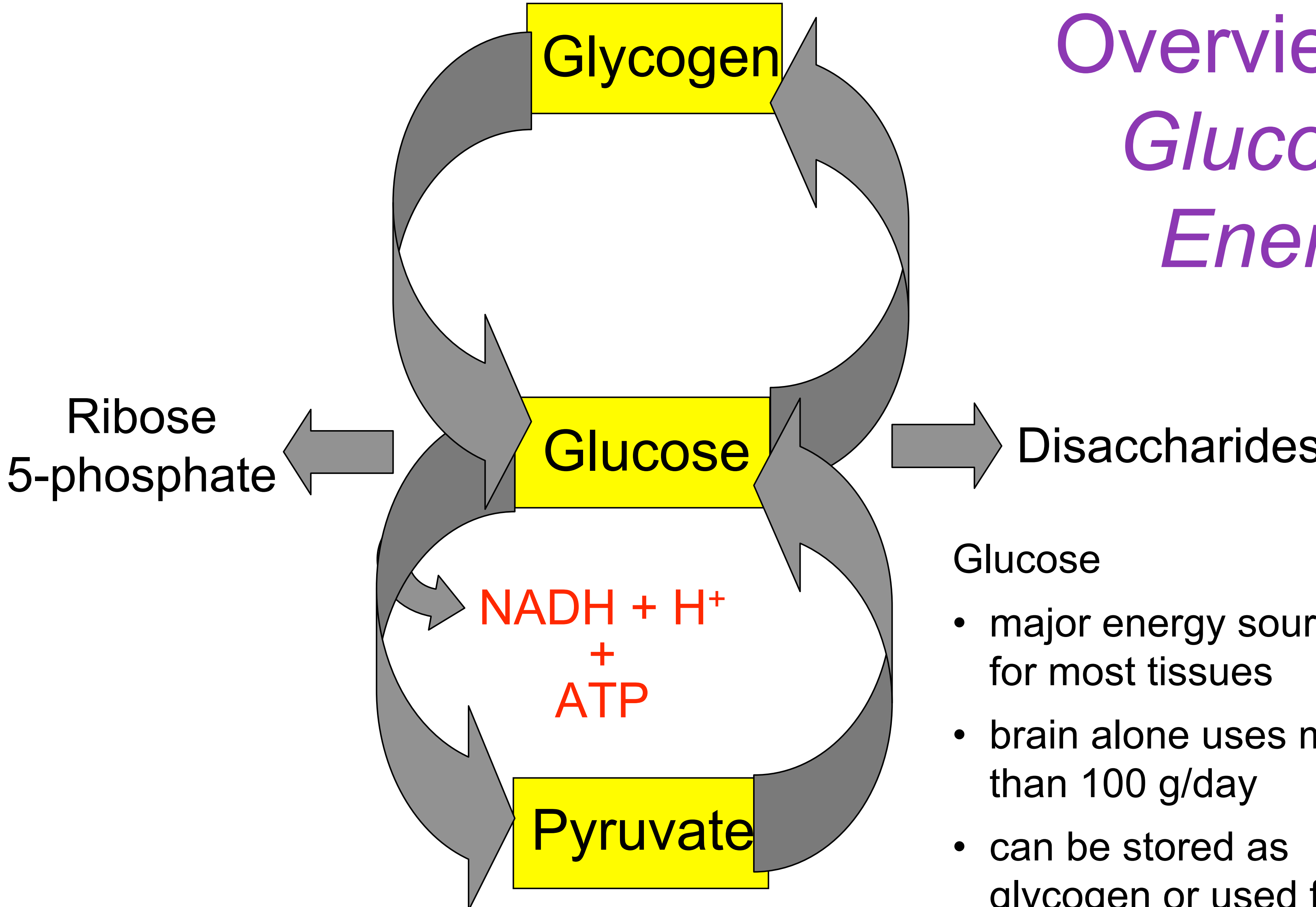
# Key knowledge base

- Know the names and structures of all intermediates in the glycolytic pathway. Know the name of each enzyme that catalyzes a step of the glycolytic pathway. Know the categories of enzymes that are represented in the glycolytic pathway (e.g., kinases, dehydrogenases, isomerases, mutase).
- What cell compartment contains the glycolytic enzymes? That is, in eukaryotic cells, where is glycolysis carried out?
- Know the reactions that describe the metabolic fate of pyruvate under anaerobic conditions. Where in the cell are conditions anaerobic? Know the general metabolic fate of pyruvate under aerobic conditions. Where in the cell are conditions aerobic?
- Understand the regulation of the activity of phosphofructokinase by the action of a bifunctional enzyme. Understand the regulation of pyruvate kinase. For each of these enzymes, an intermediate in the glycolytic pathway is an 'effector' molecule (binds to and regulates the activity of a protein ). Which intermediates are these? Which proteins do they affect? How?
- Know the structures of AMP, ADP, ATP, $NAD^+$, and NADH. Be able to recognize the structures of FAD and CoA.

# Overview: *Glucose Energy*



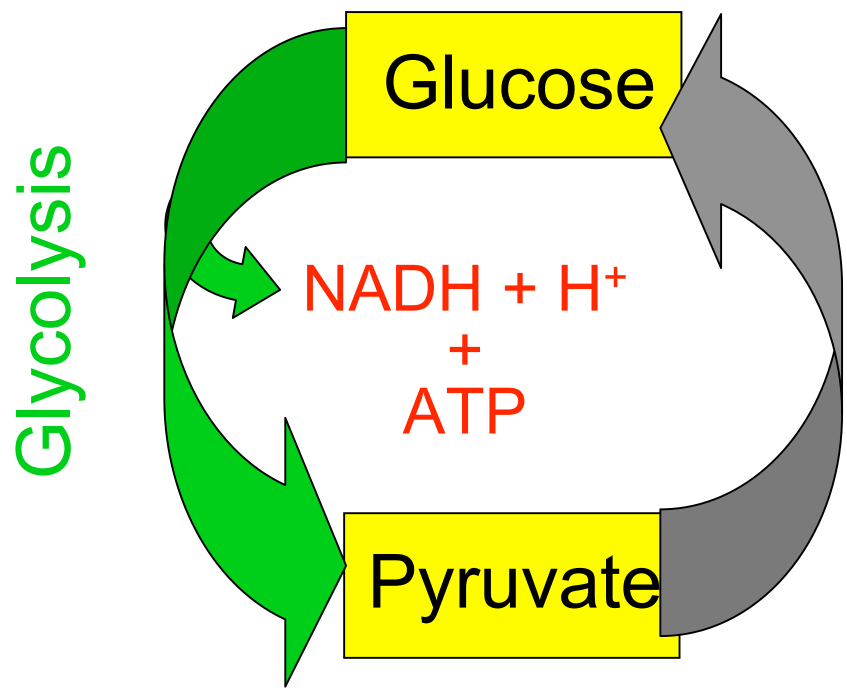

Glucose

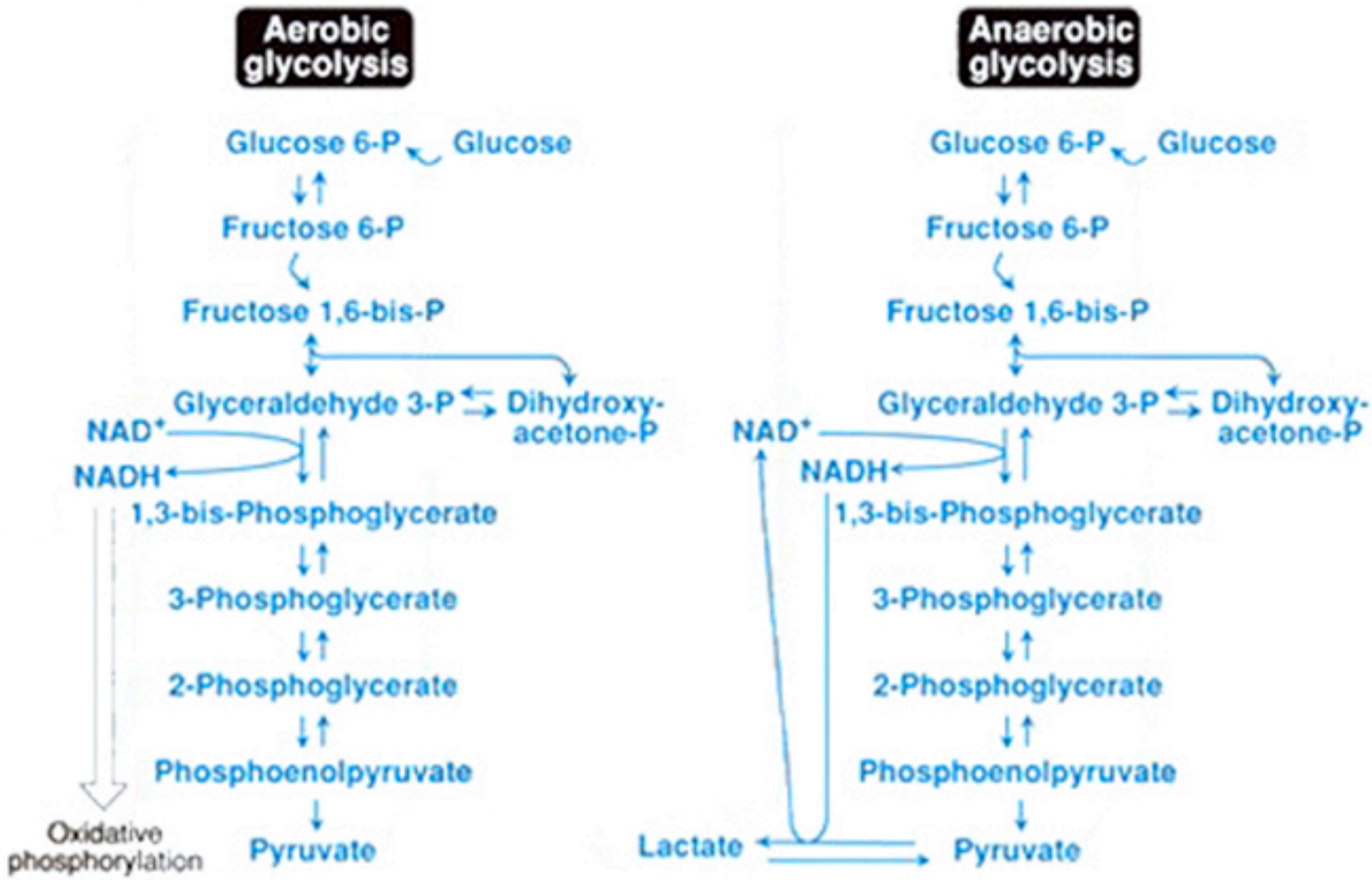
- major energy source for most tissues
- brain alone uses more than 100 g/day
- can be stored as glycogen or used for biosynthesis.

# Overview: *Introduction*

Glycolysis

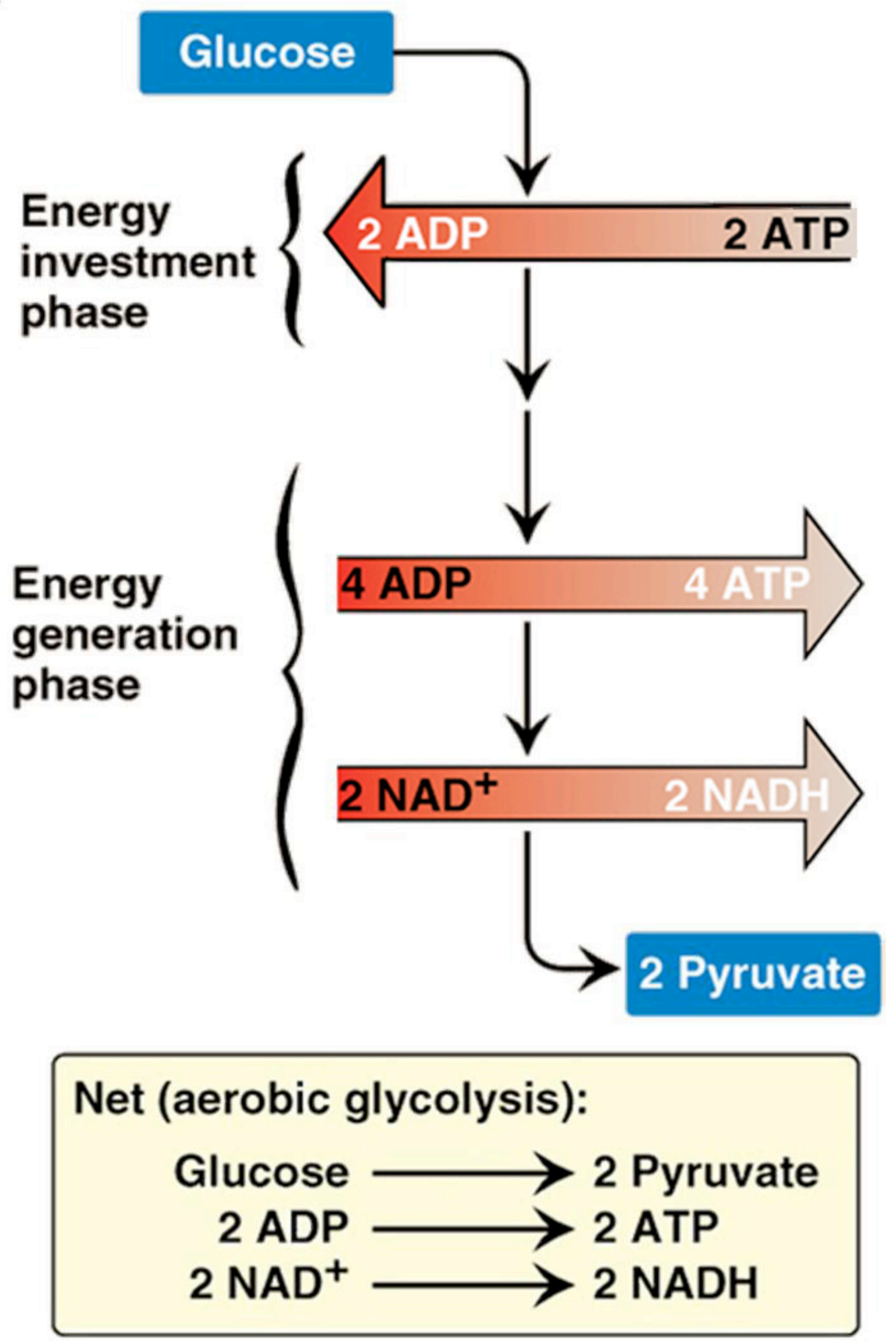
- catabolic process in which glucose is broken down to pyruvate with formation of ATP



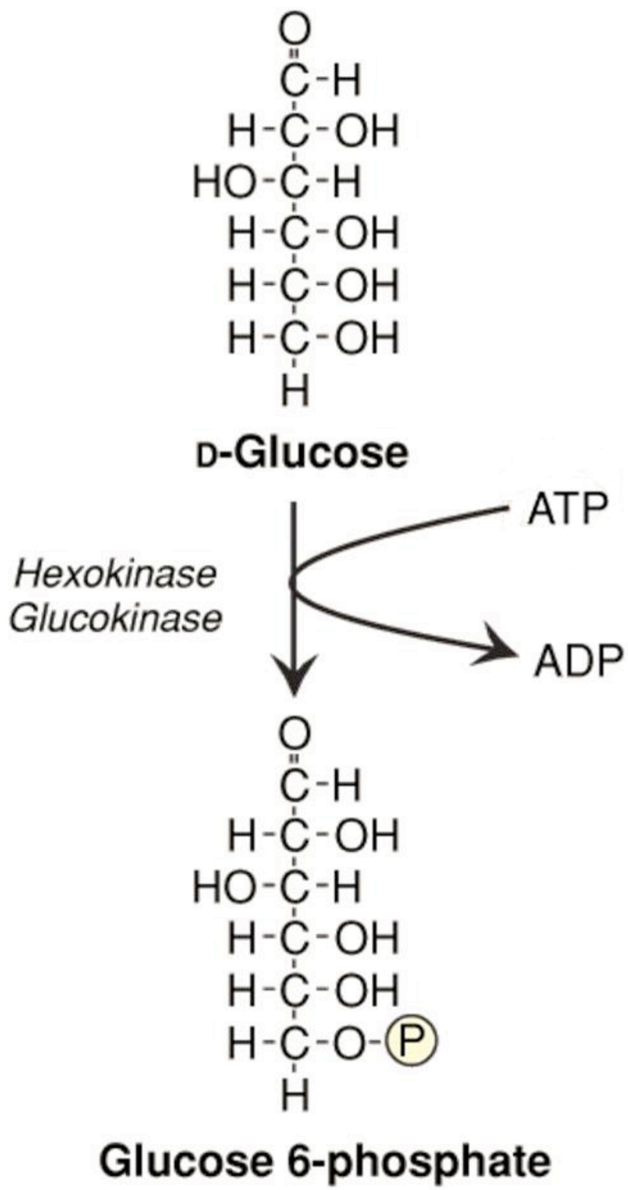


Aerobic glycolysis
Glucose 6-P
Glucose
Fructose 6-P
Fructose 1,6-bis-P
Glyceraldehyde 3-P
Dihydroxy-acetone-P
NAD+
NADH
1,3-bis-Phosphoglycerate
3-Phosphoglycerate
2-Phosphoglycerate
Phosphoenolpyruvate
Pyruvate
Oxidative phosphorylation
Anaerobic glycolysis
Glucose 6-P
Glucose
Fructose 6-P
Fructose 1,6-bis-P
Glyceraldehyde 3-P
Dihydroxy-acetone-P
NAD+
NADH
1,3-bis-Phosphoglycerate
3-Phosphoglycerate
2-Phosphoglycerate
Phosphoenolpyruvate
Lactate
Pyruvate

# Glycolysis: *overview*



# Glycolysis: *Stage I*

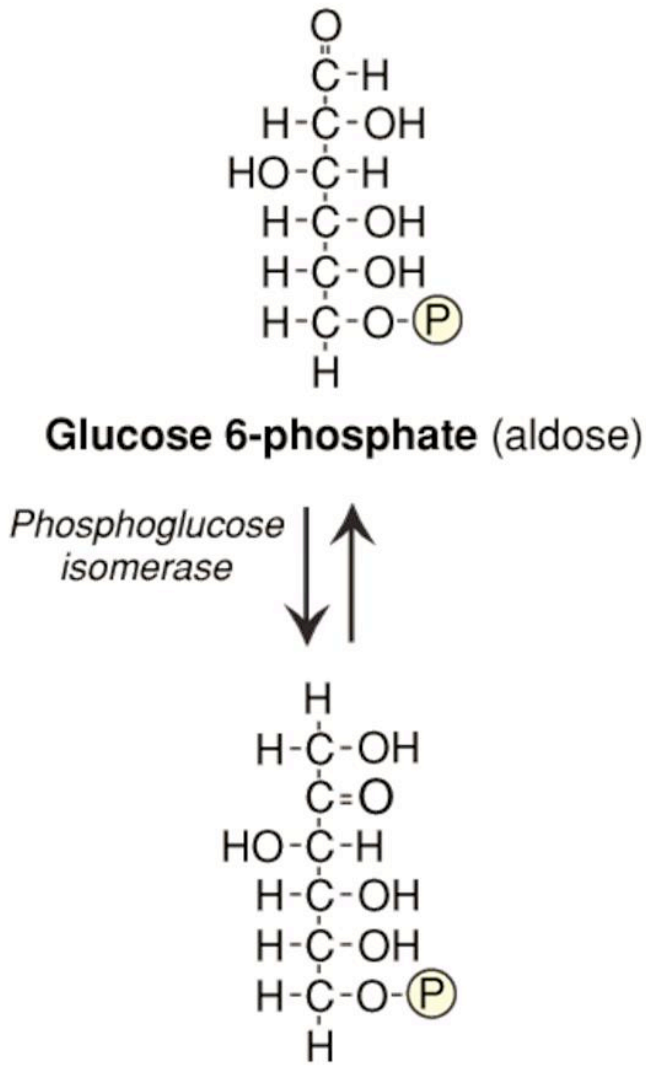



Transform glucose into a diphosphate hexose that is readily cleaved into activated phosphotrioses.

***Step 1. Phosphorylation reaction***

Glucose (aldo-hexose) is phosphorylated by ATP

# Glycolysis: *Stage I*

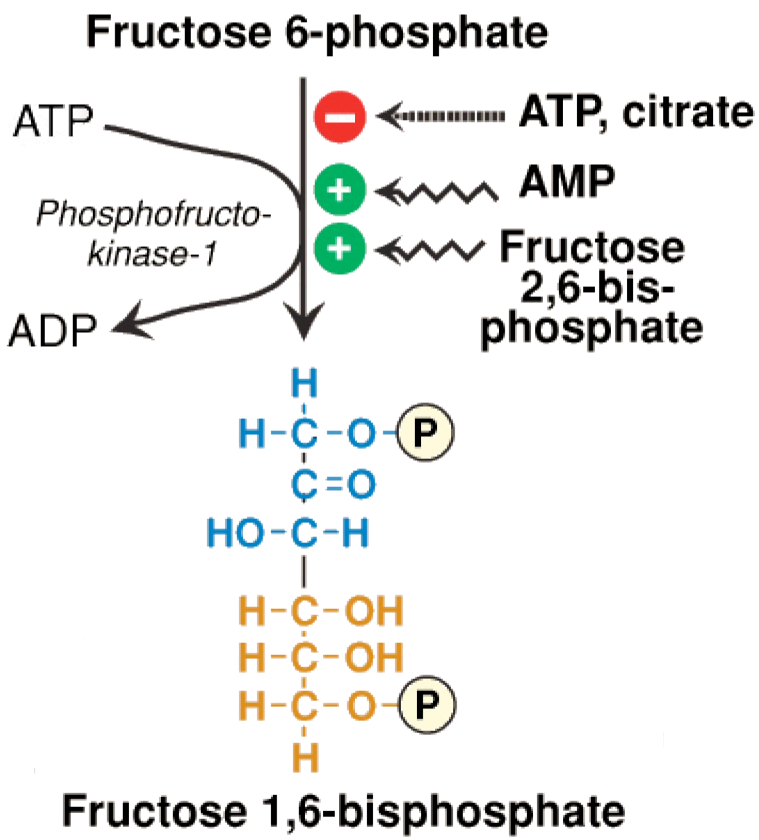



**Fructose 6-phosphate** (ketose)

***Step 2. Isomerization reaction***

The phosphorylated aldo-hexose is converted to a phosphorylated keto-hexose.

# Glycolysis: *Stage I*




***Step 3. Phosphorylation reaction***

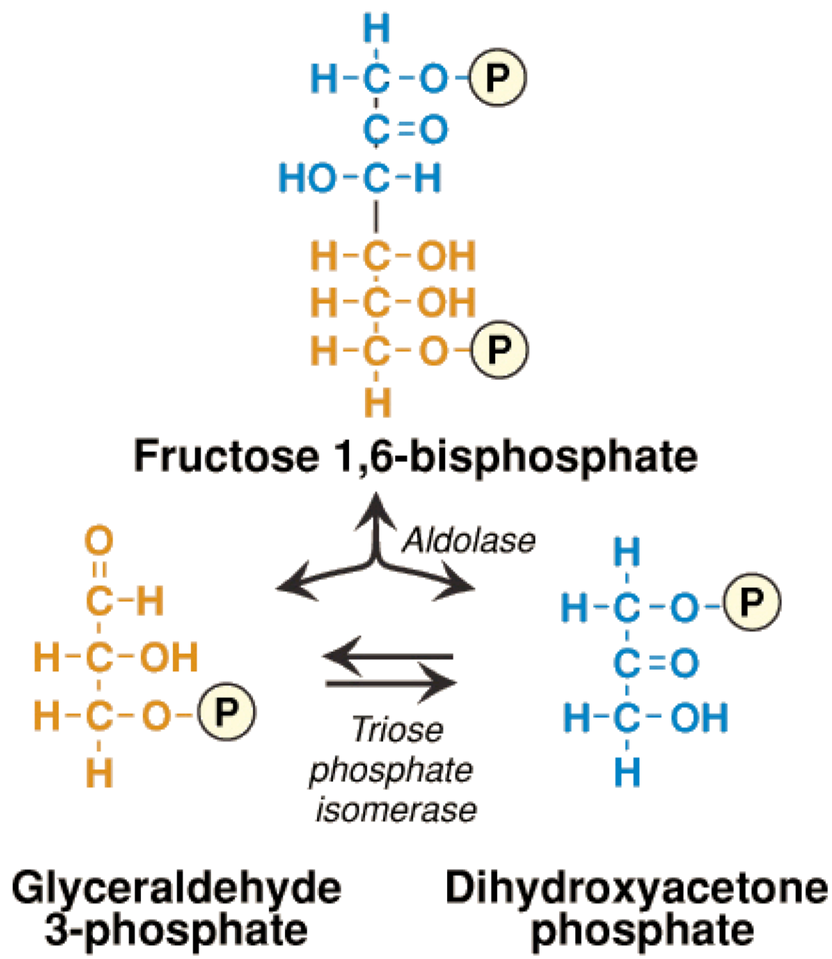
The phosphorylated ketohexose is lastly converted to a diphospho-ketohexose by a 2nd ATP molecule.

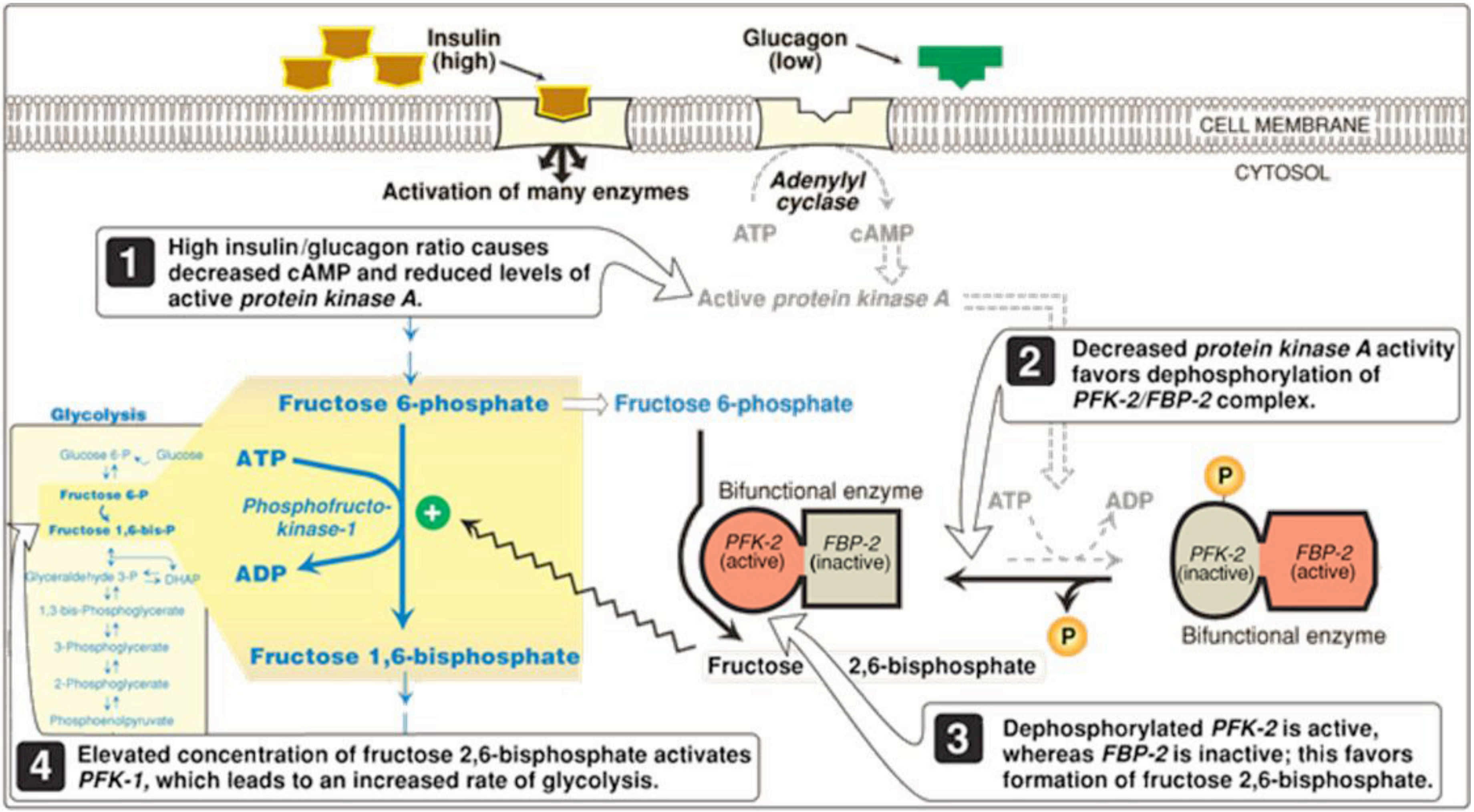
# Glycolysis: *Stage I*

Diphosphohexose is transformed into two phosphotrioses.

4. ***Cleavage of fructose diphosphate to an aldo-triose phosphate and a keto-triose phosphate.***

5. ***Isomerization of the keto-triose phosphate to the aldo-triose phosphate.***





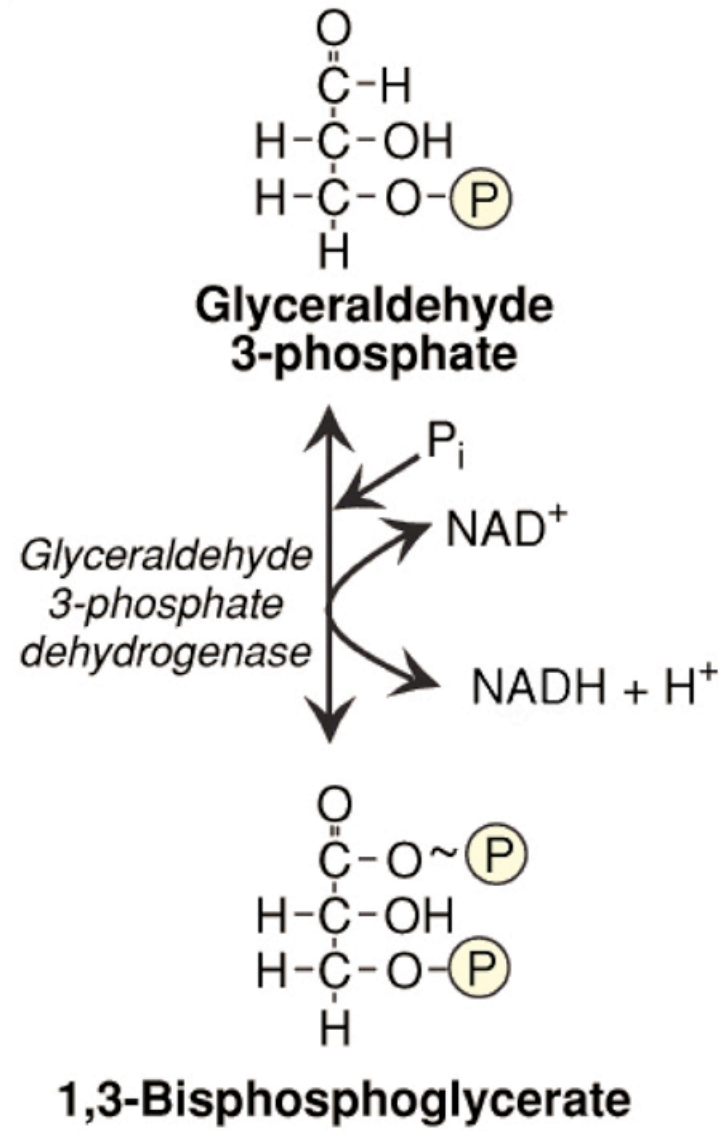
Insulin (high)
Glucagon (low)
CELL MEMBRANE
CYTOSOL
Activation of many enzymes
Adenylyl cyclase
ATP
cAMP
1 High insulin/glucagon ratio causes decreased cAMP and reduced levels of active protein kinase A.
Active protein kinase A
2 Decreased protein kinase A activity favors dephosphorylation of PFK-2/FBP-2 complex.
Glycolysis
Glucose 6-P
Glucose
Fructose 6-P
Fructose 1,6-bis-P
Glyceraldehyde 3-P
DHAP
1,3-bis-Phosphoglycerate
3-Phosphoglycerate
2-Phosphoglycerate
Phosphoenolpyruvate
Fructose 6-phosphate
ATP
Phosphofructo-kinase-1
ADP
Fructose 1,6-bisphosphate
Fructose 6-phosphate
Bifunctional enzyme
PFK-2 (active)
FBP-2 (inactive)
ATP
ADP
P
PFK-2 (inactive)
FBP-2 (active)
P
Bifunctional enzyme
Fructose 2,6-bisphosphate
3 Dephosphorylated PFK-2 is active, whereas FBP-2 is inactive; this favors formation of fructose 2,6-bisphosphate.
4 Elevated concentration of fructose 2,6-bisphosphate activates PFK-1, which leads to an increased rate of glycolysis.

# Glycolysis: *Stage II*

Convert two moles of glyceraldehyde 3-phosphate (phospho-triose) to two moles of 3-phosphoglycerate (carboxylic acid).

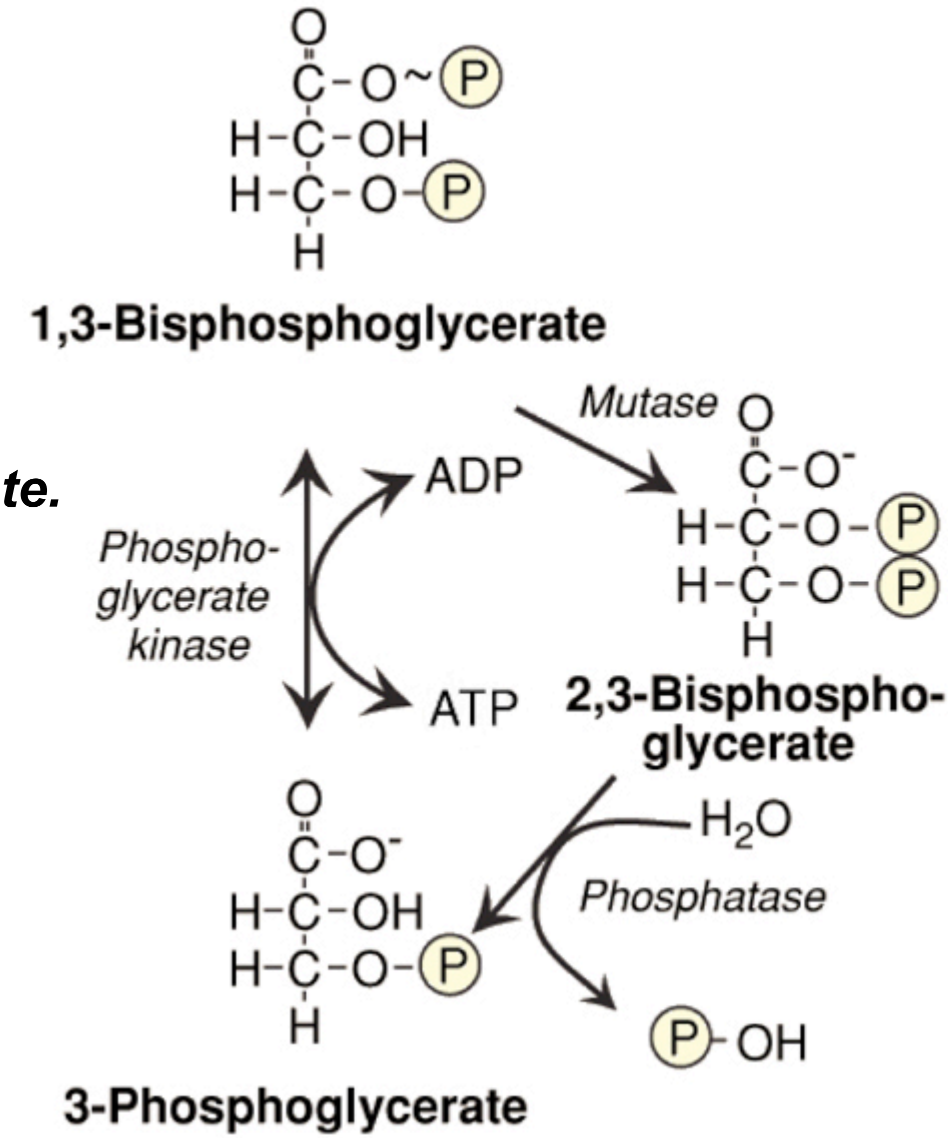
Recover two ATP molecules used in Stage I

1. ***Aldehyde of glyceraldehyde 3-phosphate is converted to a high energy acyl-phosphate group by coupled reactions with NAD$^+$ and inorganic phosphate, $P_i$.***



# Glycolysis: *Stage II*

2. ***1,3-bisphosphoglycerate is converted to 3-phosphoglycerate. In a coupled reaction, ATP is formed from ADP and $P_i$.***

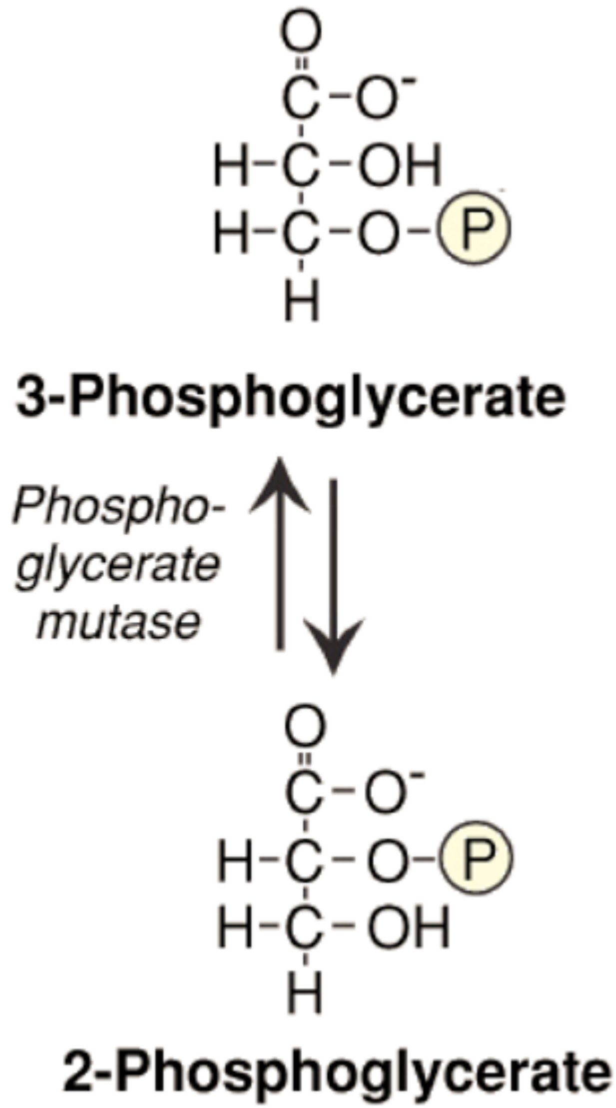


# Glycolysis: *Stage II*

Convert 2 moles of 3-phosphoglycerate to 2 moles pyruvate.

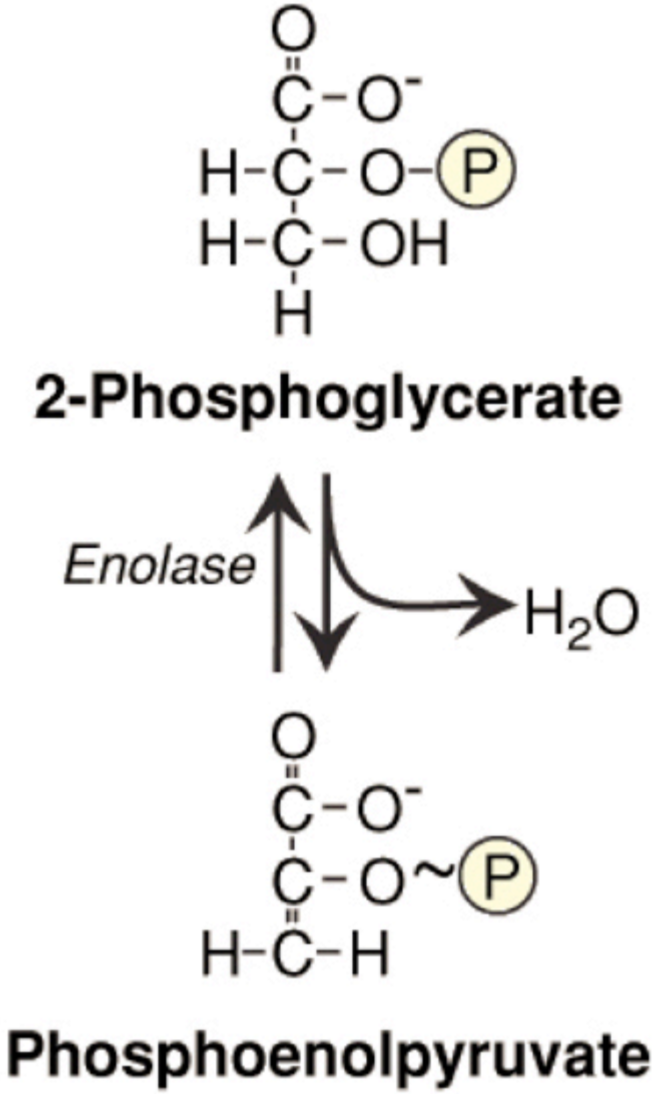
Make two molecules of ATP

***3. Internal rearrangement of phosphate group in 3-phosphoglycerate.***



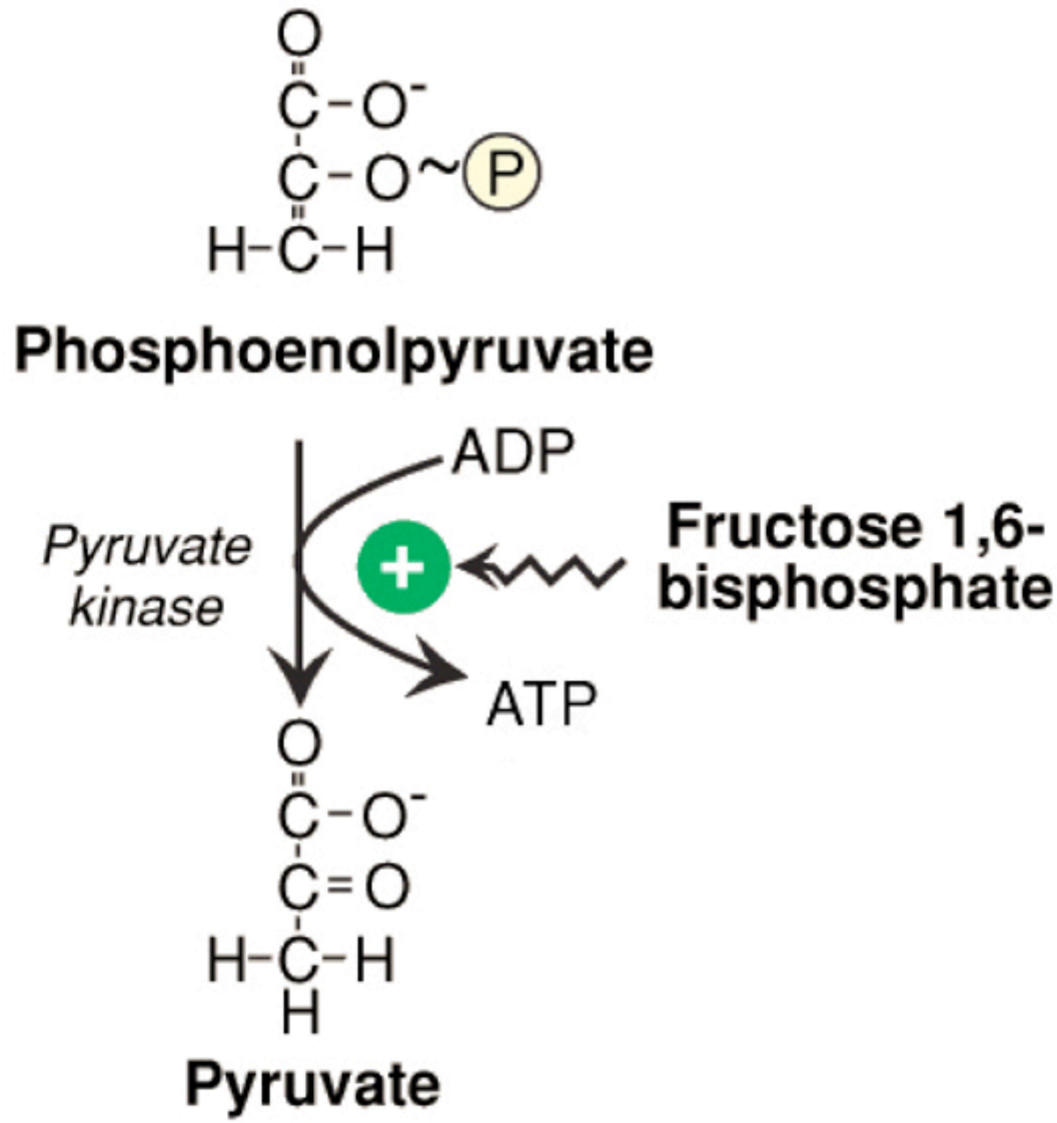
# Glycolysis: *Stage II*

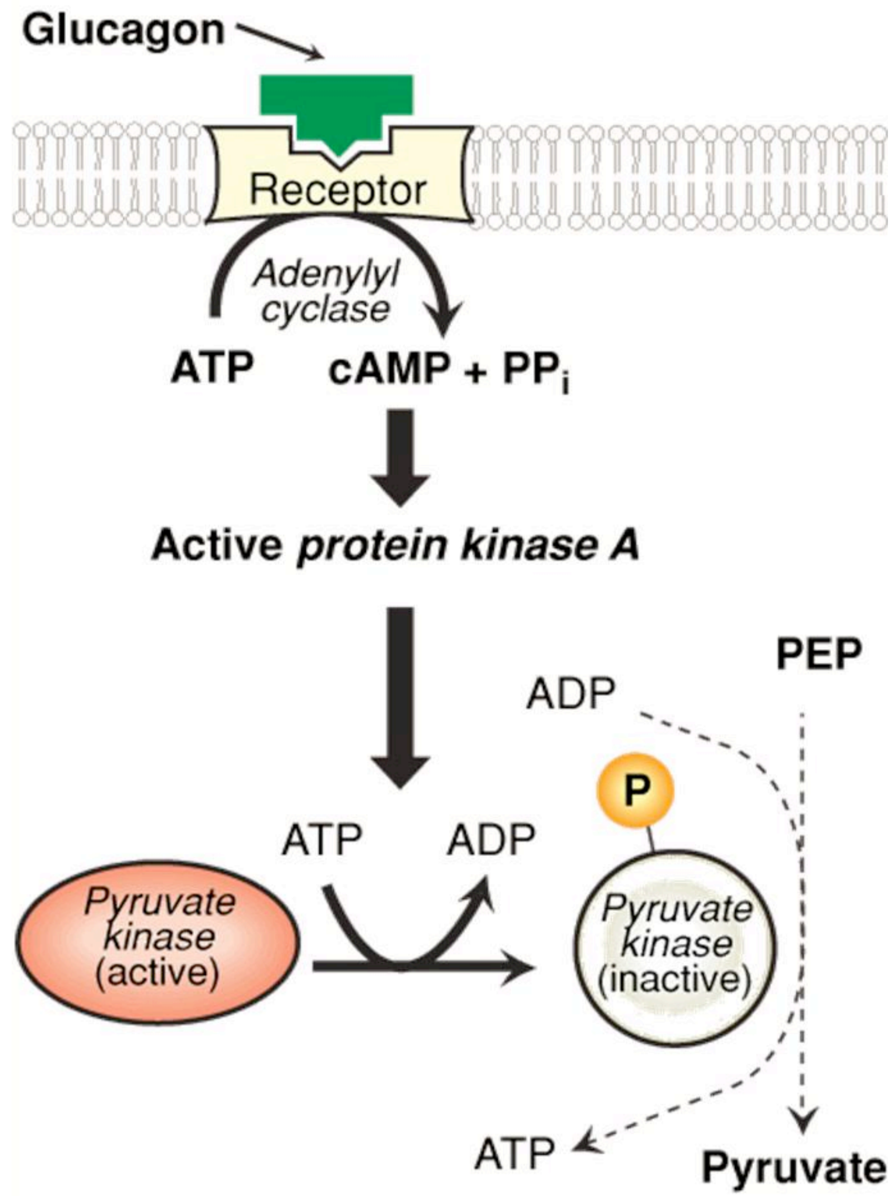
4. ***Conversion of 2-phosphoglycerate to a high energy (activated) enol-phosphate.***



# Glycolysis: *Stage II*

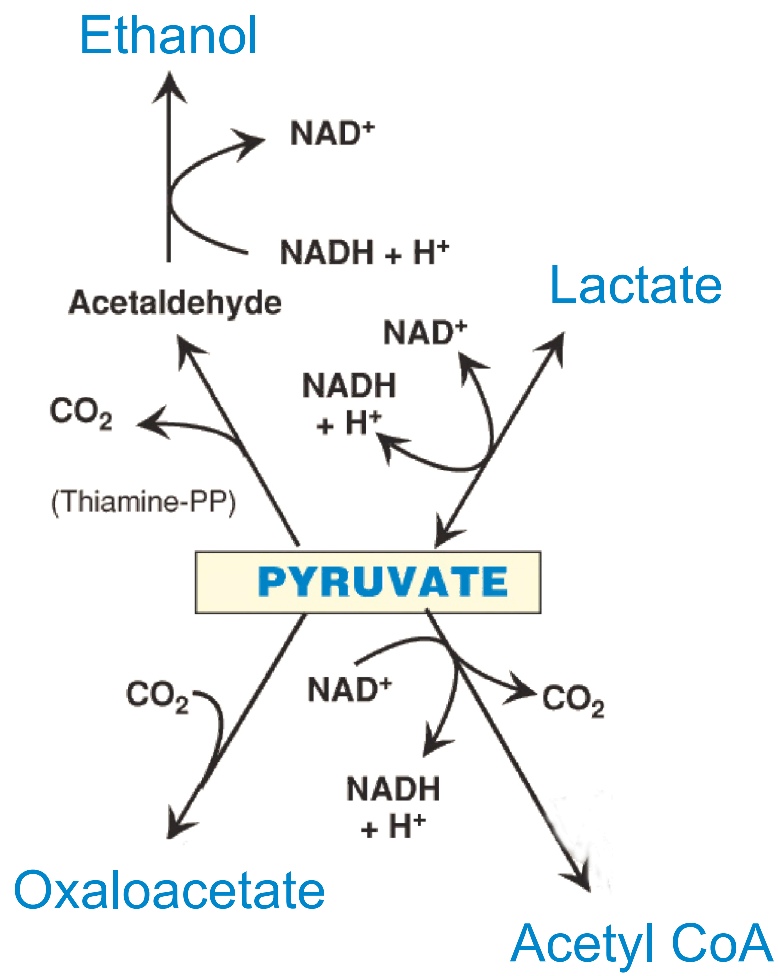
5. ***Conversion of activated phosphoenolpyruvate to pyruvate and ATP.***

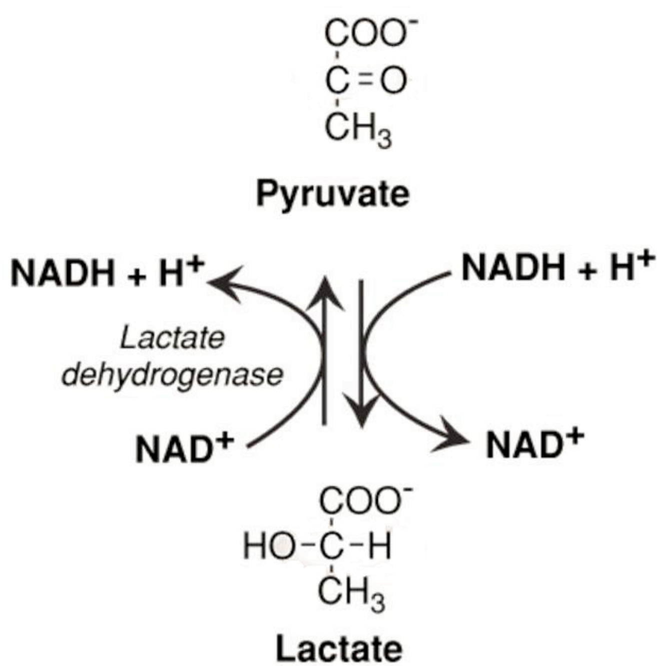


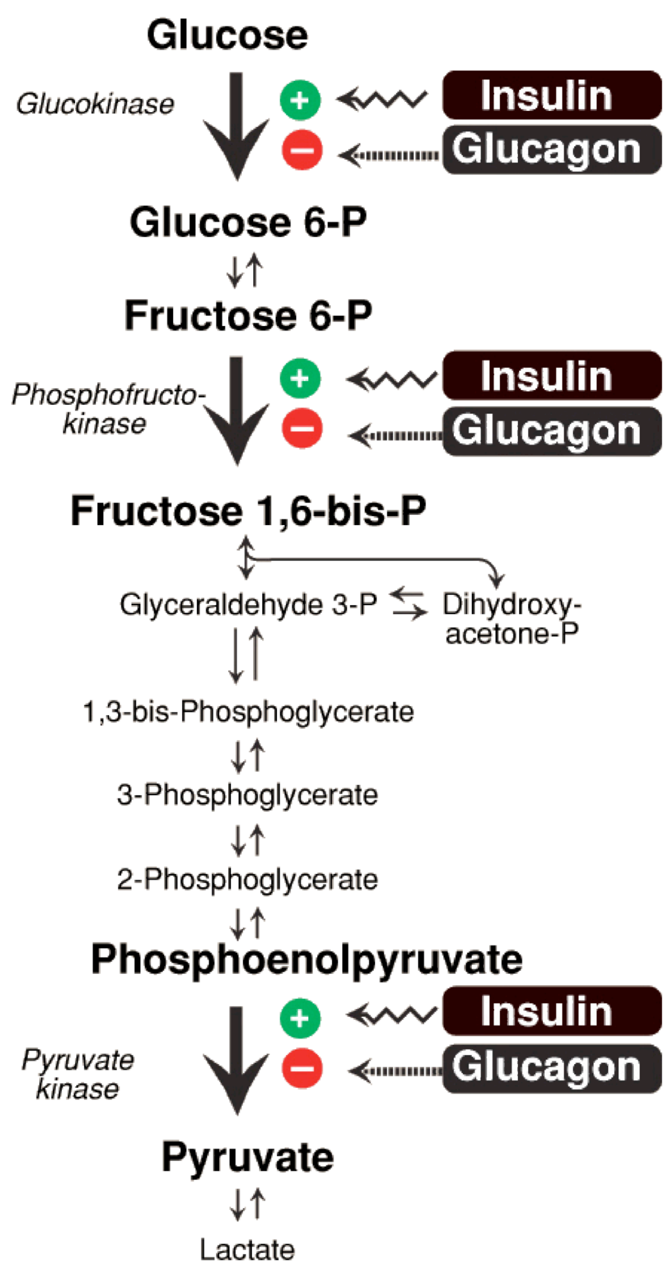


Glucagon
Receptor
Adenylyl cyclase
ATP
cAMP + PP$_i$
Active *protein kinase A*
PEP
ADP
P
ATP
ADP
*Pyruvate kinase* (active)
*Pyruvate kinase* (inactive)
ATP
Pyruvate

# Metabolic fate of pyruvate




COO-
C=O
CH3
Pyruvate
NADH + H+
NADH + H+
Lactate
dehydrogenase
NAD+
NAD+
COO-
HO-C-H
CH3
Lactate




## Well-fed state

- ↑ Ingestion of glucose
- ↑ Blood glucose
- ↑ Release of insulin
- ↑ Protein phosphatase activity
- ↑ Fructose 2,6-bisphosphate

## Fasting state

- ↓ Blood glucose
- ↑ Release of glucagon
- ↑ cAMP
- ↑ Protein kinase activity
- ↓ Fructose 2,6-bisphosphate