Glucose Metabolism

Creation and Breakdown

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What will be covered?

EVERYTHING you need to know about Glucose! Hefty, yes but extremely important for your midterm. This entails:

1. The molecule
2. Glycolysis
3. Pyruvate Dehydrogenation
4. Gluconeogenesis
5. PPP (Pentose Phosphate Pathway)

The Glucose Molecule

What you need to know about the lead of the show

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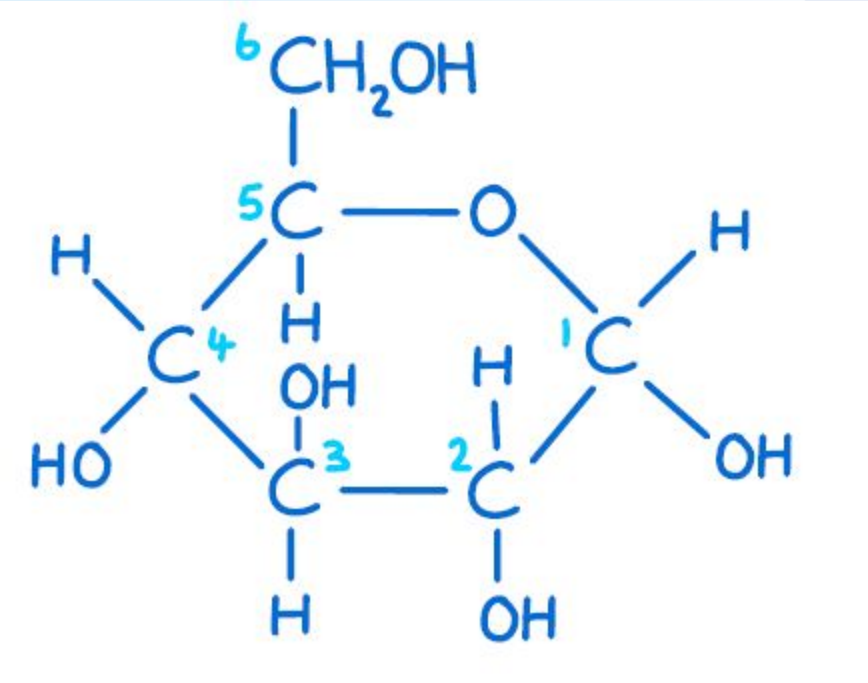
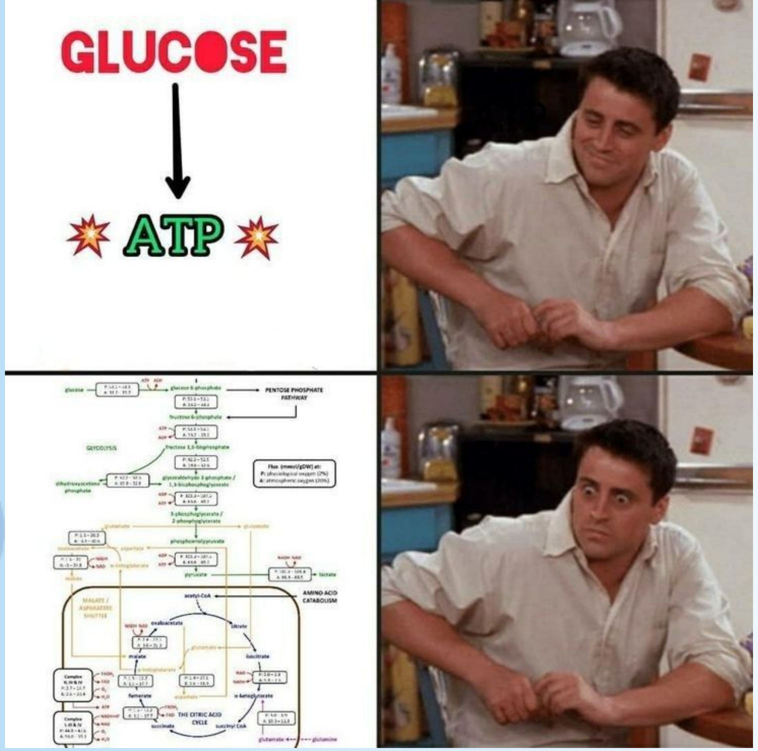
The Molecule

- **Glucose:** a 6-carbon monosaccharide ($C_6H_{12}O_6$)
- Primary energy substrate for most cells
- **Obligatory fuel for:**
  - Erythrocytes (no mitochondria → glycolysis only)
  - Brain (under physiological conditions)
- Maintained within a narrow range (~70–100 mg/dL fasting)
- Central to two opposing processes:
  - **Breakdown (catabolism)** → ATP production
  - **Synthesis (anabolism)** → maintaining blood glucose





Glycolysis

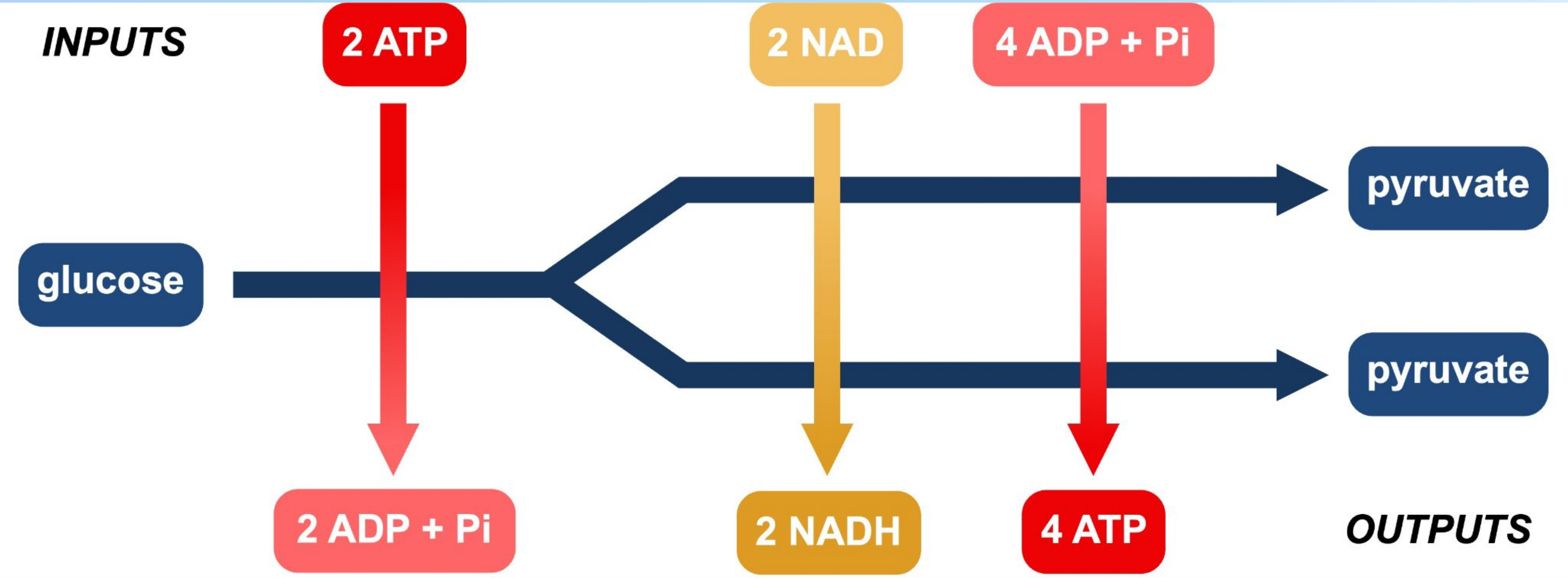
The breakdown (literally)

1. Glycolysis

What is it? In short, it's just:

The ATP-dependent breakdown of <u>Glucose</u> into <u>Pyruvate</u>

It's a <u>10-step</u> process, which entails an <u>Investement Phase</u> and a <u>Payoff Phase.</u>



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But first, enzymes!

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Quick Recap!

Enzyme types:	What do they do?
Oxidoreductases	Oxidation-reduction reactions
Transferases	Group transfer
Hydrolases	Hydrolysis reactions (transfer of functional group to water)
Lyases	Addition or removal of groups to form double bonds
Isomerases	Isomerization (intramolecular group transfer)
Ligases	Joining of two groups together

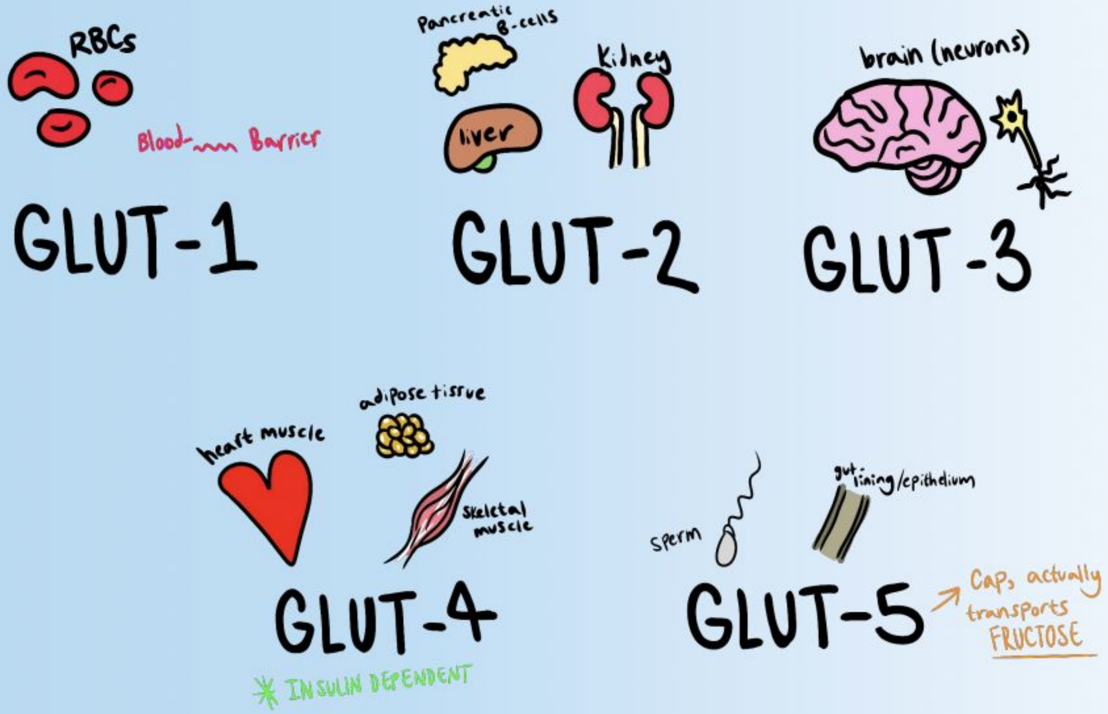
When and Where does Glycolysis occur?

When?
1. "Fed" state: When you have just eaten and have elevated glucose in the blood
   - Insulin: Fed state hormone, signals glucose to go into cells
2. When in need of ATP
3. Under aerobic & anaerobic condition

Where?
1. Molecularly: Cell cytosol
2. All living cells, especially RBCs!
 - RBCs do not have mitochondria to power Kreb's cycle & oxidative phosphorylation to make ATP

The GLUTs

- GLUT: Transport glucose from extracellular space to intracellular space
- Respective tissues have their respective glucose transporters
- GLUT4: upregulated when insulin is present
- GLUT5: transports fructose, not glucose



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Step 1 (Investment Phase)

Reaction:

Glucose + ATP → Glucose-6-phosphate + ADP

Key Features:

- **Irreversible step**
- **Consumes 1 ATP**
- Traps glucose inside the cell (phosphorylated form cannot diffuse out)

Enzymes:

Hexokinase (most tissues)

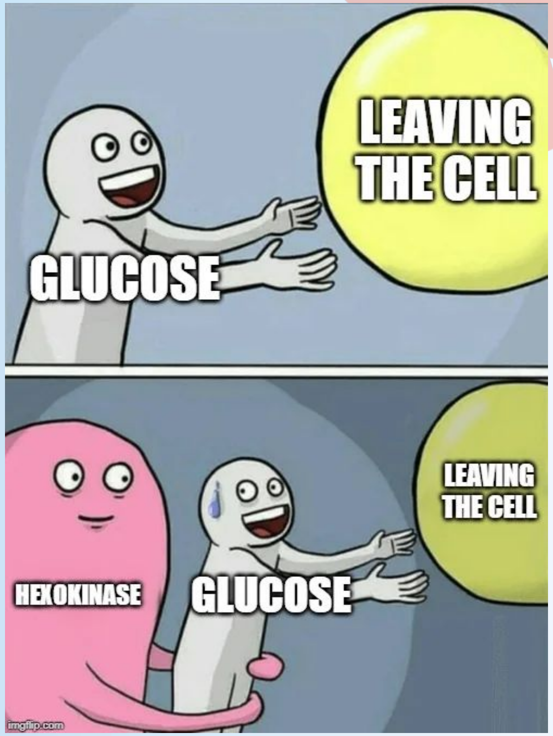
Glucokinase (liver, pancreatic β-cells)

❗ **Regulation :**

1. Hexokinase inhibited by **glucose-6-phosphate**
2. Glucokinase: not inhibited

Hexokinase vs. Glucokinase

Enzyme:	**Hexokinase**	**Glucokinase**
Where:	Most tissues	Liver
Km	Low Km *High affinity towards glucose – converts glucose at low concentrations*	High Km *Low affinity towards glucose – converts glucose only at high concentrations*
Effect of G6P	Negative feedback	None
Effect of insulin	None	Stimulated



Step 2 - Isomerization (Investment Phase)

Reaction:

Glucose-6-phosphate ⇌ Fructose-6-phosphate

Key Features:

- **Reversible reaction**
- Converts **aldose** → **ketose**
- No ATP consumed or produced

Functional Importance:

- Rearranges molecule to allow **symmetrical cleavage later (Step 4)**
- Prepares substrate for **rate-limiting step (PFK-1)**

Enzyme:

Phosphoglucose isomerase

Step 3 - Rate Limiting Step (Investment Phase)

Reaction:

Fructose-6-phosphate + ATP →
Fructose-1,6-bisphosphate + ADP

Key Features:

- Irreversible step
- Consumes 1 ATP
- Committed step of glycolysis

Enzyme:

Phosphofructokinase-1 (PFK-1)

Regulation:

- **Activated by:** AMP, ADP
- **Inhibited by:** ATP, citrate

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Step 4 - Cleavage (Investment Phase)

Reaction:

Fructose-1,6-bisphosphate ⇌ Dihydroxyacetone phosphate (DHAP) + Glyceraldehyde-3-phosphate (G3P)

Key Features:

- **Reversible reaction**
- Cleavage of 6-carbon → two 3-carbon molecules
- No ATP consumed or produced

Functional Importance:

- Generates **two triose phosphates**
- Only **G3P continues directly in glycolysis**

Enzyme:

Aldolase

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Step 5 (Investment Phase)

Reaction:

Dihydroxyacetone phosphate (DHAP) ⇌ Glyceraldehyde-3-phosphate (G3P)

Key Features:

- **Reversible reaction**
- No ATP consumed or produced
- Converts DHAP → G3P

Functional Importance:

- Only **G3P continues in glycolysis**
- Results in **2 molecules of G3P per glucose**

Enzyme:

Triose phosphate isomerase

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Step 6 - Oxidation & NADH Production (Payoff Phase)

Reaction:

Glyceraldehyde-3-phosphate + Pi + NAD^+ →
1,3-bisphosphoglycerate + NADH + H^+

Key Features:

- **Reversible reaction**
- Produces **NADH (per G3P)**
- Forms **high-energy intermediate (1,3-BPG)**
- No ATP used or produced

Functional Importance:

- First step of **energy generation phase**
- Provides substrate for **ATP production in next step**

Enzyme:

Glyceraldehyde-3-phosphate dehydrogenase

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Step 7 - ATP Generation (Payoff Phase)

Reaction:

1,3-bisphosphoglycerate + ADP →
3-phosphoglycerate + ATP

Key Features:

- **Reversible reaction**
- **Substrate-level phosphorylation**
- Produces **1 ATP per G3P (2 ATP per glucose)**

Functional Importance:

- First ATP-producing step of glycolysis
- Recovers ATP invested in earlier steps

Enzyme:

Phosphoglycerate kinase

Step 8 - Mutase Reaction (Payoff Phase)

Reaction:

3-phosphoglycerate ⇌ 2-phosphoglycerate

Key Features:

- **Reversible reaction**
- Intramolecular shift of phosphate group (C3 → C2)
- No ATP consumed or produced

Functional Importance:

- Repositions phosphate to enable formation of a **high-energy intermediate in next step**

Enzyme:

Phosphoglycerate mutase

Step 9 - Dehydration (Payoff Phase)

Reaction:

2-phosphoglycerate ⇌ Phosphoenolpyruvate (PEP) + H_2O

Key Features:

- **Reversible reaction**
- **Dehydration reaction** (removal of H_2O)
- Forms **phosphoenolpyruvate (PEP)** – high-energy intermediate

Functional Importance:

- Generates molecule with **very high phosphoryl transfer potential**
- Prepares for **ATP production in Step 10**

Enzyme:

Enolase

Step 10 - Pyruvate Formation (Payoff Phase)

Reaction:

Phosphoenolpyruvate (PEP) + ADP
→ Pyruvate + ATP

Key Features:

- **Irreversible reaction**
- **Substrate-level phosphorylation**
- Produces **1 ATP per PEP (2 ATP per glucose)**

Enzyme:

Pyruvate kinase

Regulation:

- **Activated by:** Fructose-1,6-bisphosphate (feed-forward activation)
- **Inhibited by:** ATP, alanine

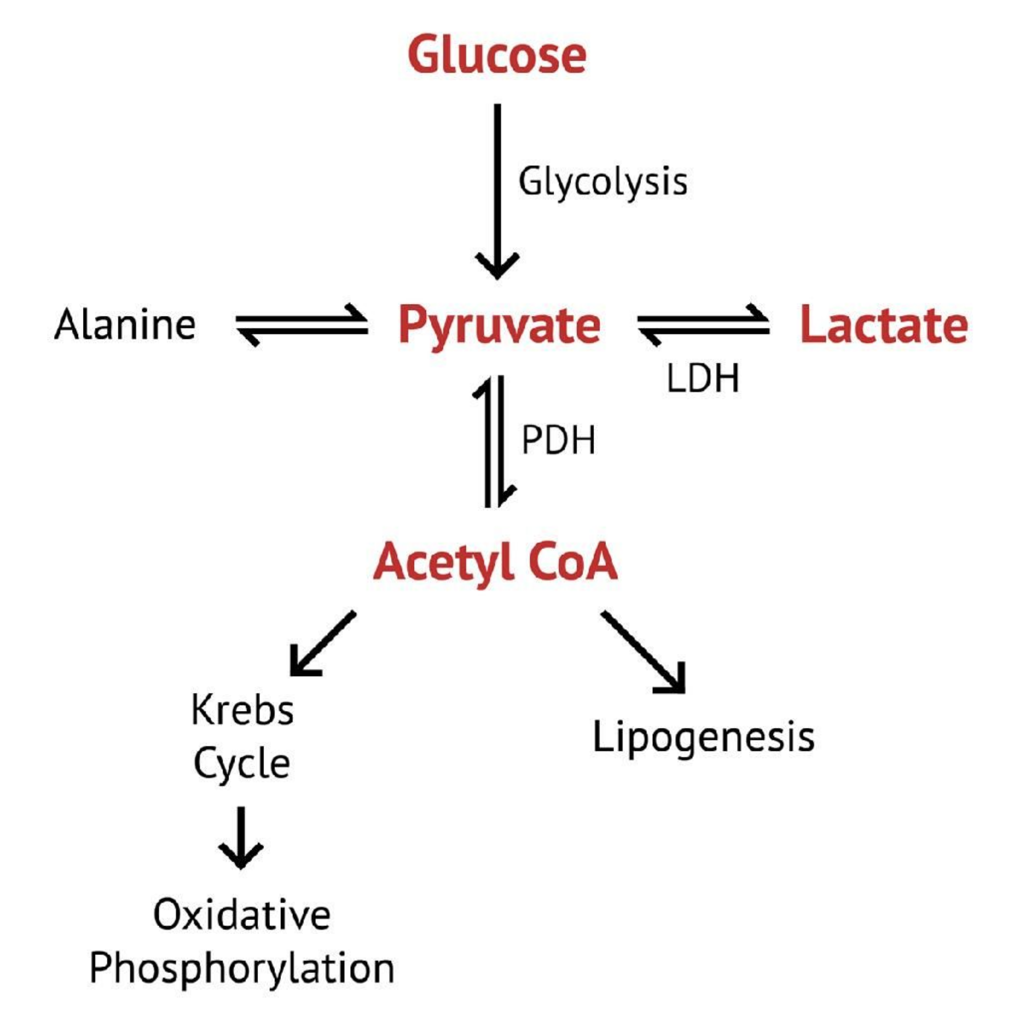
The Fate of Pyruvate

1. Aerobic Conditions (Mitochondria)

- Pyruvate → **Acetyl-CoA**
- Enzyme: Pyruvate dehydrogenase
- Enters **TCA cycle** → **oxidative phosphorylation** → **ATP**

2. Anaerobic Conditions (Cytosol)

- Pyruvate → **Lactate**
- Enzyme: Lactate dehydrogenase
- Regenerates **NAD⁺** (essential for glycolysis)



3. Gluconeogenesis (Liver/Kidney)

- Pyruvate → **Oxaloacetate**
- Enzyme: Pyruvate carboxylase
- Used for **glucose synthesis**

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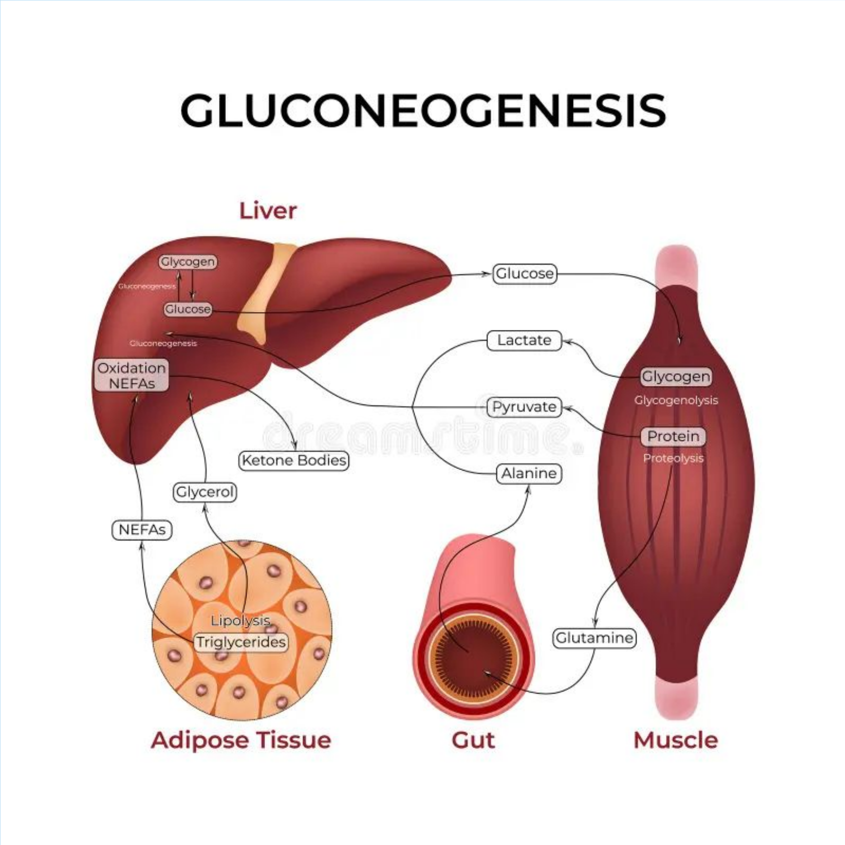
Gluconeogenesis

The rebirth (kinda)

Overview

- **Definition:** Synthesis of glucose from non-carbohydrate precursors
- **Main organs:** Liver (primary), kidney (secondary)



Occurs during:

- Fasting
- Starvation
- Prolonged exercise

Substrates:

- Lactate (Cori cycle)
- Alanine (muscle)
- Glycerol (fat metabolism)

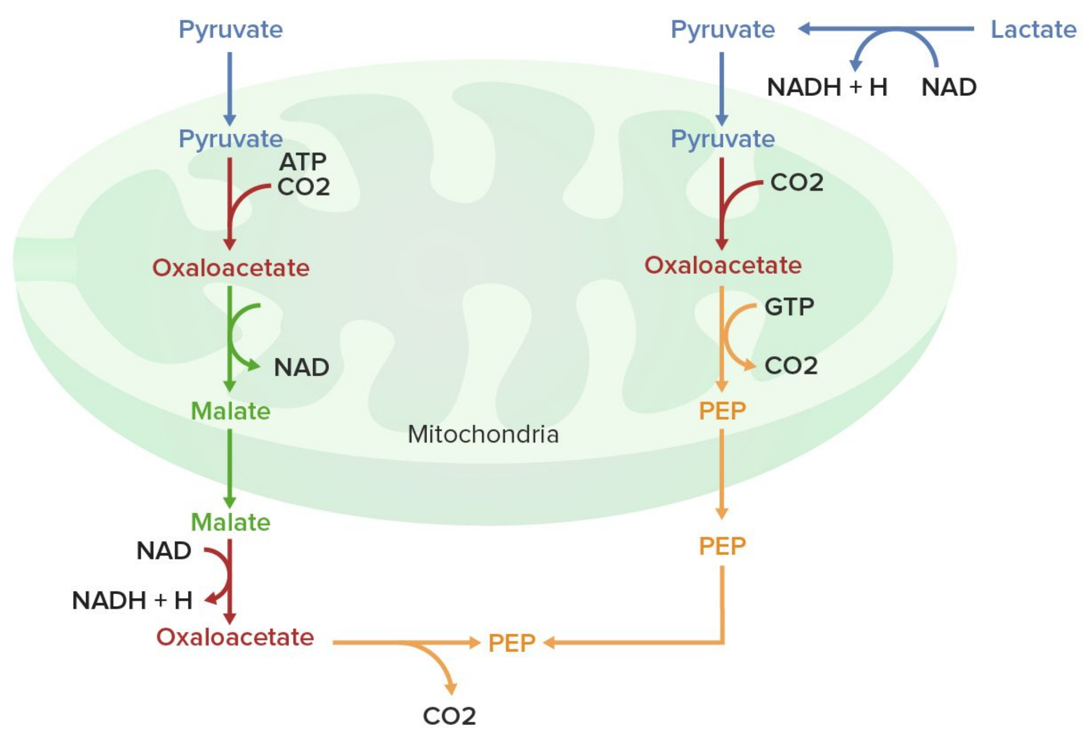
Cellular Location and Energy Cost

Cellular Locations:

- Mitochondria
- Cytosol
- Endoplasmic reticulum

Energy Requirement:

- **4 ATP + 2 GTP + 2 NADH per glucose**



Why it's not just reverse glycolysis:

Glycolysis irreversible steps:

- Hexokinase
- **PFK-1**
- Pyruvate kinase

Therefore:

- Cannot simply reverse glycolysis
- Requires **bypass reactions**

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Step 1 of Gluconeogenesis

Reaction:

Pyruvate + CO_2 + ATP → Oxaloacetate (OAA) + ADP + Pi

Location:

- Mitochondrial matrix

Key Features:

- **Irreversible reaction**
- Requires **biotin (CO_2 carrier)**
- **Consumes ATP**

Regulation:

- **Activated by:** Acetyl-CoA

Enzyme:

- Pyruvate carboxylase

Step 2 of Gluconeogenesis

Reaction:

Oxaloacetate + GTP → Phosphoenolpyruvate (PEP) + GDP + CO_2

Location:

- Cytosol (primarily)
- Can also occur in mitochondria

Key Features:

- **Irreversible reaction**
- **Consumes GTP**
- Decarboxylation drives reaction forward

Functional Importance:

- Completes bypass of **pyruvate kinase**
- Produces **high-energy PEP**

Enzyme:

- Phosphoenolpyruvate carboxykinase (PEPCK)

Step 3 of Gluconeogenesis

Reaction:

Phosphoenolpyruvate (PEP) ⇌ 2-phosphoglycerate

Key Features:

- **Reversible reaction**
- Hydration of PEP (reverse of dehydration in glycolysis)
- No ATP or GTP required

Functional Importance:

- Begins reversal of glycolytic energy-yielding phase
- Moves pathway toward glucose synthesis

Enzyme:

- Enolase

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Step 4 of Gluconeogenesis

Reaction:

2-phosphoglycerate ⇌ 3-phosphoglycerate

Key Features:

- **Reversible reaction**
- Intramolecular shift of phosphate group (C2 → C3)
- No ATP or GTP required

Functional Importance:

- Repositions phosphate for subsequent steps
- Continues reversal of glycolysis

Enzyme:

- Phosphoglycerate mutase

Step 5 of Gluconeogenesis

Reaction:

3-phosphoglycerate + ATP →
1,3-bisphosphoglycerate + ADP

Key Features:

- **Reversible reaction (in opposite direction of glycolysis)**
- **Consumes ATP**
- Forms **high-energy intermediate (1,3-BPG)**

Functional Importance:

- Reverses substrate-level phosphorylation of glycolysis
- Prepares for NADH-dependent step

Enzyme:

- Phosphoglycerate kinase

Step 6 of Gluconeogenesis

Reaction:

1,3-bisphosphoglycerate + NADH + H^+ →
Glyceraldehyde-3-phosphate (G3P) + Pi + NAD^+

Key Features:

- **Reversible reaction (reverse of glycolysis)**
- **Consumes NADH**
- Produces **G3P**

Functional Importance:

- Continues carbon flow toward glucose
- Links gluconeogenesis to **cellular redox state**

Enzyme:

- Glyceraldehyde-3-phosphate dehydrogenase

Step 7 of Gluconeogenesis

Reaction:

Glyceraldehyde-3-phosphate (G3P) ⇌ Dihydroxyacetone phosphate (DHAP)

Followed by:

G3P + DHAP → Fructose-1,6-bisphosphate (enzyme: aldolase)

Key Features:

- **Reversible reaction**
- No ATP or NADH required
- Combines two 3-carbon molecules → 6-carbon sugar

Enzyme:

- Triose phosphate isomerase

Step 8 of Gluconeogenesis

Reaction:

Fructose-1,6-bisphosphate → Fructose-6-phosphate + Pi

Key Features:

- **Irreversible reaction**
- Hydrolysis (removal of phosphate, not ATP production)
- **Major regulatory step**

Regulation:

- **Inhibited by:** AMP, **fructose-2,6-bisphosphate**
- **Activated by:** ATP

Enzyme:

- **Fructose-1,6-bisphosphatase** (FBPase-1)

Step 9 of Gluconeogenesis

Reaction:

Fructose-6-phosphate ⇌ Glucose-6-phosphate

Key Features:

- **Reversible reaction**
- Converts **ketose** → **aldose**
- No ATP or NADH required

Functional Importance:

- Produces **glucose-6-phosphate**, the direct precursor of free glucose

Enzyme:

- Phosphoglucose isomerase

Step 10 of Gluconeogenesis

Reaction:

Glucose-6-phosphate → Glucose + Pi

Location:

- **Endoplasmic reticulum (ER)**

Key Features:

- **Irreversible reaction**
- Hydrolysis (no ATP produced)
- Final step of gluconeogenesis

Physiological Importance:

- Allows **free glucose to enter bloodstream**
- Present only in:
  - **Liver**
  - **Kidney**

Enzyme:

Glucose-6-phosphatase

Summary

Key Functions:

- Maintains **blood glucose during fasting**
- Supplies glucose to:
  - Brain
  - Erythrocytes

Energy Cost:

- **4 ATP + 2 GTP + 2 NADH per glucose**

Reciprocal Regulation:

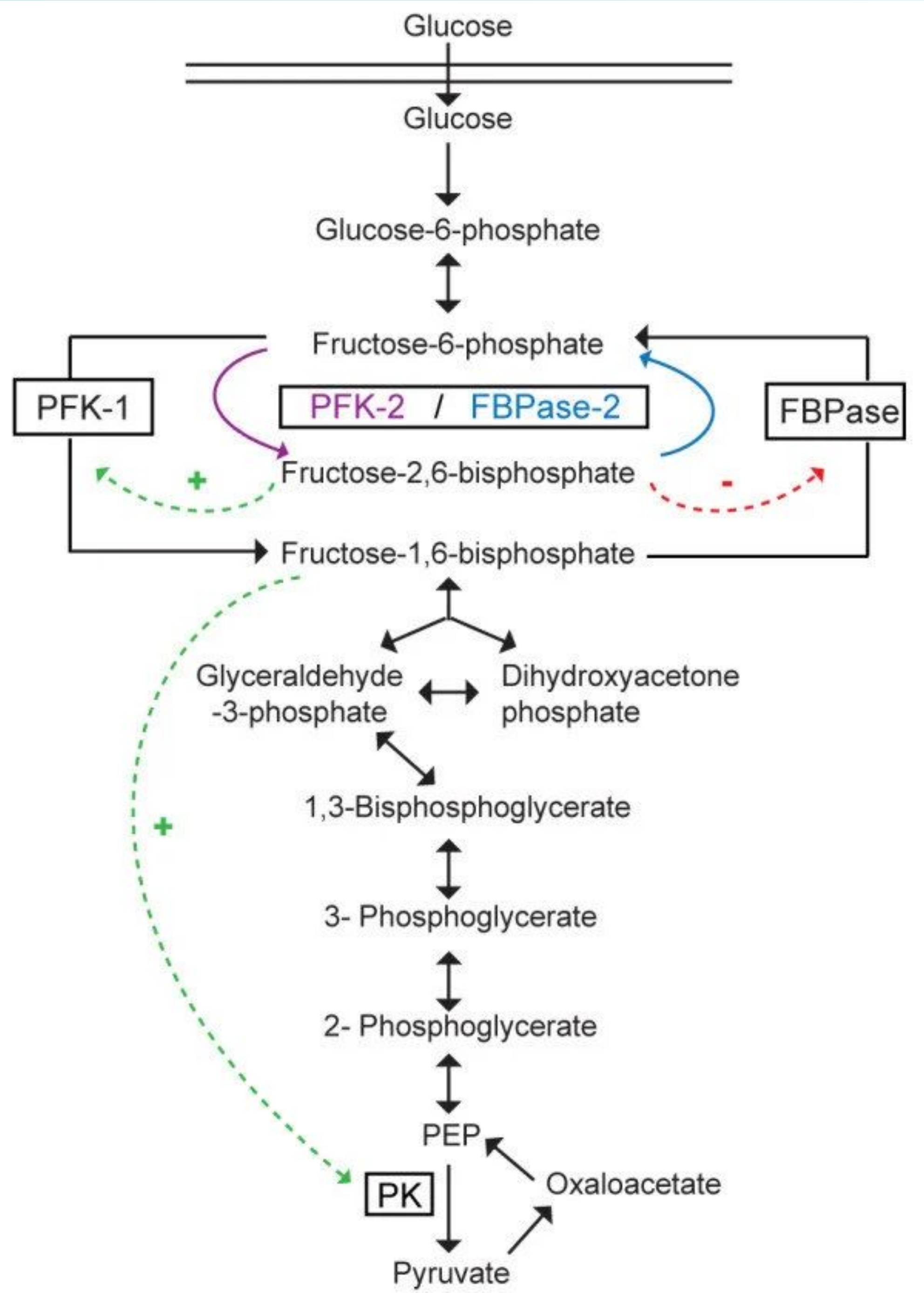
- Opposes **glycolysis**
- Prevents **futile cycling**

Hormonal Control:

- **Glucagon → stimulates**
- **Insulin → inhibits**

Key Regulatory Point:

- **Fructose-2,6-bisphosphate**
  - ↓ gluconeogenesis
  - ↑ glycolysis



Pentose Phosphate Pathway

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What does it mean?

Definition:

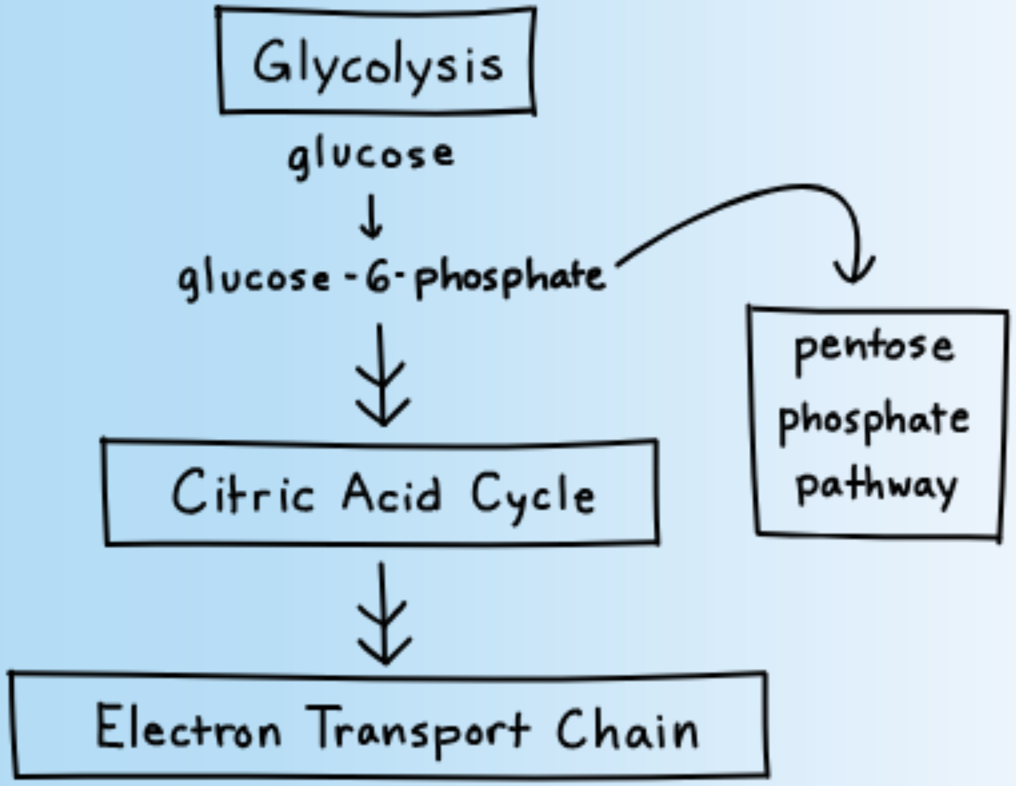
- Alternative pathway of **glucose-6-phosphate metabolism**
- Occurs in the **cytosol**

Primary Functions:

- **NADPH production**
  - Reductive biosynthesis (fatty acids, cholesterol)
  - Maintenance of **reduced glutathione (antioxidant defense)**
- **Ribose-5-phosphate production**
  - Required for **nucleotide and nucleic acid synthesis**

Key Features:

- **No ATP produced**
- Does **not directly generate energy**
- Highly active in:
  - Liver
  - Adipose tissue
  - Red blood cells



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Step 1 (Rate-Limiting Step)

Reaction:

Glucose-6-phosphate + $NADP^+$ →
6-phosphogluconolactone + NADPH + H^+

Key Features:

- **Irreversible reaction**
- **Rate-limiting step of PPP**
- Produces **NADPH**

Regulation:

- **Activated by:** $NADP^+$
- **Inhibited by:** NADPH

Enzyme:

Glucose-6-phosphate dehydrogenase (G6PD)

Step 2

Reaction:

6-phosphogluconolactone + H_2O → 6-phosphogluconate

Key Features:

- **Reversible reaction**
- Hydrolysis (addition of water)
- No ATP or NADPH produced

Functional Importance:

- Opens lactone ring → forms stable intermediate
- Prepares substrate for **next oxidative step**

Enzyme:

Lactonase

Step 3 - Final Oxidative Phase

Reaction:

6-phosphogluconate + $NADP^+$ → Ribulose-5-phosphate + NADPH + CO_2

Key Features:

- **Irreversible reaction**
- Produces **NADPH**
- Releases **CO_2** (oxidative decarboxylation)

Functional Importance:

- Completes **oxidative phase**
- Generates second molecule of **NADPH**

Enzyme:

6-phosphogluconate dehydrogenase

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Step 4

Reactions:

Ribulose-5-phosphate ⇌ **Ribose-5-phosphate**

Ribulose-5-phosphate ⇌ **Xylulose-5-phosphate**

Key Features:

- **Reversible reactions**
- No ATP or NADPH involved
- Generates **pentose sugars**

Functional Importance:

- **Ribose-5-phosphate → nucleotide synthesis**
- Xylulose-5-phosphate → continues pathway

Enzymes:

Phosphopentose isomerase

Phosphopentose epimerase

Final Steps

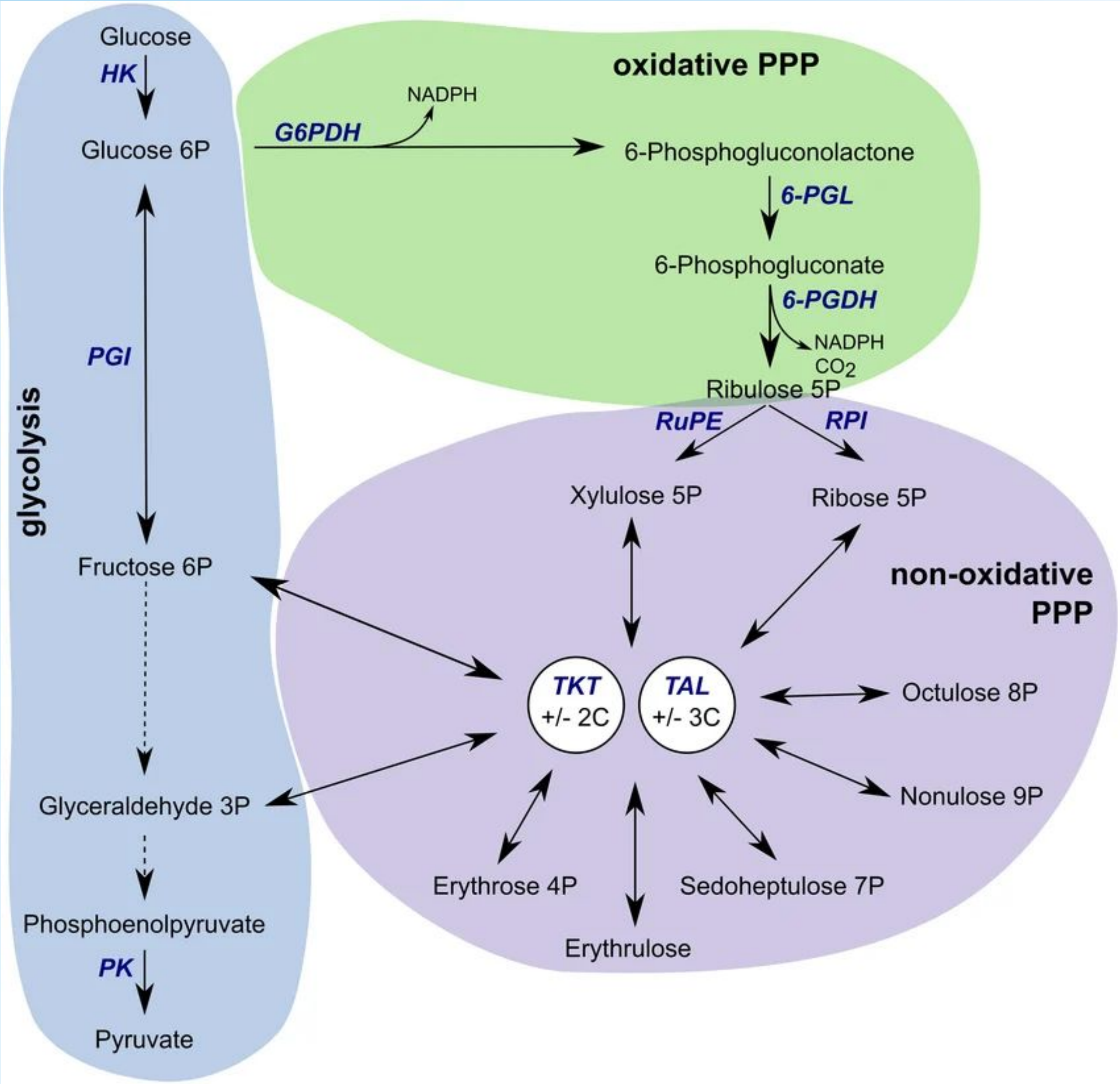
Key Reactions:

- Ribose-5-phosphate + Xylulose-5-phosphate → Glyceraldehyde-3-phosphate + Sedoheptulose-7-phosphate
- Sedoheptulose-7-phosphate + Glyceraldehyde-3-phosphate → Fructose-6-phosphate + Erythrose-4-phosphate
- Xylulose-5-phosphate + Erythrose-4-phosphate → Fructose-6-phosphate + Glyceraldehyde-3-phosphate

Enzymes:

Transketolase (thiamine / vitamin B_1)

Transaldolase



You know what time it is…

WhooClap!