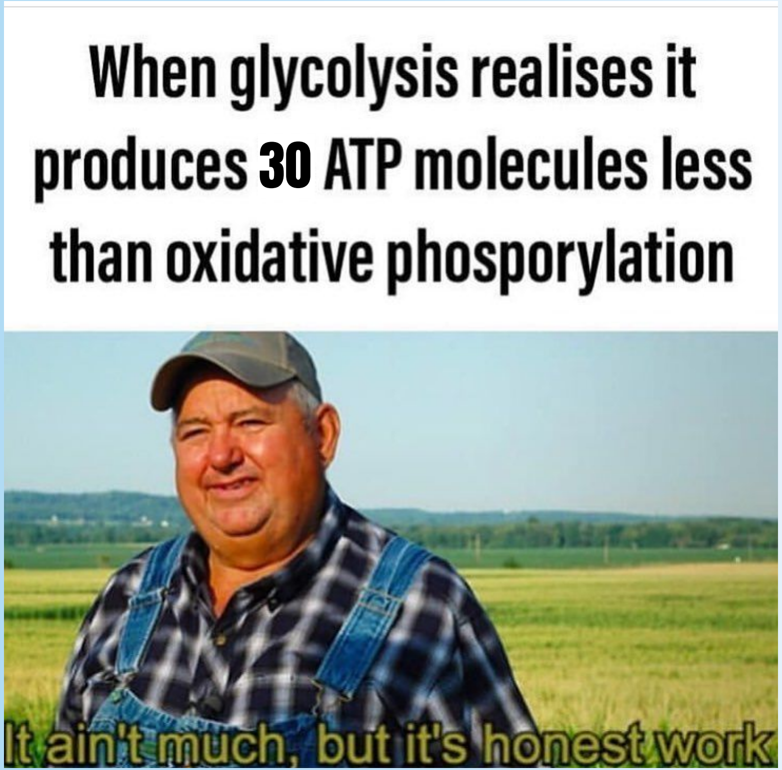
# Glycolysis & Pentose Phosphate Pathway

Karolina Orocz

# Glycolysis

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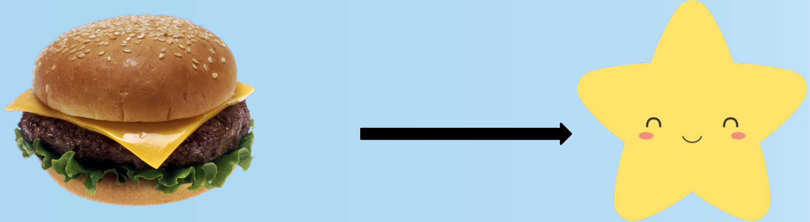
# Glycolysis

Breaking down **glucose** into **pyruvate**



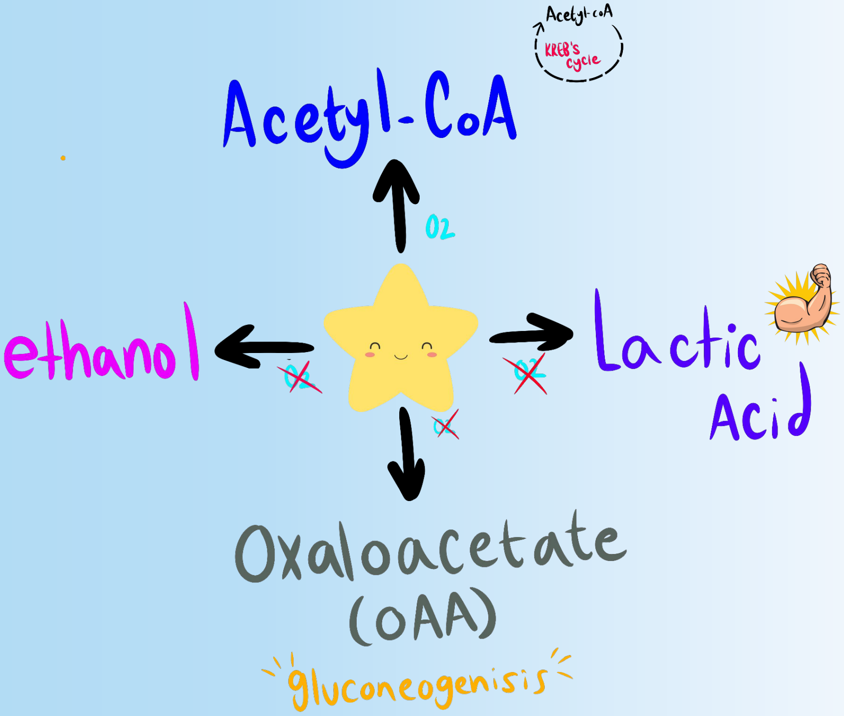
# Pyruvate conversions

Substrates:

- **Acetyl-CoA:** For Krebs cycle
- **Oxaloacetate:** For gluconeogenesis

Byproducts:

- **Lactic acid:** Produced during anaerobic conditions
- **Ethanol:** Produced in yeast & bacteria



# When glycolysis occurs

- “Fed” state: When you have just eaten and have elevated glucose in the blood
    - Insulin: Fed state hormone, signals glucose to go into cells
- When in need of ATP
- Under aerobic & anaerobic conditions

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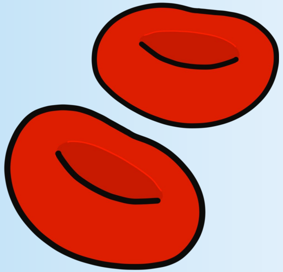
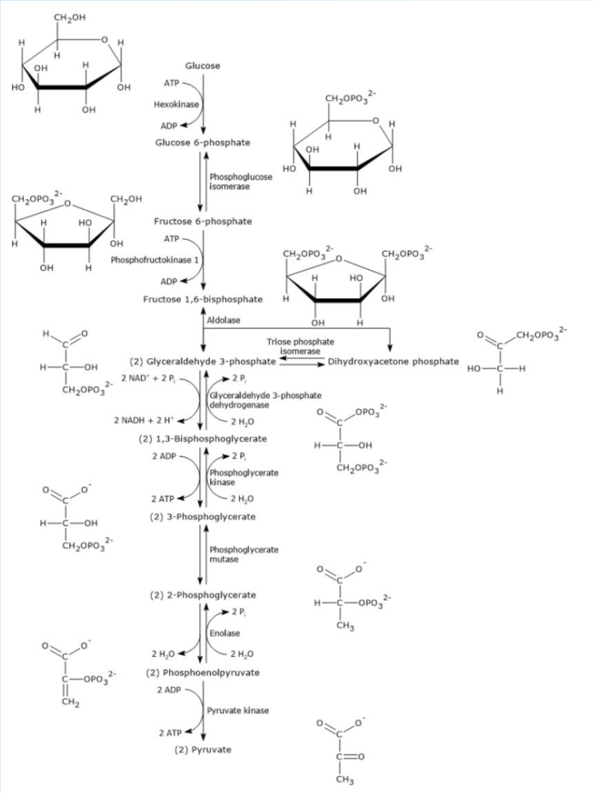
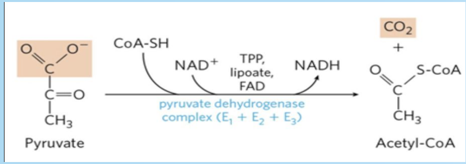
# Where glycolysis occurs

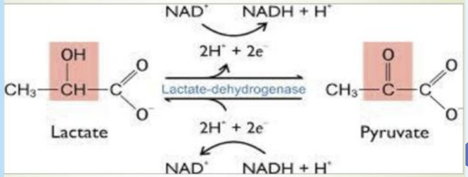
- Molecularly: Cell cytosol
- All living cells, *especially* RBCs!
  - RBCs do not have mitochondria to power Kreb's cycle & oxidative phosphorylation to make ATP



# Let’s start!

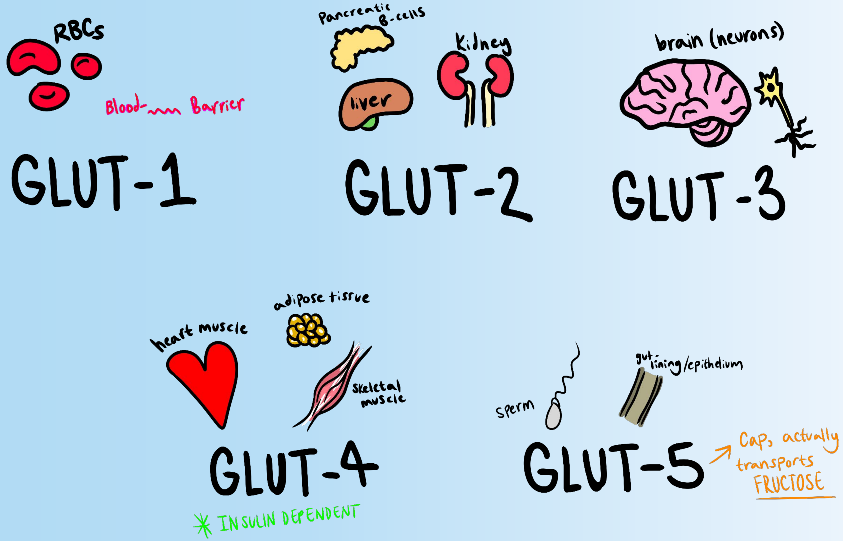

Glucose
ATP
Hexokinase
ADP
Glucose 6-phosphate
Phosphoglucose isomerase
Fructose 6-phosphate
ATP
Phosphofructokinase 1
ADP
Fructose 1,6-bisphosphate
Aldolase
Triose phosphate isomerase
(2) Glyceraldehyde 3-phosphate
Dihydroxyacetone phosphate
2 NAD⁺ + 2 Pi
Glyceraldehyde 3-phosphate dehydrogenase
2 NADH + 2 H⁺
(2) 1,3-Bisphosphoglycerate
2 ADP
Phosphoglycerate kinase
2 ATP
(2) 3-Phosphoglycerate
Phosphoglycerate mutase
(2) 2-Phosphoglycerate
Enolase
2 H2O
(2) Phosphoenolpyruvate
2 ADP
Pyruvate kinase
2 ATP
(2) Pyruvate


CoA-SH
NAD⁺
TPP, lipoate, FAD
NADH
CO2
pyruvate dehydrogenase complex (E1 + E2 + E3)
Pyruvate
Acetyl-CoA


NAD⁺
NADH + H⁺
2H⁺ + 2e⁻
Lactate-dehydrogenase
Lactate
Pyruvate

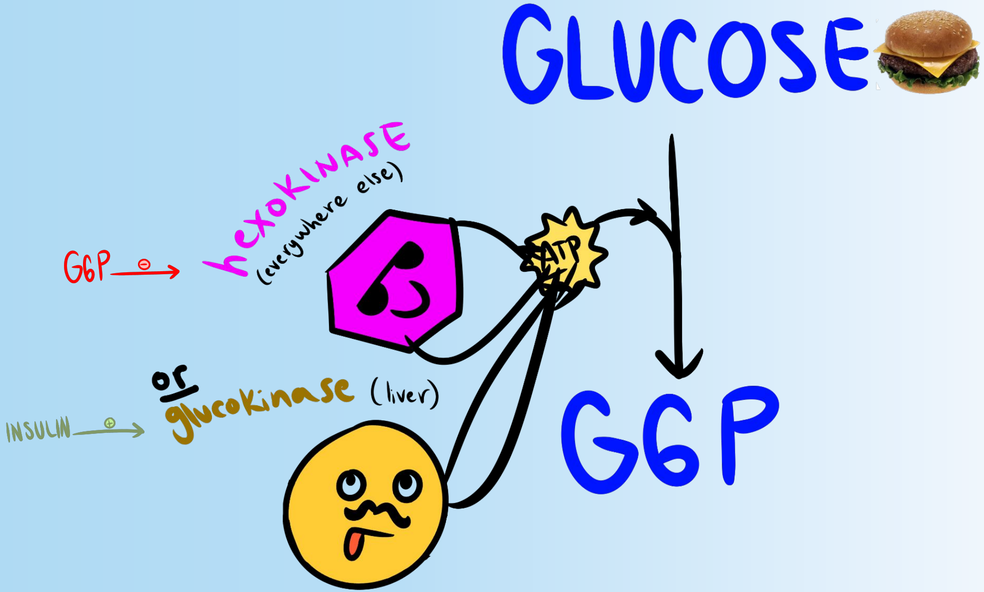
# Glucose transporters (GLUTs)

- 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

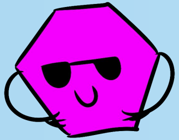


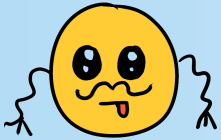
# Step 1:

- Converting glucose into glucose-6-phosphate (G6P) allows glucose to be trapped inside the cell
- Irreversible reaction



# Hexokinase vs Glucokinase:





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

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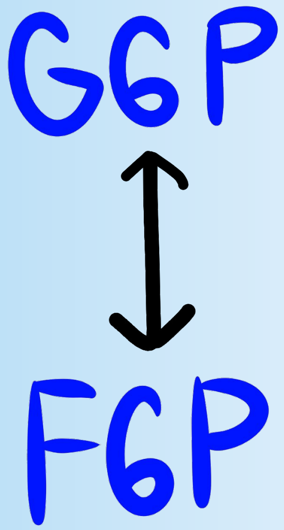
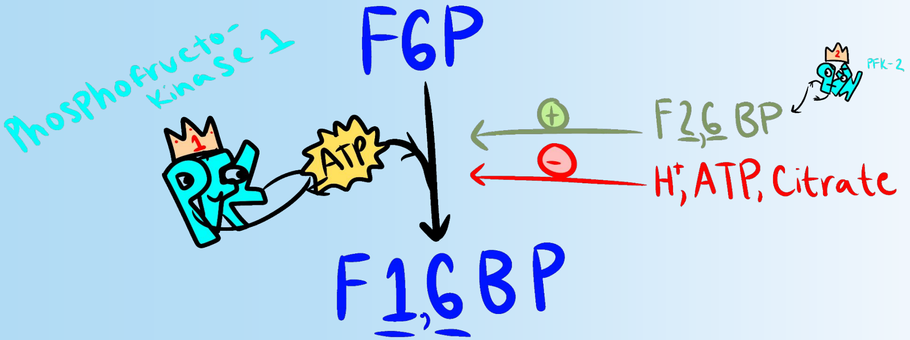
# Step 2:

- G6P: Glucose-6-phosphate
- F6P: Fructose-6-phosphate
- Rx done by G6P isomerase



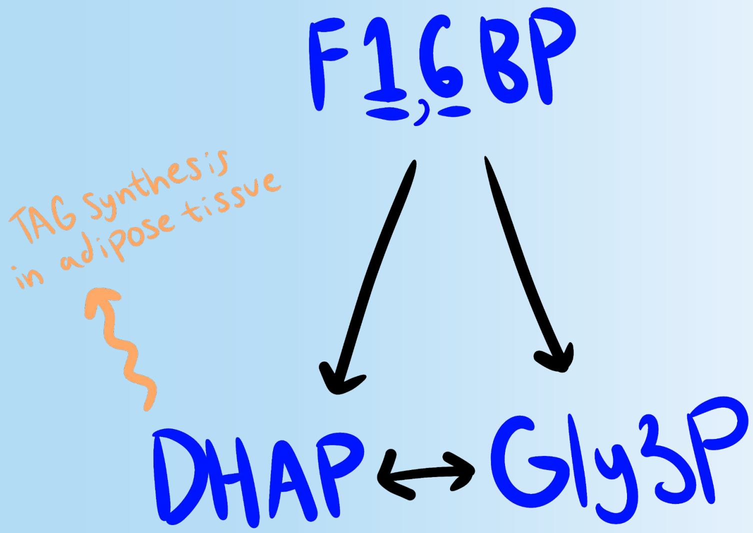
# Step 3:

- Rate-limiting step: Determines how fast/how much glycolysis occurs
- Irreversible reaction
- F6P: Fructose-6-phosphate
- F1,6BP: Fructose-1,6-bisphosphate
- PFK-2: Makes fructose-2,6-bisphosphate, which activates PFK-1



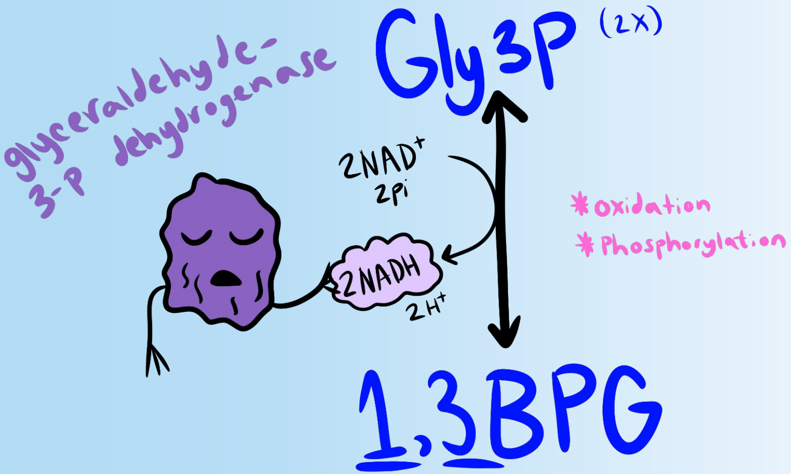
# Step 4:

- Irreversible reaction
- DHAP: Dihydroxyacetone phosphate
  - Involved in phospholipid synthesis
- Gly3P: Glyceraldehyde 3-phosphate
  - Need 2 Gly3P molecules to continue with glycolysis



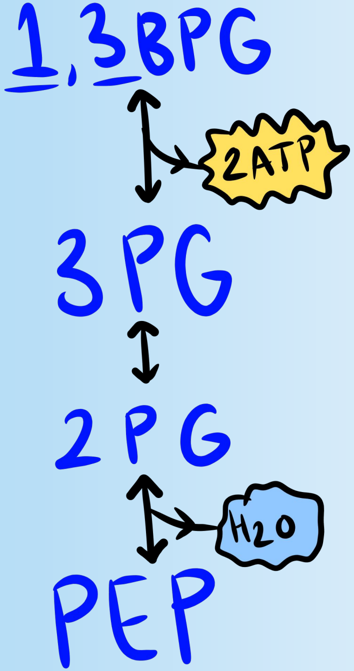
# Step 5:

- 1,3BPG: 1,3-bisphosphoglyceric acid
- Gly3P dehydrogenase:
    - Its reaction involves oxidation and phosphorylation of Gly3P



# Step 6,7, & 8:

- 3PG: 3 phosphoglyceric acid
- 2PG: 2 phosphoglyceric acid
- PEP: Phosphoenolpyruvate
  - High energy molecule!

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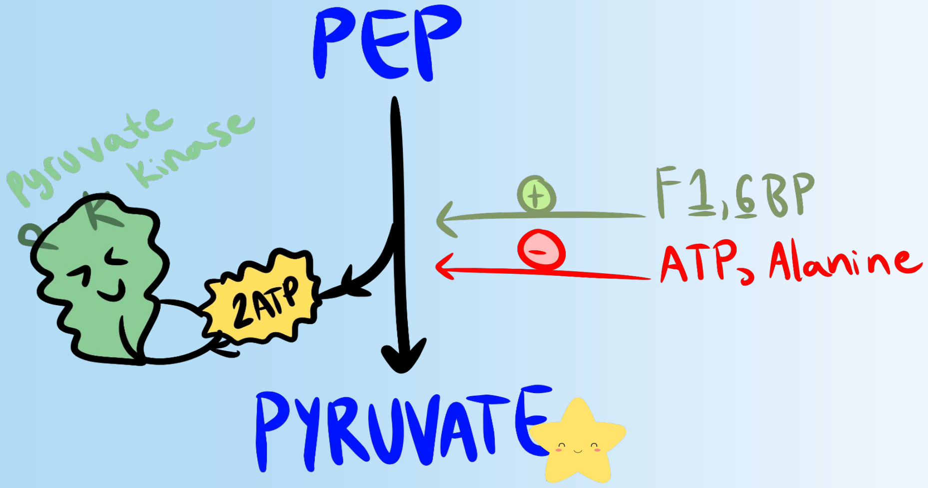
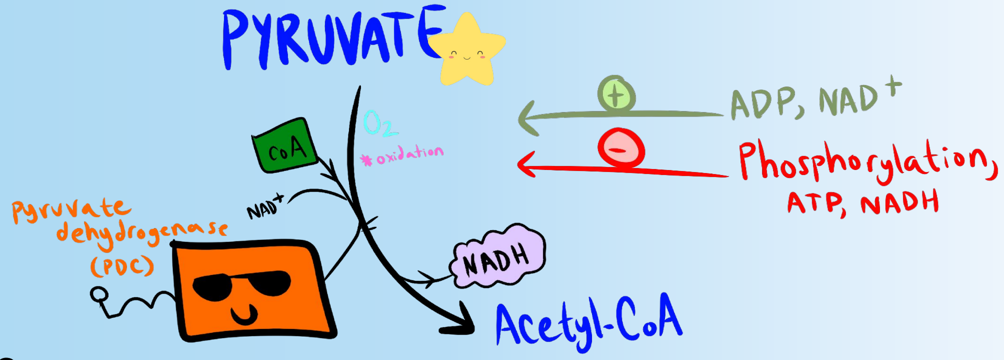
# Step 9:

- Irreversible reaction
- Activators: F1,6BP
  - Same molecule from earlier on in glycolysis
- Inhibitors: ATP, alanine
  - More ATP = high energy supply = inhibits glycolysis (negative feedback)
  - Alanine: Amino acid derived from pyruvate



# Step 7a: Aerobic respiration

- Irreversible reaction
- When there is O2, pyruvate is converted into acetyl-CoA by pyruvate dehydrogenase complex (PDC)
  - This reaction is called pyruvate decarboxylation
- Acetyl-CoA is a substrate of the Krebs cycle

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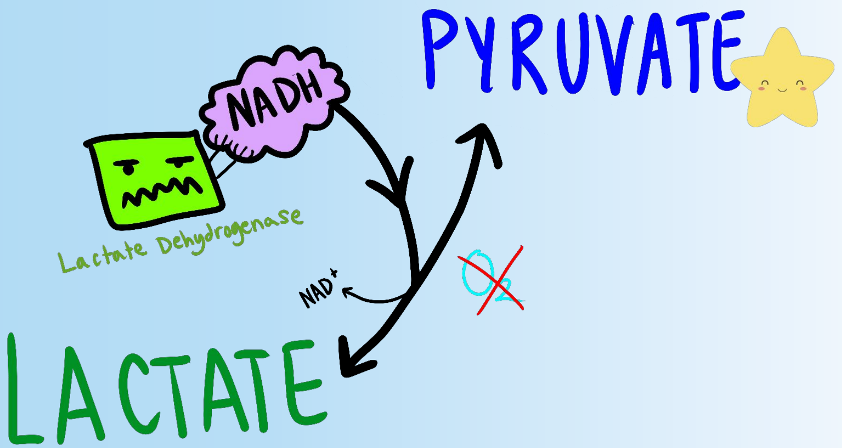
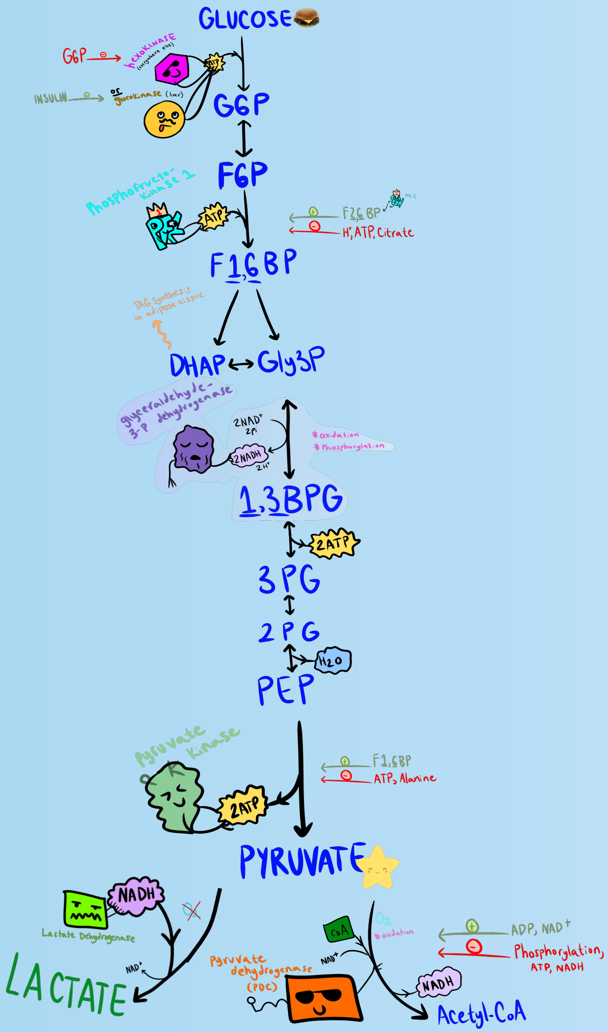
# Step 7b: Anaerobic respiration

- When there is no O2, pyruvate is converted into lactic acid by lactate dehydrogenase
- High amounts of lactic acid are damaging to tissues



# Glycolysis overview:

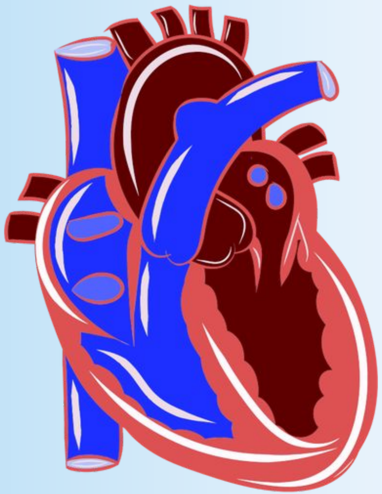


# Clinical correlation: Myocardial infarction

The heart needs a lot of ATP & O2 to function!

<u>Heart ATP supply:</u>

- **95% of ATP** comes from mitochondrial oxidative phosphorylation
  - Aerobic process
- **5% of ATP** comes from Glycolysis
  - Aerobic & anaerobic process



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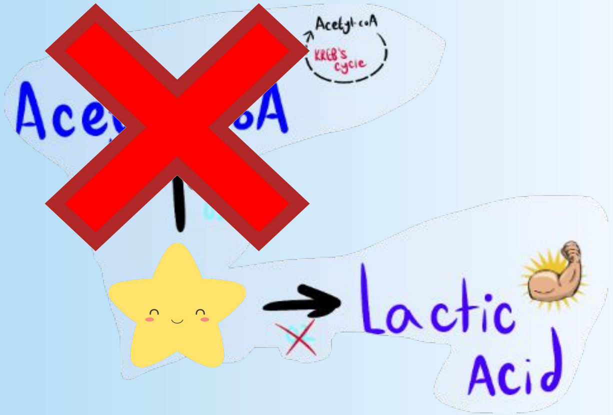
Myocardial infarction:

- Hypoxia of myocardium due to lack of blood flow
- No $O_2$ = anaerobic condition = no mitochondrial oxidative phosphorylation = heart loses major ATP supply
  - Cellular respiration makes ~ 32 ATP
- Glycolysis under anaerobic conditions:
  - Good: Can still make ~ 2 ATP
  - Bad: Makes lactate instead of acetyl-CoA under anaerobic conditions
    - Lactic acid damages tissues

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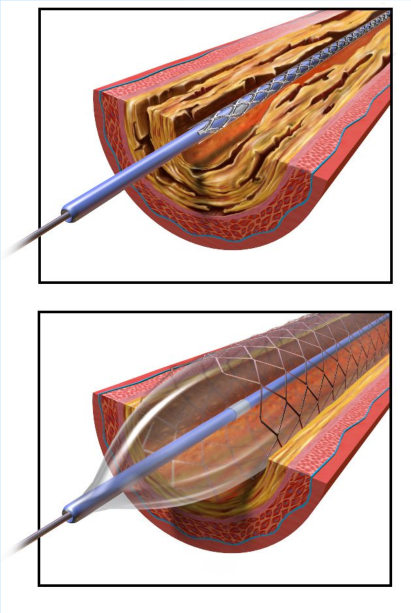
Treatment:

- Treat underlying cause: reperfusion & O2 delivery



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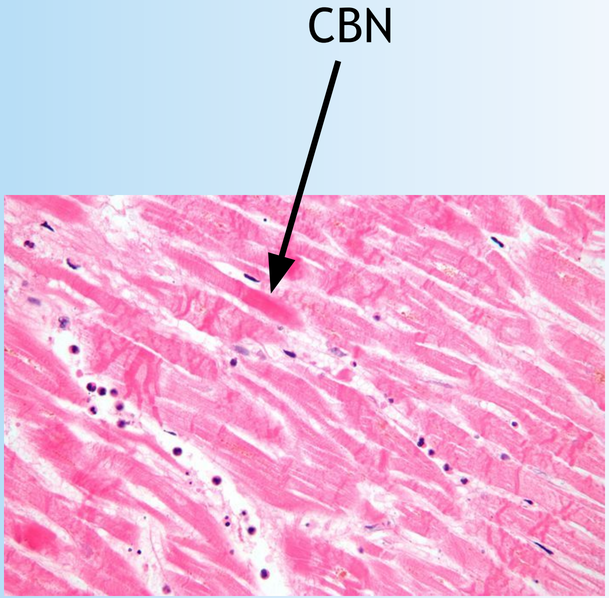
Ischemia-reperfusion injury:

- ROS:
  - Ischemia damages mitochondria = unable to reduce O2 = ROS production
- Increased Ca2+:
  - Damaged SERCA = more Ca2+ in cardiomyocyte
  - Hypercontraction = contraction band necrosis
- Altered metabolism:
  - Delayed recovery of aerobic metabolism
  - Lactate production



# Glycolysis high yield recap

- Hexokinase vs glucokinase
- Hexokinase/Glucokinase, PFK-1, PK, PDC: irreversible reactions
- Which molecules activate or inhibit glycolysis enzymes
- Rate-limiting step
- Insulin: glycolysis hormone
- Glycolysis NET profit:
    - 2 pyruvate
    - 2 ATP
    - 2 NADH

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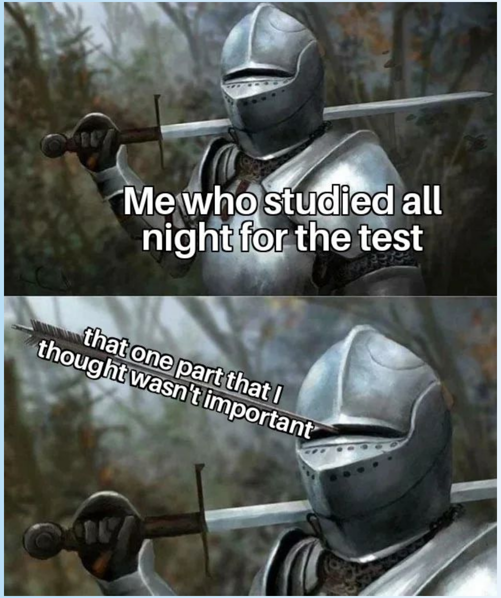
# Pentose Phosphate Pathway (PPP)

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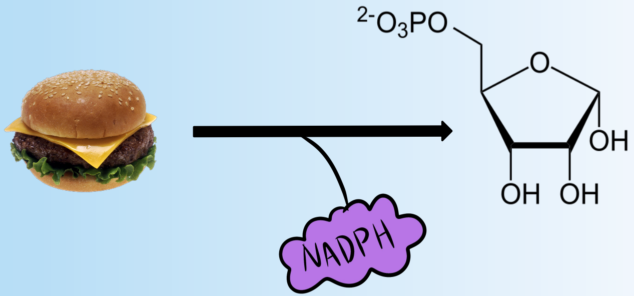
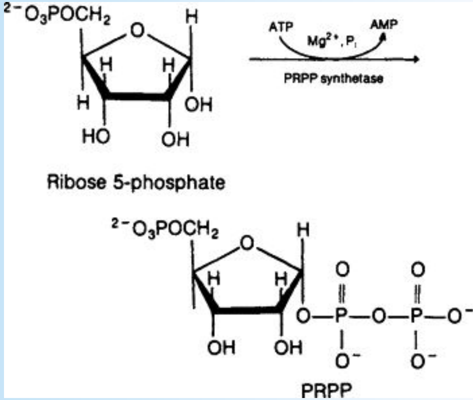
# PPP

- Alternative way to metabolize glucose
- Products:
    - NADPH
    - Ribose-5-P
- No ATP created or used



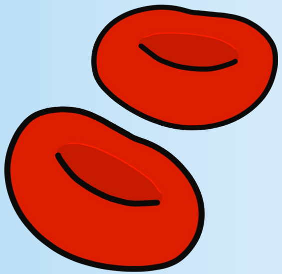
# When PPP occurs

- When we need **NADPH:**
  - Cholesterol synthesis: substrate for HMG-CoA reductase to make mevalonate
  - Fatty acid synthesis
  - Riddance of ROS via glutathione reduction
- When we need **Ribose-5-Phosphate:**
  - For the sugar base of DNA & RNA
  - To make PRPP: PRPP is a precursor for purines & pyrimidines
  - To make F6P & Gly3P: Substrates in glycolysis
  - To make E4P: Makes aromatic amino acids
- When our body is in a "Fed" state
  - Regulated by insulin



# Where PPP occurs

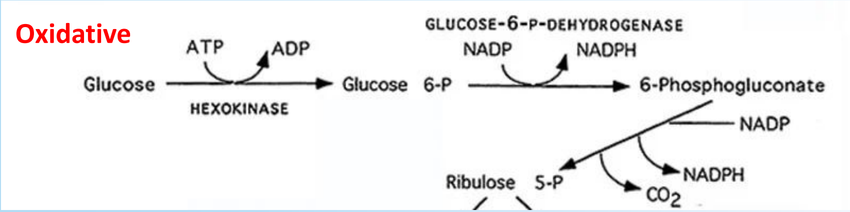
- Molecularly: Cell cytosol
- In RBCs: G6P dehydrogenase (first enzyme of PPP) protects RBCs from H2O2 (a ROS)



# Two phases of PPP

**<u>Oxidative phase:</u>**

- First phase
- Oxidation: Losing electrons
  - Ex: G6P donates electron (H+) to NADP to make NADPH
- Irreversible
- Aerobic (O2)
- Products: NADPH & Ribulose-5-P

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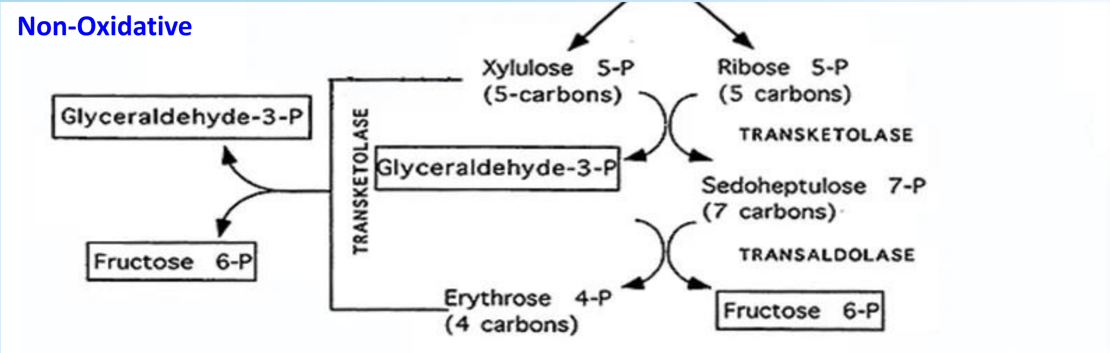
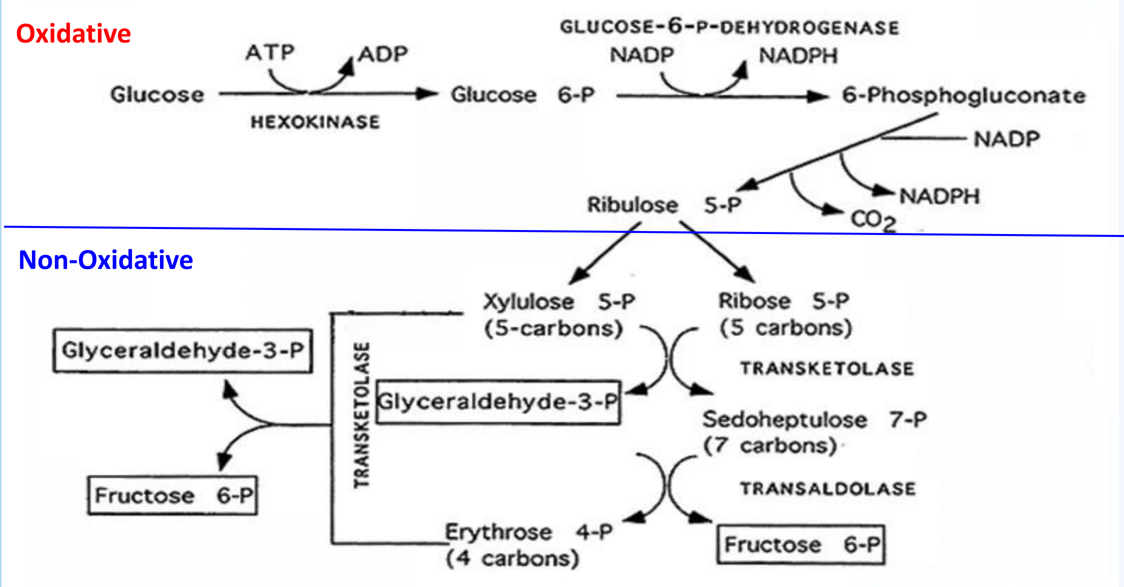
## Non-Oxidative phase:

- Second phase
- Reversible
- Anaerobic
- Products:
    - Ribose-5-P
    - F6P, G3P
    - E4P

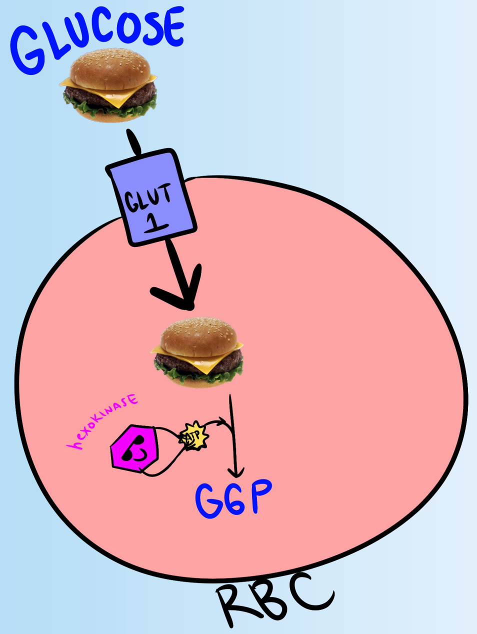


# Let’s start!


Oxidative
GLUCOSE-6-P-DEHYDROGENASE
ATP
ADP
NADP
NADPH
Glucose
HEXOKINASE
Glucose 6-P
6-Phosphogluconate
NADP
NADPH
Ribulose 5-P
$CO_2$
Non-Oxidative
Xylulose 5-P
(5-carbons)
Ribose 5-P
(5 carbons)
TRANSKETOLASE
Glyceraldehyde-3-P
Glyceraldehyde-3-P
TRANSKETOLASE
Sedoheptulose 7-P
(7 carbons)
TRANSALDOLASE
Fructose 6-P
Erythrose 4-P
(4 carbons)
Fructose 6-P

# Glucose transporter & hexokinase

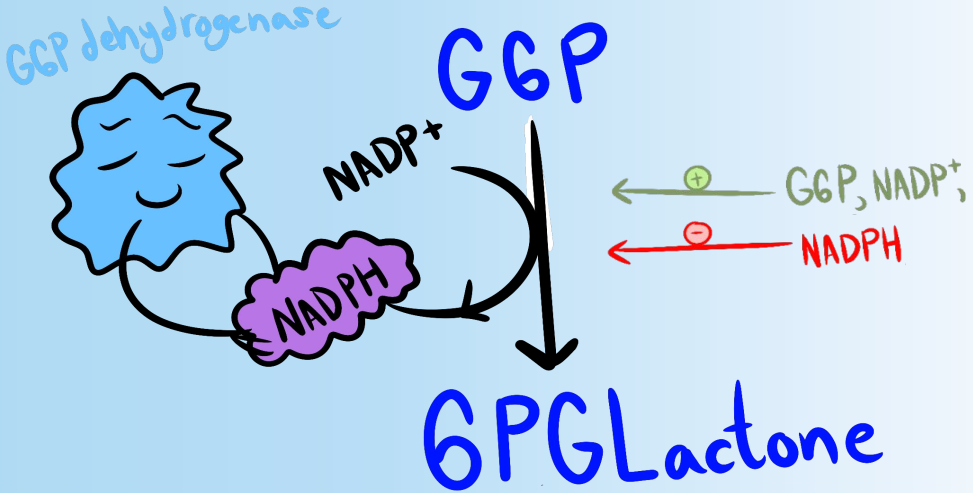
- Glucose must first be transported into the cell via GLUT
  - GLUT1 for RBCs
- Glucose must be converted into glucose-6-phosphate (G6P) in order to be “trapped” in the cell
  - Done via hexokinase (except in liver, which has glucokinase)



# Step 1

- Oxidative/Irreversible rx
- 6PGlactone:

  6-phosphogluconolactone
- 1 NADPH is made

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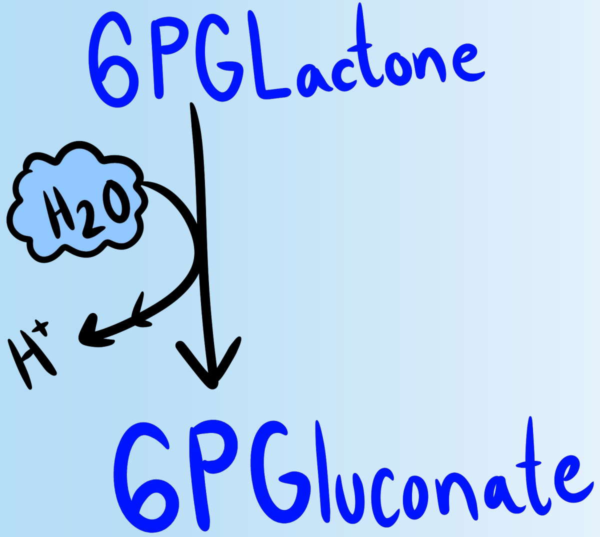
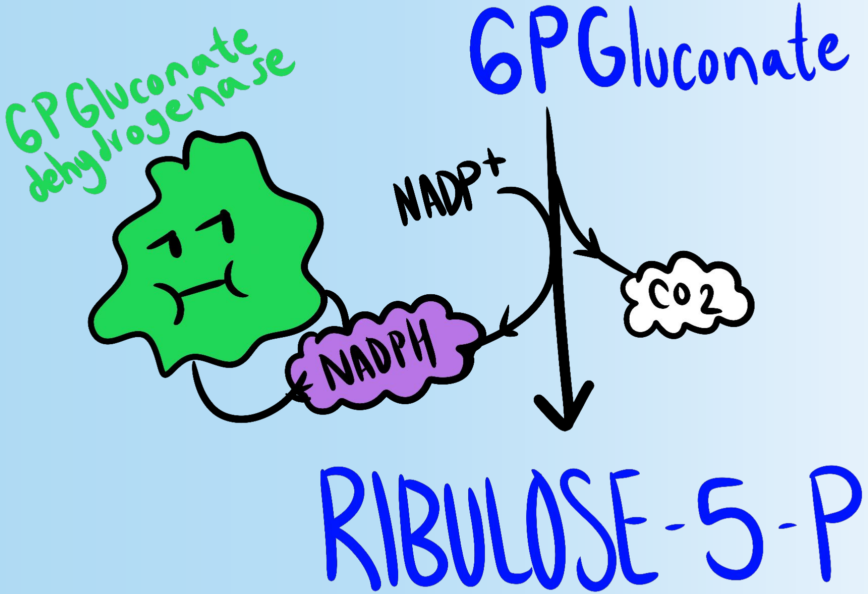
# Step 2

- Oxidative/Irreversible rx
- 6PGluconate: 6-phosphogluconate



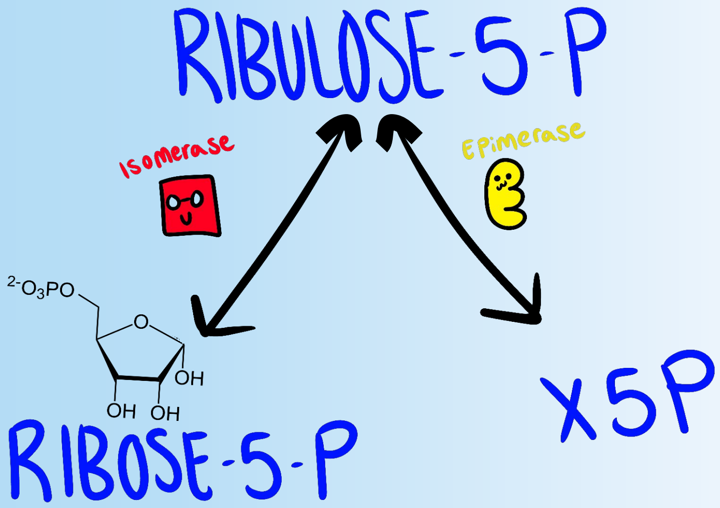
# Step 3

- Oxidative/Irreversible rx
- 1 NADPH is made



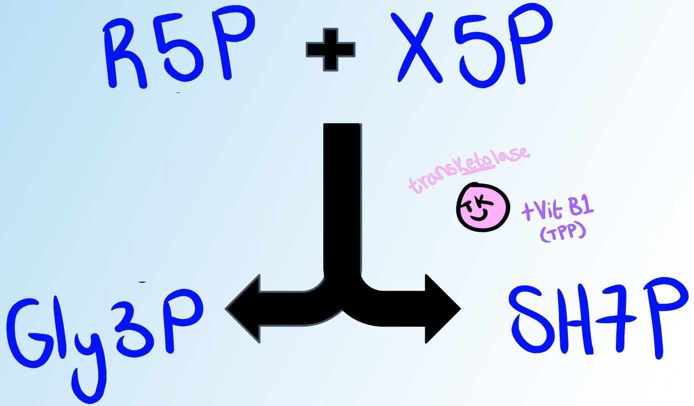
# Step 3

- Non-oxidative/reversible rx
- X5P: xylulose-5-phosphate
- Main product: Ribose-5-P



# Step 4

- Non-oxidative/reversible rx
- Adding two molecules with 5 carbons means you have 10 carbons in total
    - You can split up these carbons in different ways in order to make new molecules that add up to 10 carbons
    - Ex) R5P + X5P = 10 C => Gly3P + SH7P = 10 C
- Gly3P: glycolysis substrate
- SH7P: sedoheptulose 7-phosphate
- Transketolase enzymes requires vitamin B1 (thiamine)

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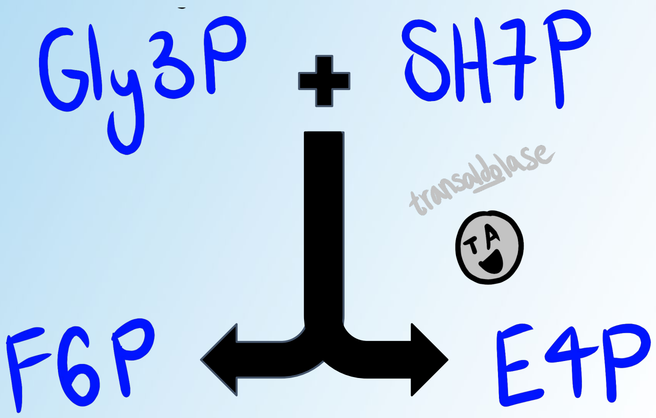
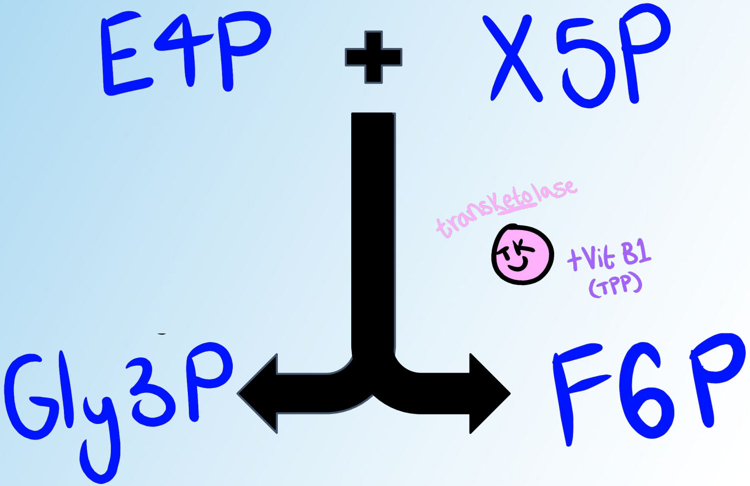
# Step 5

- Non-oxidative/reversible rx
- Rx is the same idea as in Step 4
  - Gly3P + SH7P = 10 C, => F6P + E4P = 10 C
  - Rx done by transaldolase
- F6P: glycolysis substrate

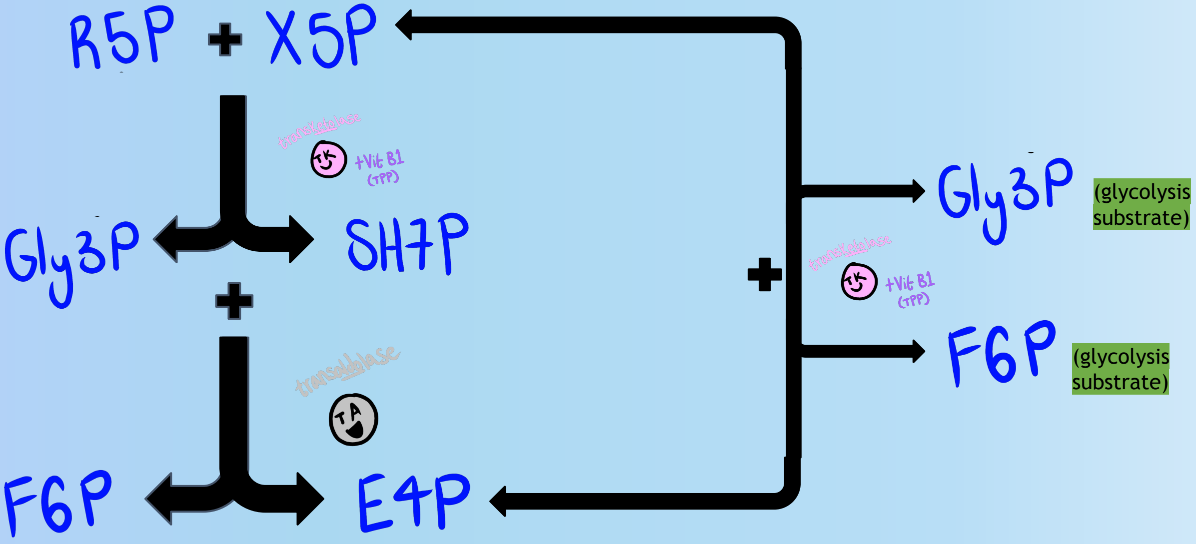


# Step 6

- Non-oxidative/reversible rx
- Rx is same idea as in Step 4, but with 9 C in total instead of 10 C
  - E4P + X5P = 9 C, => Gly3P + F6P = 9 C
- Same transketolase enzyme as in Step 4



# Overview of non-oxidative phase interconversions:

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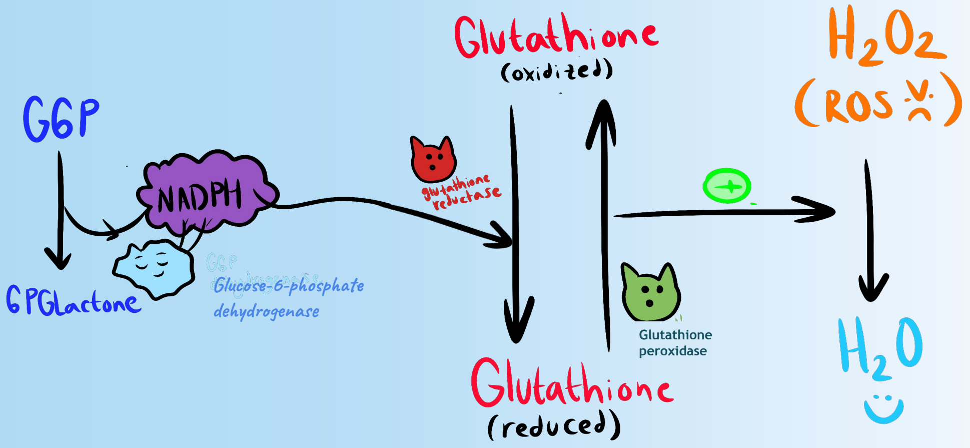
# Clinical correlation: G6PD deficiency

<u>Normal Conditions:</u>

- G6P Dehydrogenase:
  - 1st PPP enzyme
  - Byproduct: NADPH
  - Super important for RBC protection from ROS
- NADPH reduces glutathione
- Re-oxidizing glutathione turns H2O2 (ROS) into H2O

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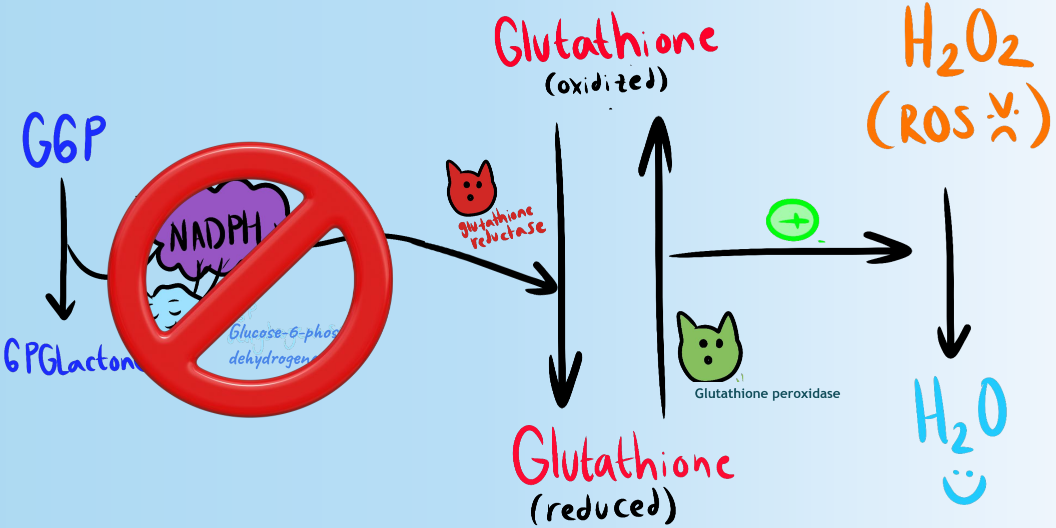
G6P dehydrogenase deficiency:

- No NADPH
- H2O2 (ROS) buildup
- RBC membrane damage (hemolytic anemia)

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# PPP high yield recap

- Occurs in cytosol
- Insulin: PPP hormone
- Oxidative vs non-oxidative stage
- Rate-limiting step
- Non-oxidative stage products: substrates for glycolysis & gluconeogenesis
- G6PD deficiency
- PPP NET profit:
  - 2 NADPH
  - 1 $CO_2$
  - 1 Ribose-5-phosphate

# Thank you!

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