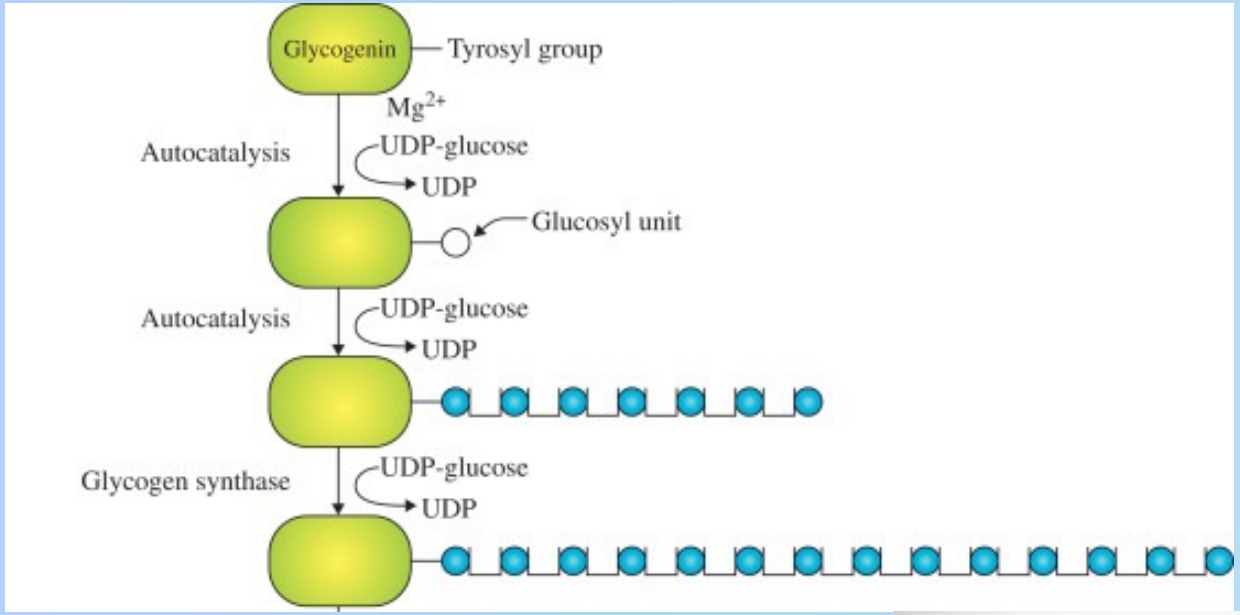


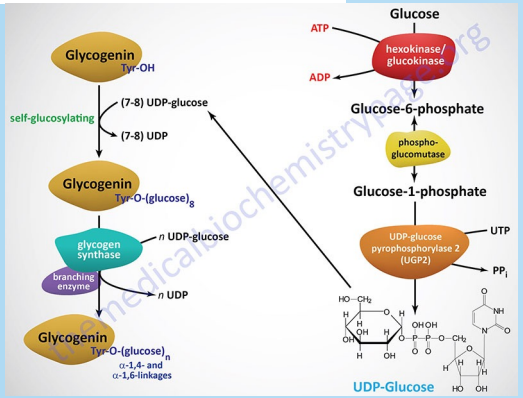
Glycogenin

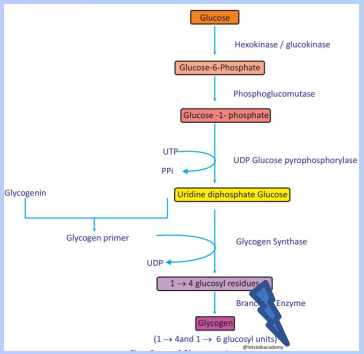
Glycogenesis



Protein attached to a tyrosine residue.

Autocatalysis UDP glucose to make a short chain so newer UDP glucose has a point to attach to. Acts as its own enzyme

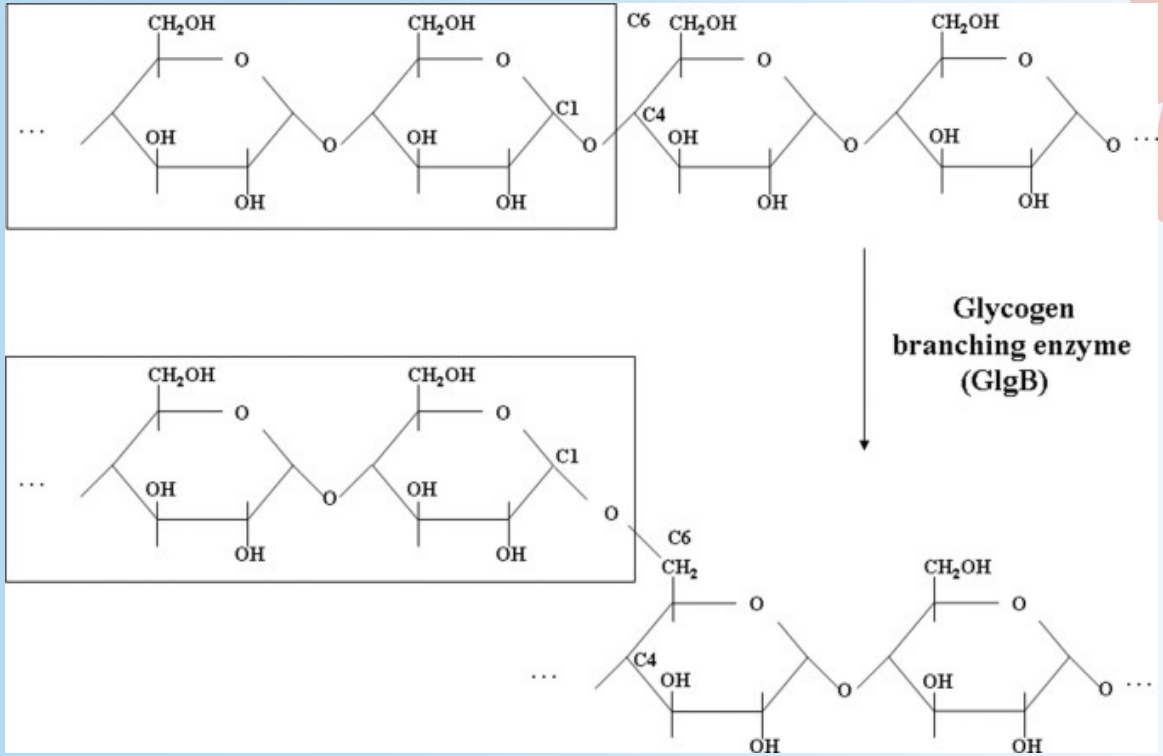


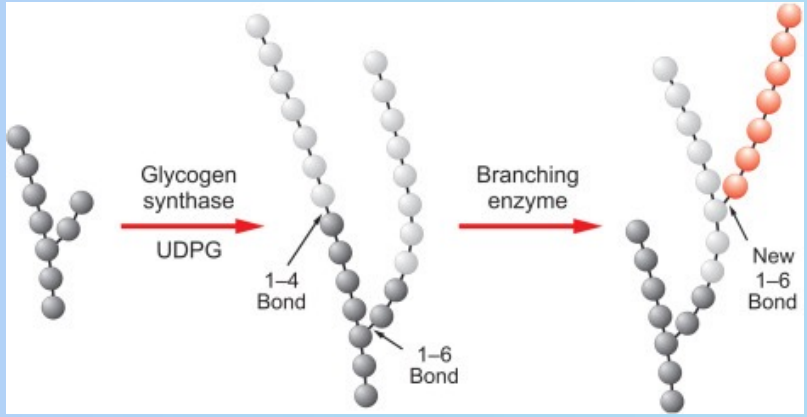


Branching enzyme

Glycogenesis

- Shortens chains at least 11 glucose long by branching them. And repeats this over and over again.
- Attaches as α1,6 glycosidic bonds.
- Increases solubility and density





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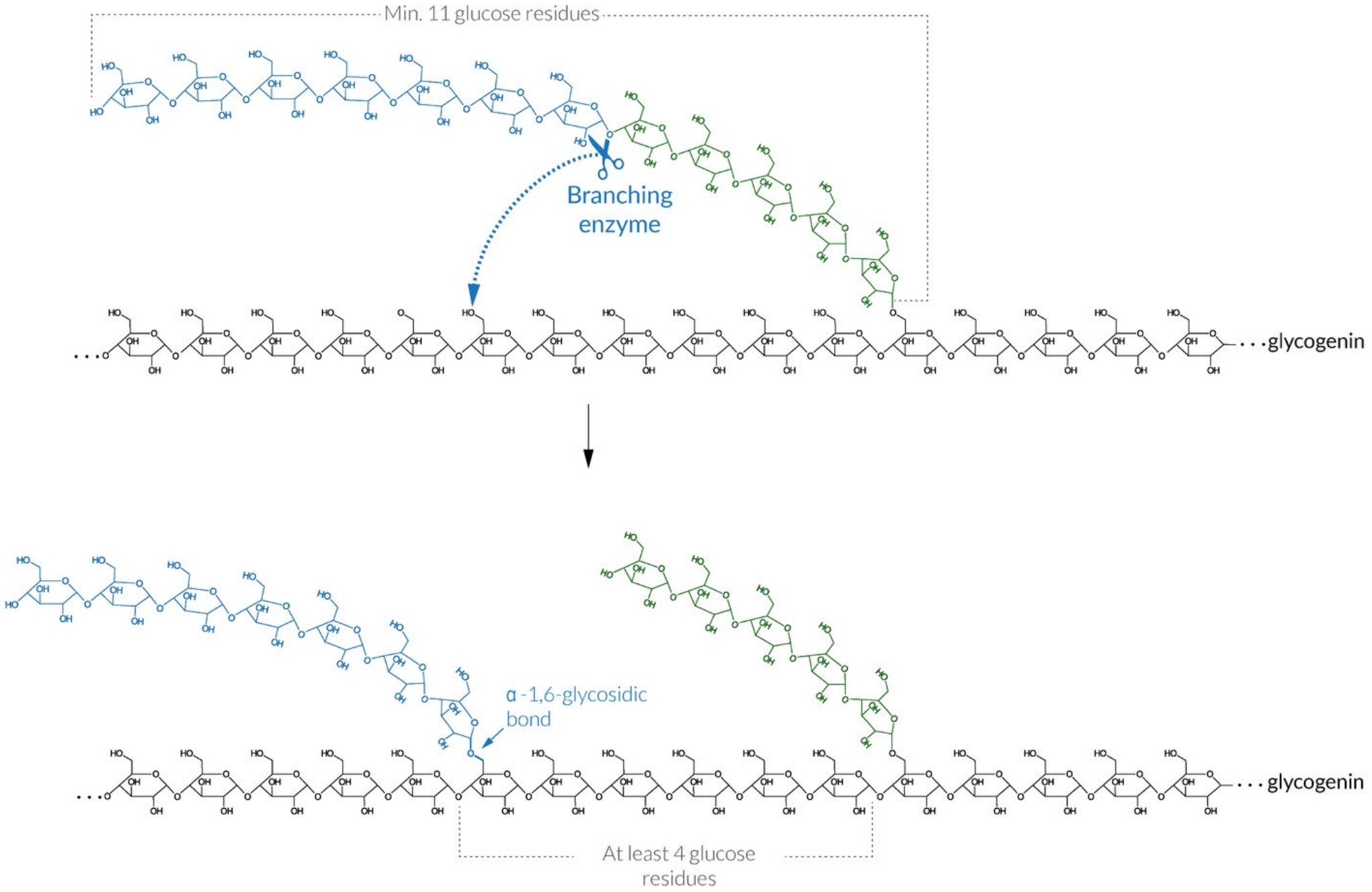
Glycogenesis



Basics

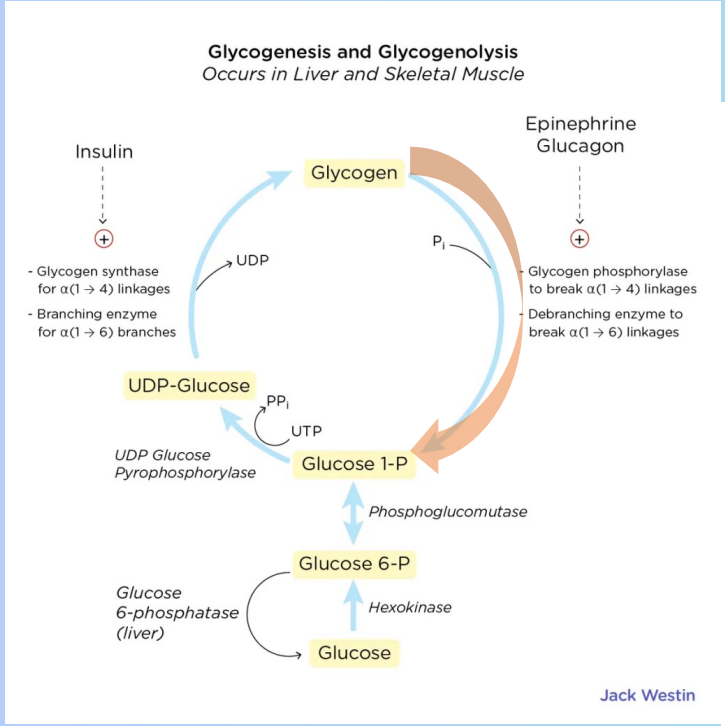
Glycogenesis

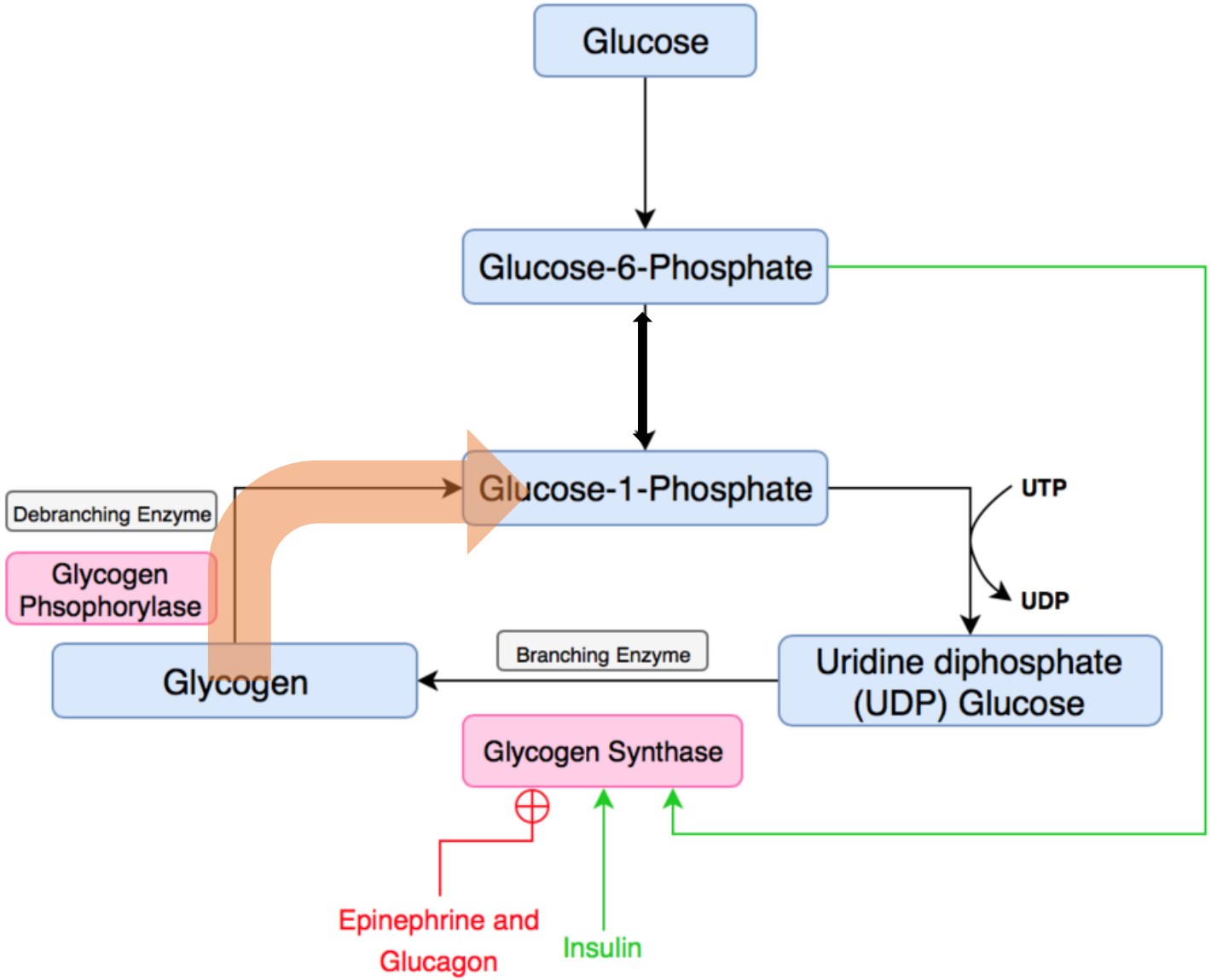
Glycogenolysis

Regulation

Disorders

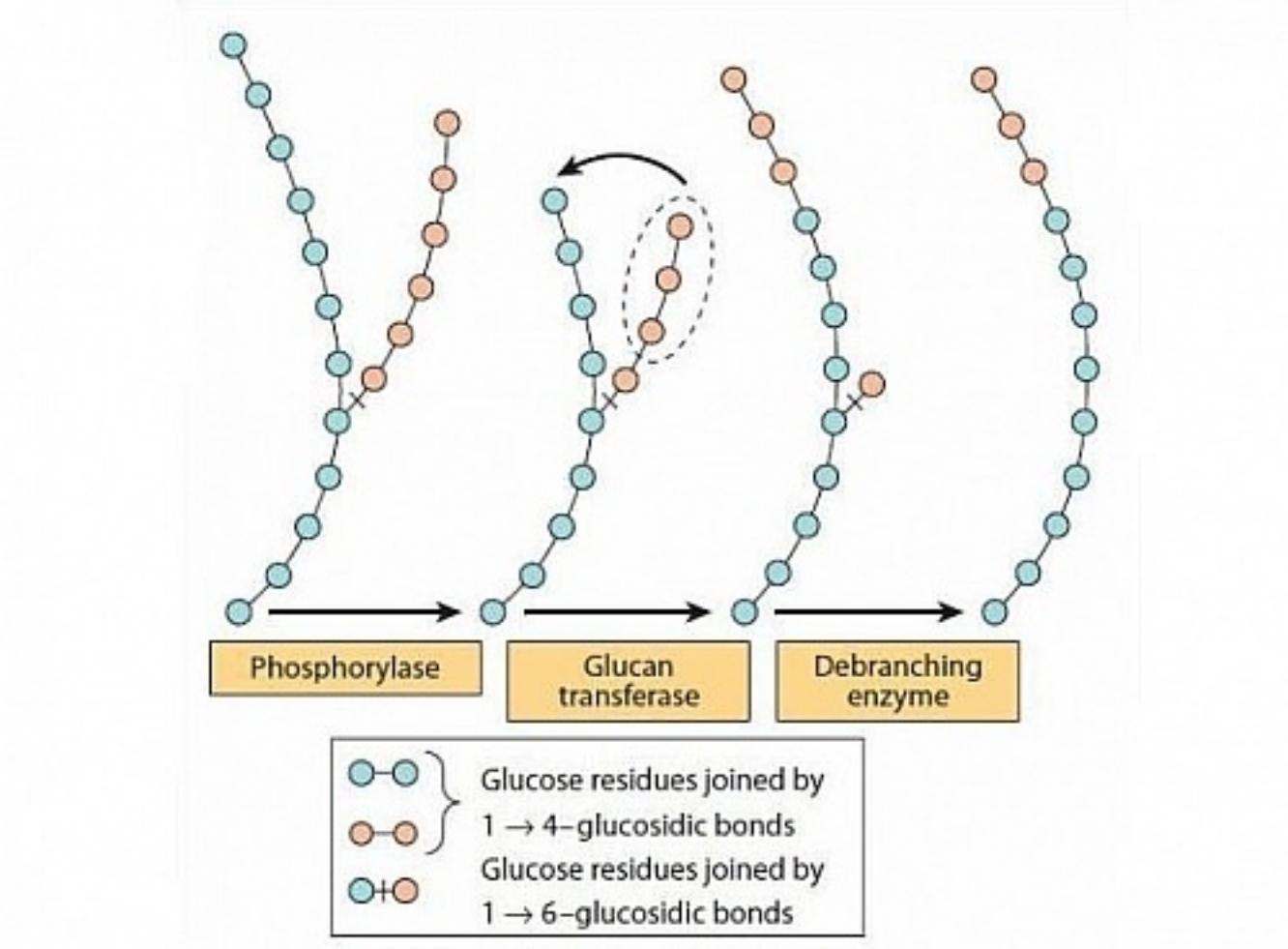
Glycogenolysis



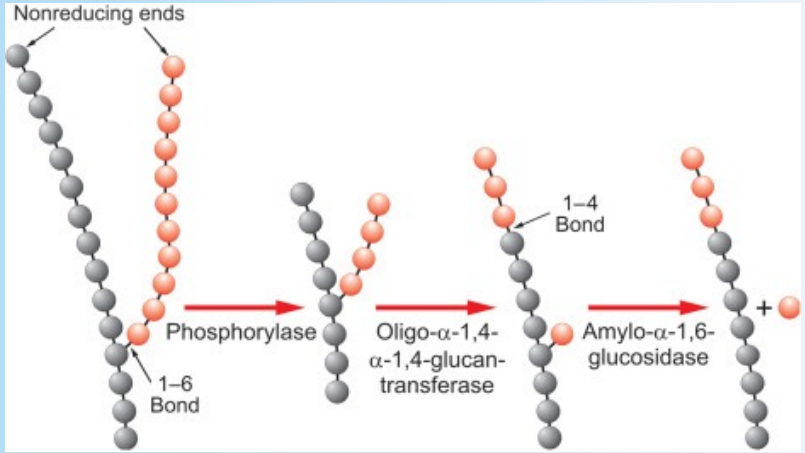


Glycogenolysis overview

Glycogenolysis



Take them off 1 at a time till we get to 4 → Move over 3 → Cut the 1 → Repeat



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Glycogen Phosphorylase

Glycogenolysis

- Break α1,4 bonds by phosphorylating
- Works from the outside → in
- Residues leave as Glucose-1-phosphate
- STOPS until 4 glycosidic residues per branch
- Uses PLP (B6 derivative)
- ACTIVE when phosphorylated
- **RATE LIMITING ENZYME**

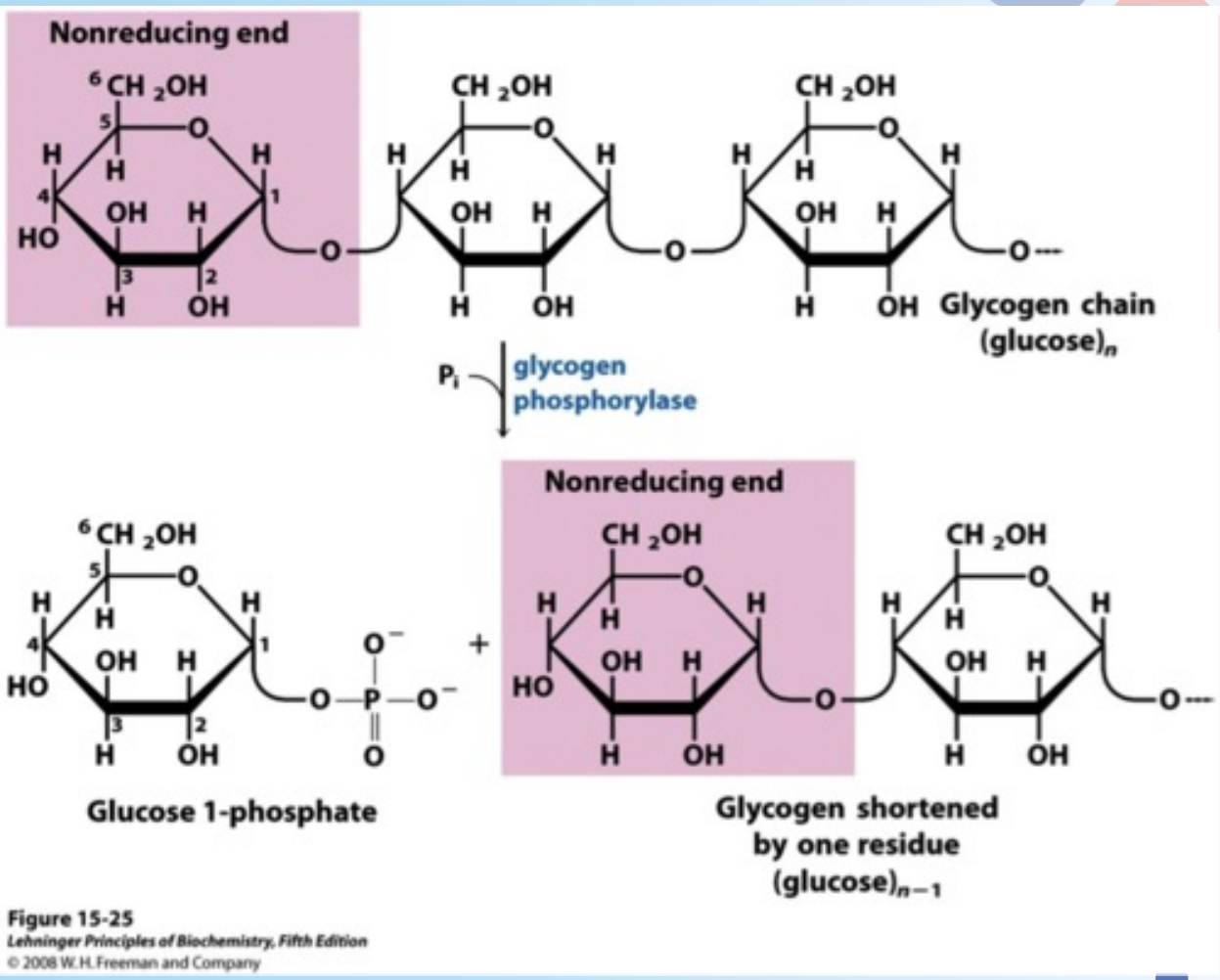
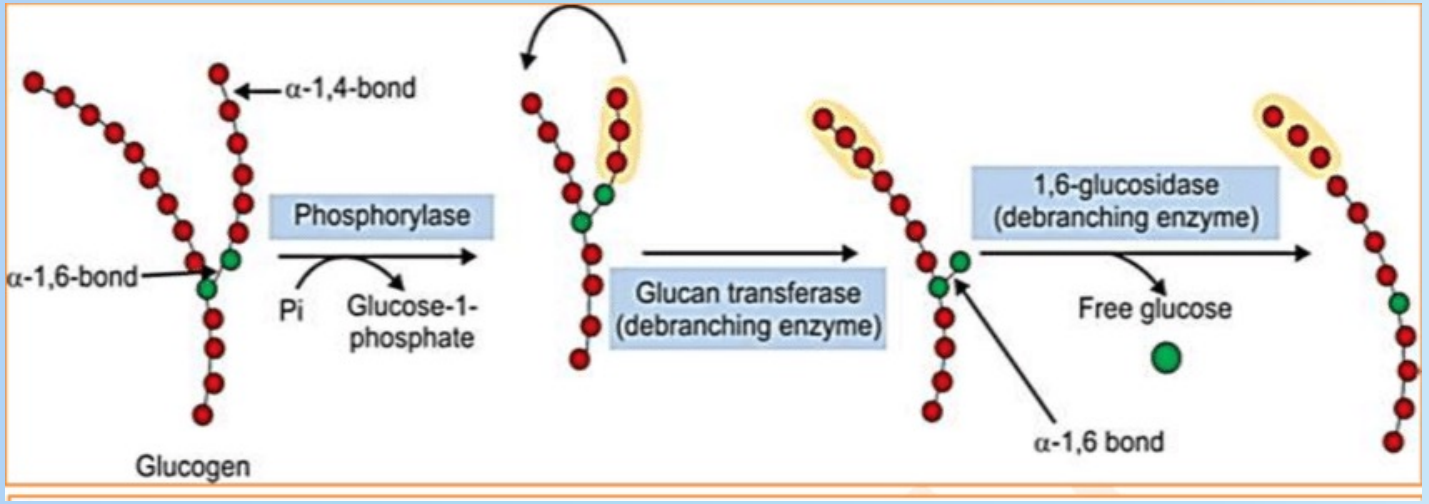


Figure 15-25
Lehninger Principles of Biochemistry, Fifth Edition

Debranching enzyme

Enzyme with 2 catalytic sites



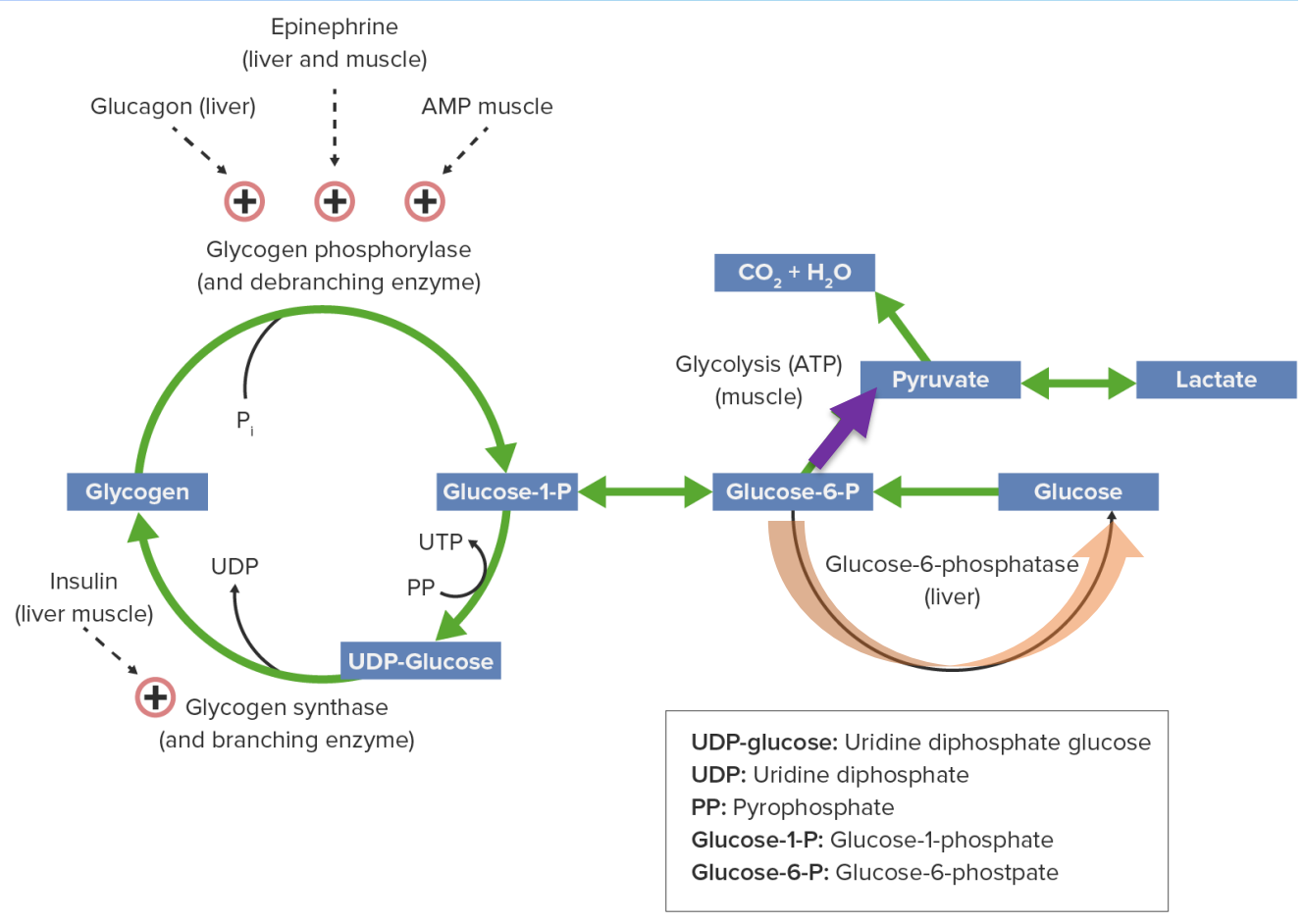
Glucan Transferase

- Moves trisaccharide unit

1,6 Glycosidase

- Cleaves branch and leaves free glucose

Glycogenolysis



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

Basics

Glycogenesis

Glycogenolysis

Regulation

Disorders

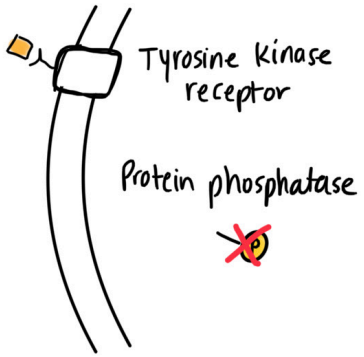
Regulation

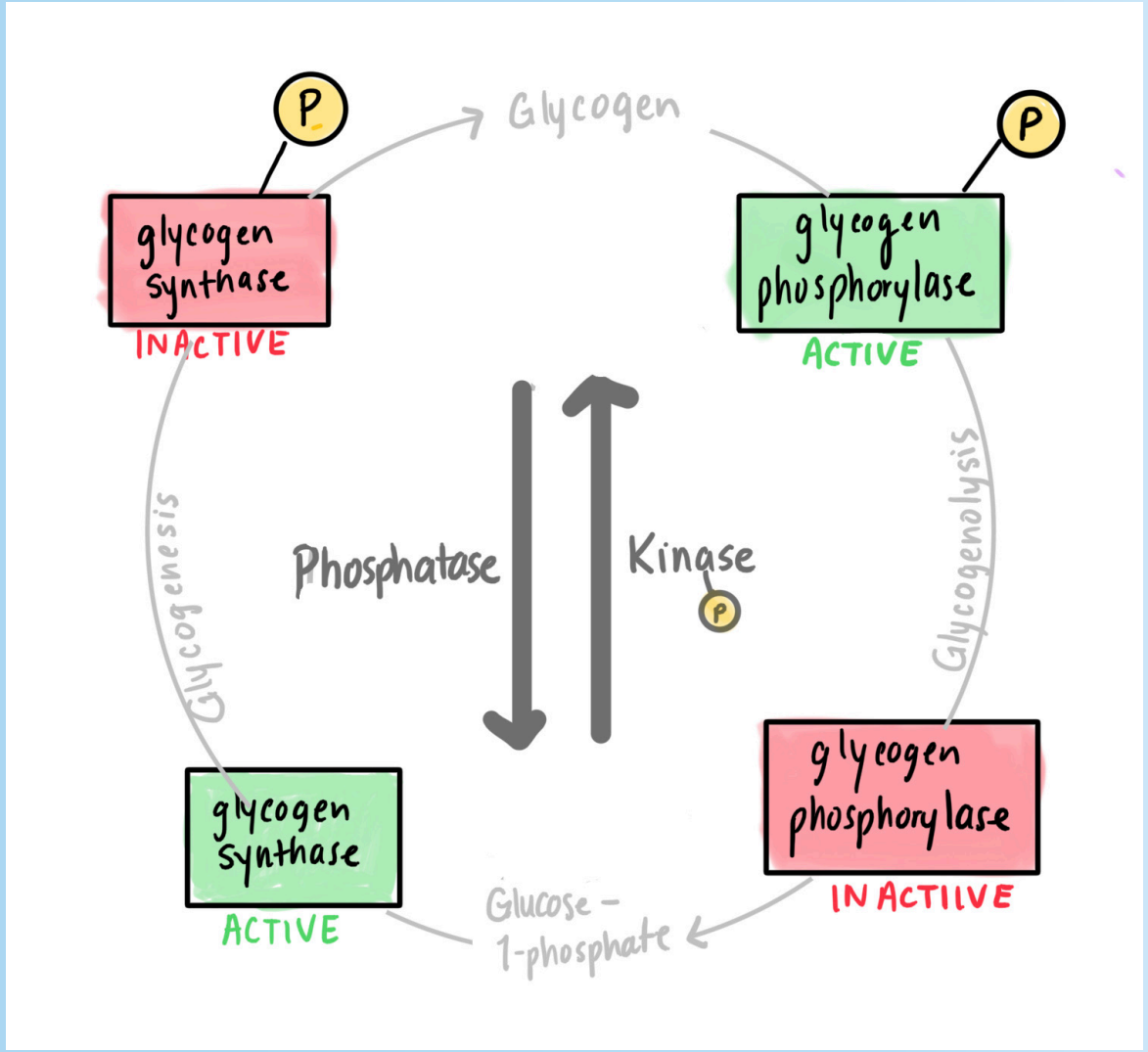
Regulation via phosphate

High glucose level

INSULIN

insulin
(causes dephosphorylation)



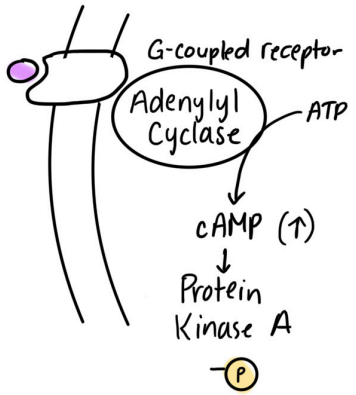


Low glucose level

GLUCAGON & epinephrine

(liver) glucagon/epinephrine
(muscle) epinephrine

(causes phosphorylation)



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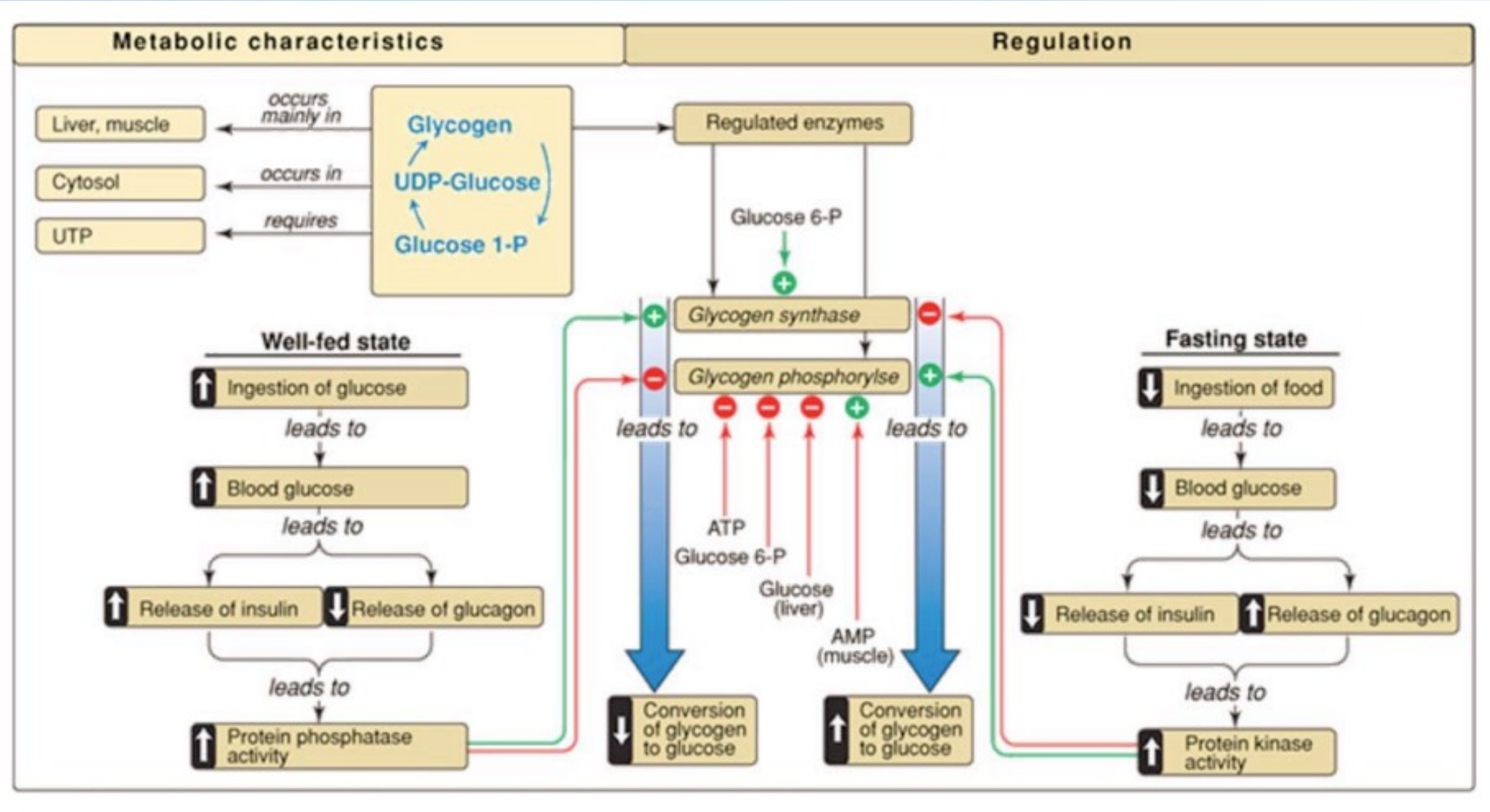
Regulation



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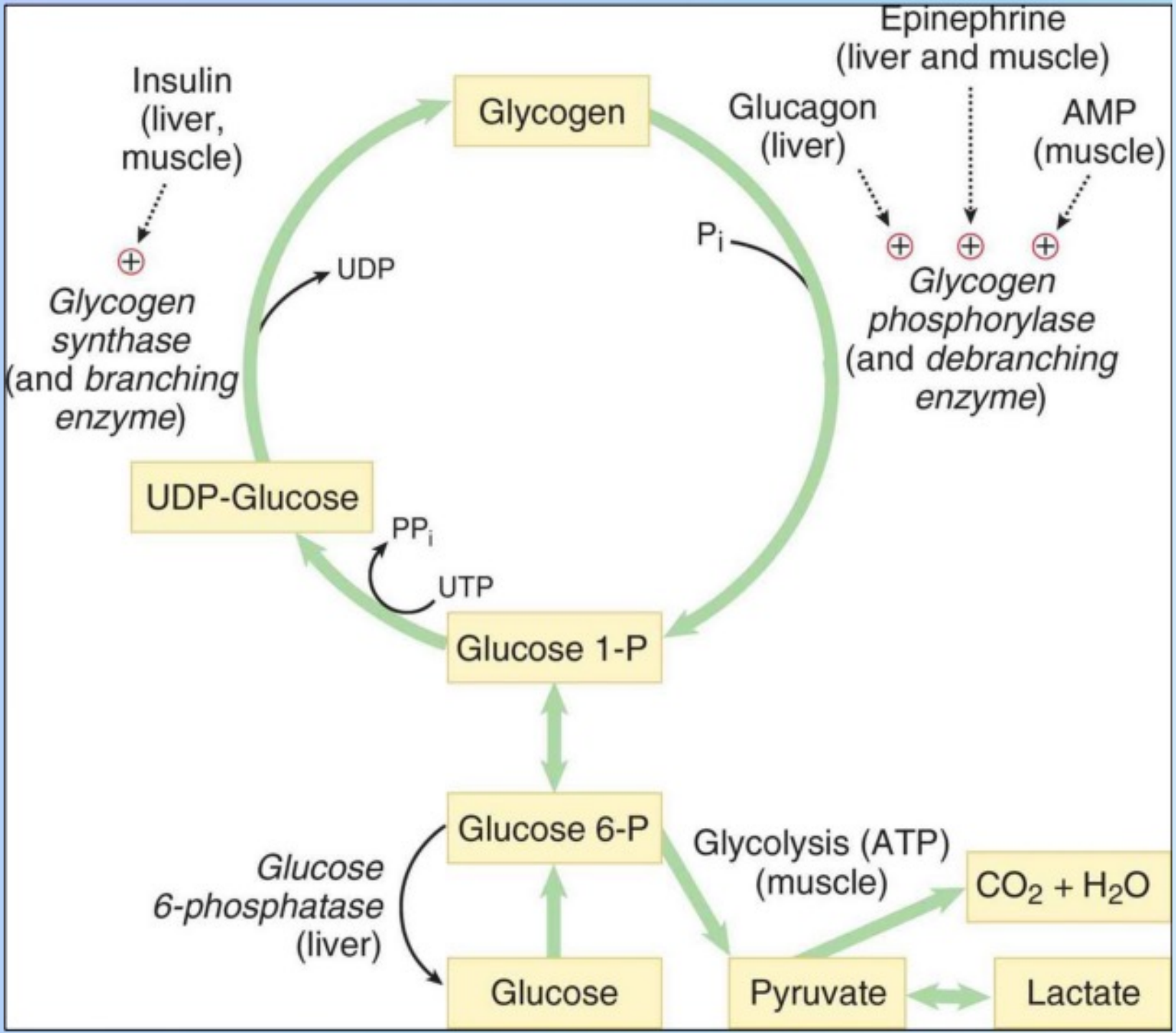
Epinephrine
(liver and muscle)
Insulin
(liver,
muscle)
Glycogen
Glucagon
(liver)
AMP
(muscle)
Pi
UDP
Glycogen
synthase
(and branching
enzyme)
Glycogen
phosphorylase
(and debranching
enzyme)
UDP-Glucose
PPi
UTP
Glucose 1-P
Glucose 6-P
Glycolysis (ATP)
(muscle)
Glucose
6-phosphatase
(liver)
CO2 + H2O
Glucose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

Basics

Glycogenesis

Glycogenolysis

Regulation

Disorders

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.

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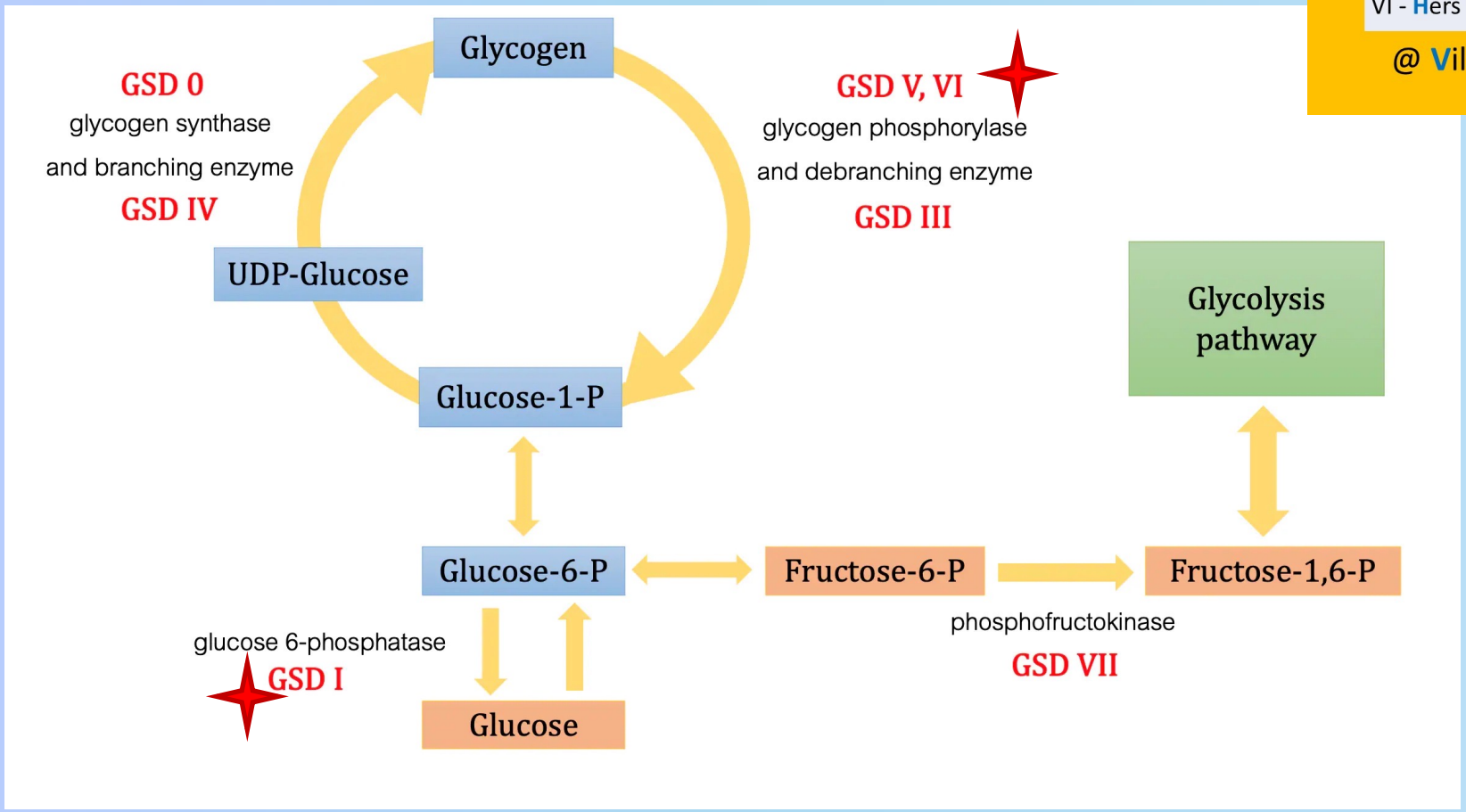

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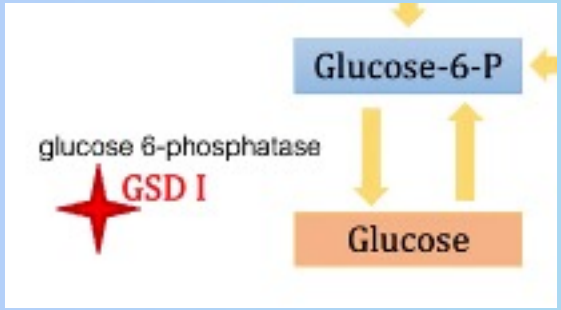
Type 1: Von Gierke Disease
Glucose-6-phosphatase deficiency

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

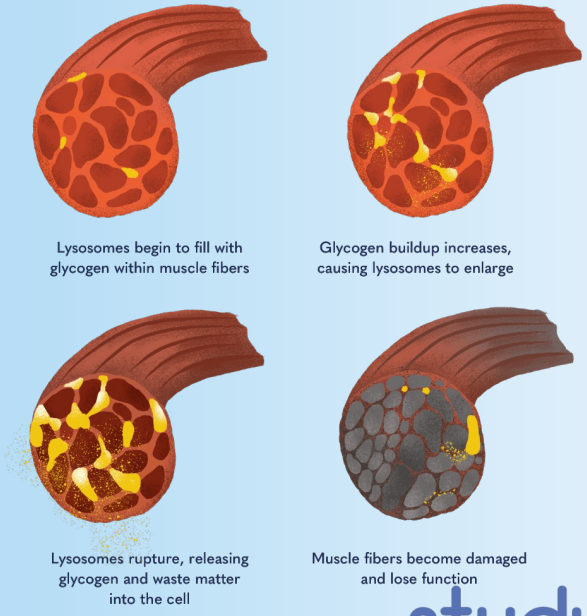


Type 2: Pompe Disease
Lysosomal GAA deficiency

Most severe disease

Affects muscle

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



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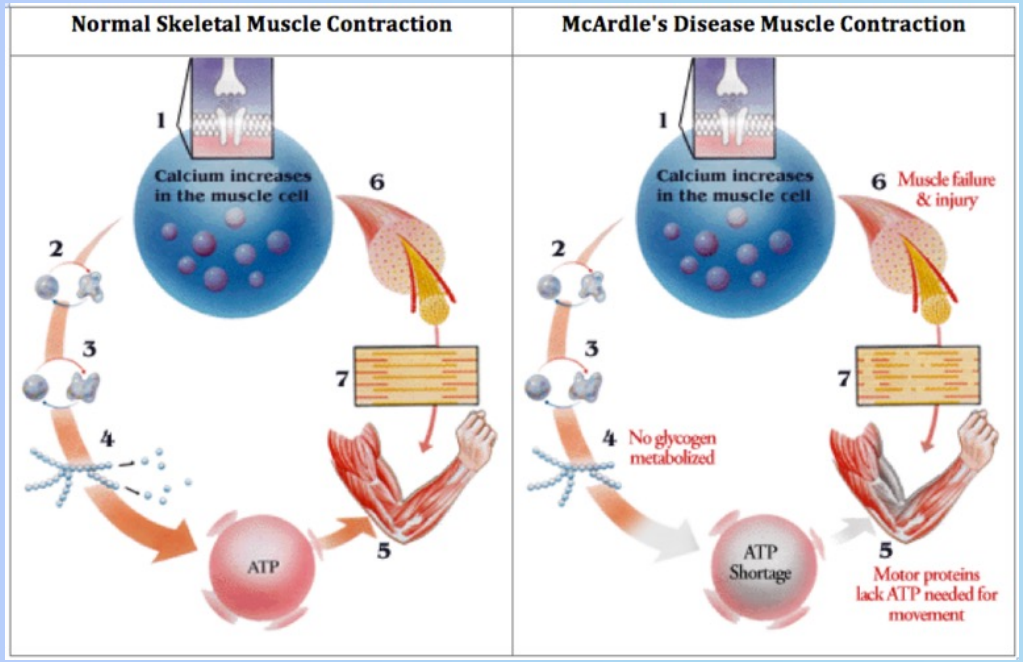
Type V: McArdle's Disease Myophosphorylase Deficiency

Autosomal recessive

Can't break down glycogen

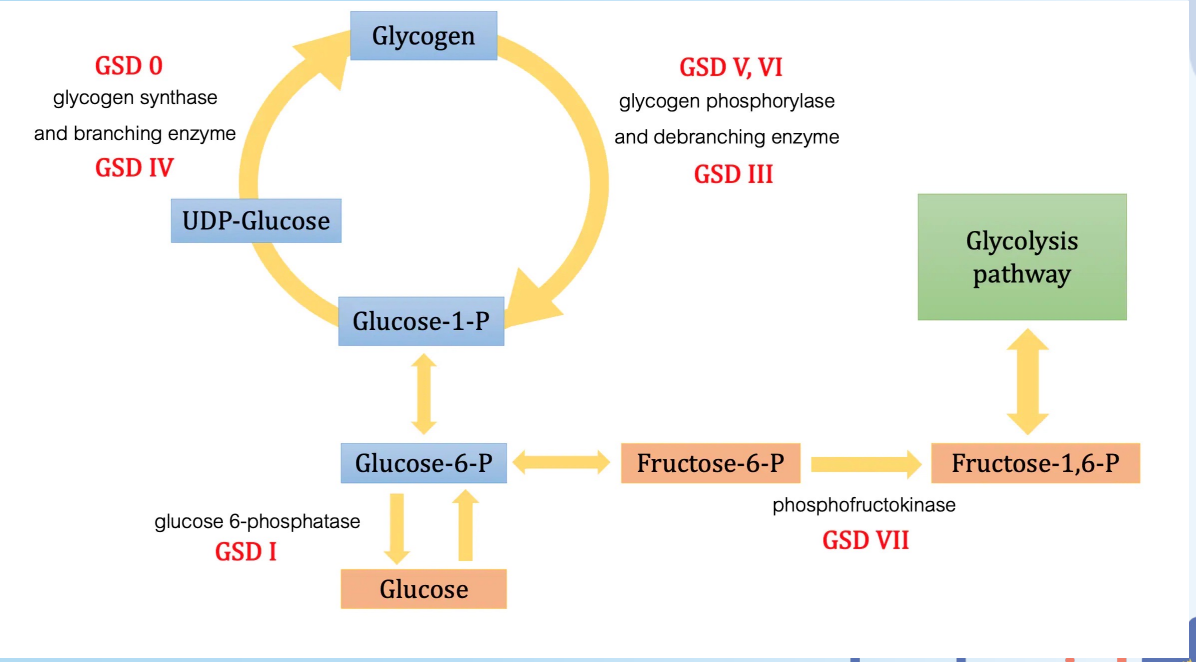
Deficiency of phosphorylase in <u>MUSCLE</u>



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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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

2.3.A3 Lipids are more suitable for long-term energy storage in humans than carbohydrates.

Why is glycogen is needed at all?

- Glycogen can be transported easily by the blood
- Fats in adipose tissue cannot be mobilized as rapidly

An analogy:

You are paid in cash (Glucose)

Put it in your → Wallet (Glycogen)

easy to get to, would be too big if you put in all your money

Deposit in the → Bank (Fat)

Can put lots of money here, more of a hassle to get it back out

Spend it! (Respiration)

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