Lecture 6

Glycolysis

Carbohydrate metabolism

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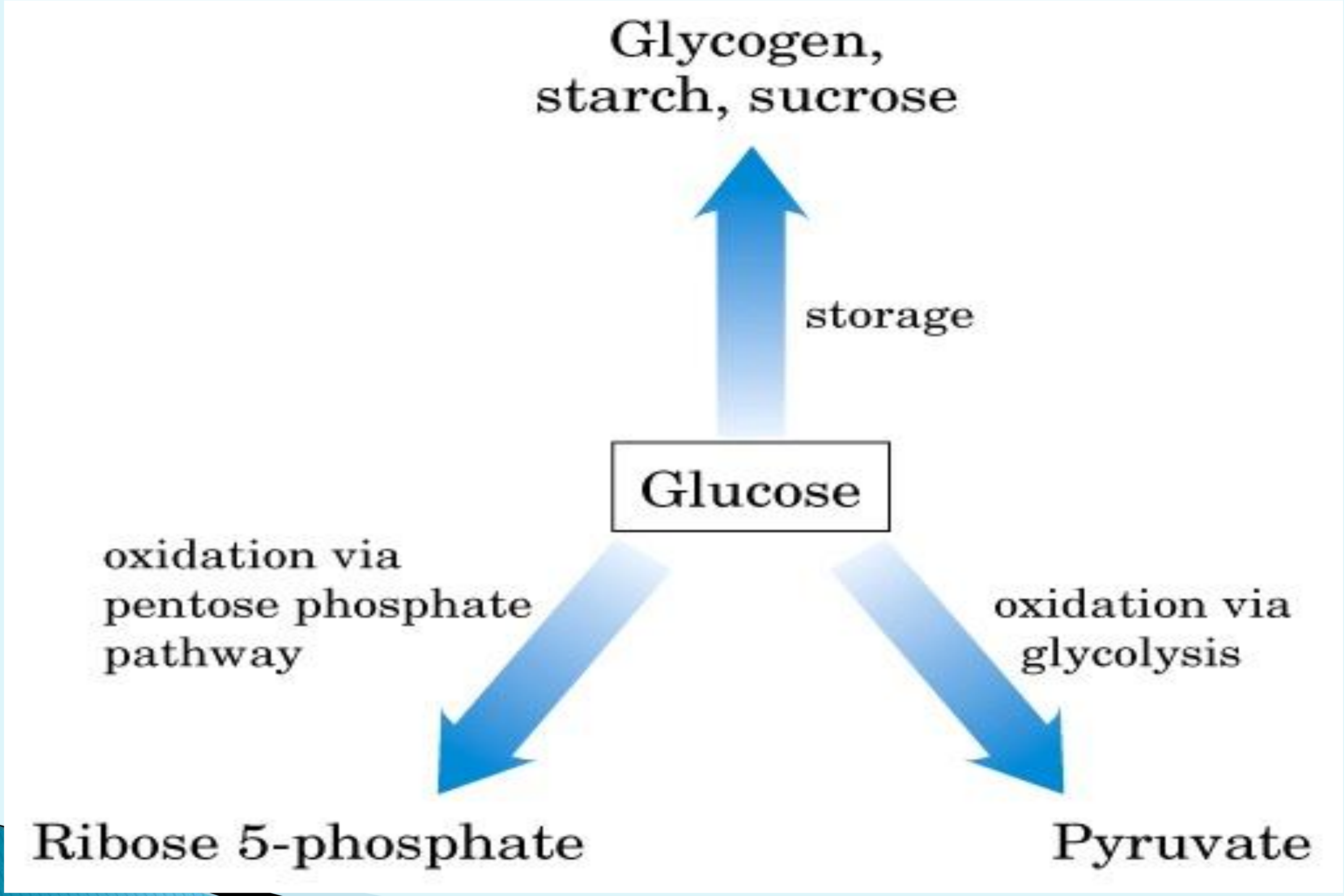
Glycolysis

- D-Glucose is a major fuel for most organisms.
- D-Glucose metabolism occupies the center position for all metabolic pathways.
- Glucose contains a great deal of potential energy. The complete oxidation of glucose yields −2,840 kJ/mol of energy

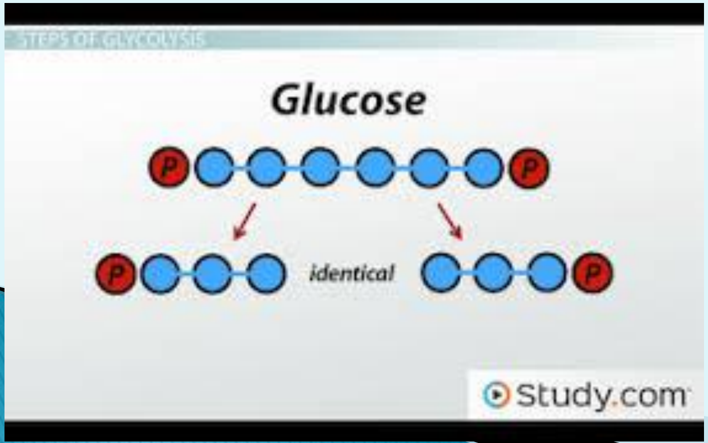
Glycolysis

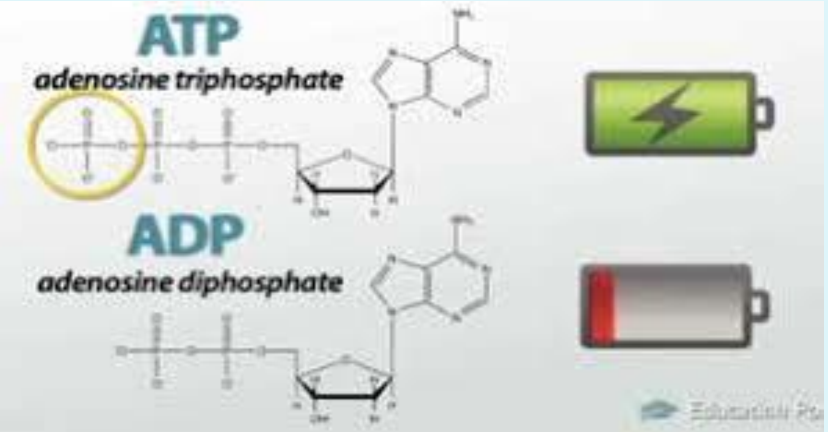


Glycogen,
starch, sucrose
storage
Glucose
oxidation via
pentose phosphate
pathway
oxidation via
glycolysis
Ribose 5-phosphate
Pyruvate

Glycolysis

- Glycolysis literally means "splitting sugars." In glycolysis, glucose (a six carbon sugar) is split into two molecules of a three-carbon sugar. Glycolysis yields two molecules of ATP (free energy containing molecule), two molecules of pyruvic acid and two "high energy" electron carrying molecules of NADH.

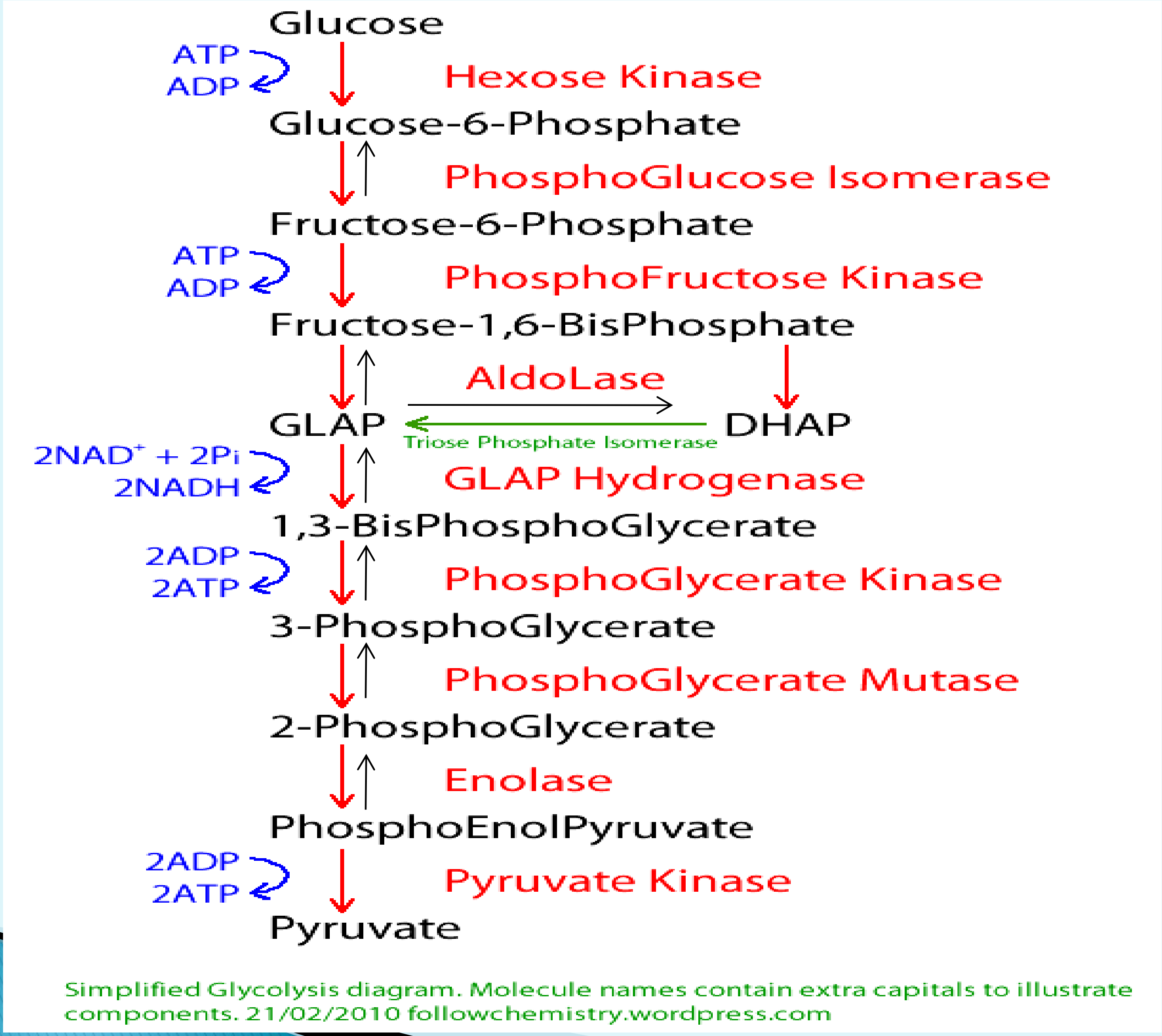


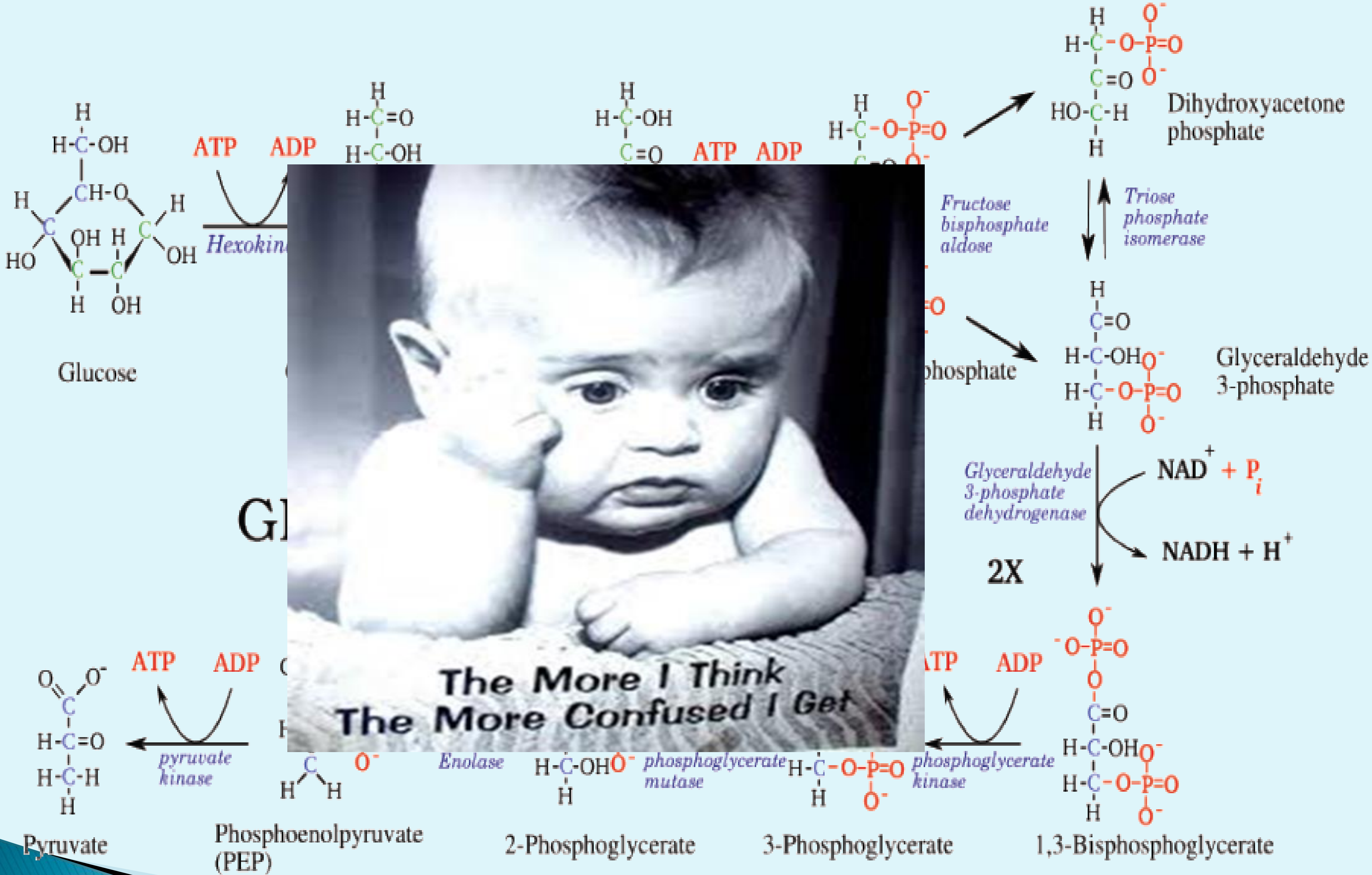


Glycolysis

- Glycolysis can occur with or without oxygen. In the presence of oxygen, glycolysis is the first stage of cellular respiration. Without oxygen, glycolysis allows cells to make small amounts of ATP.

diagram of glycolysis

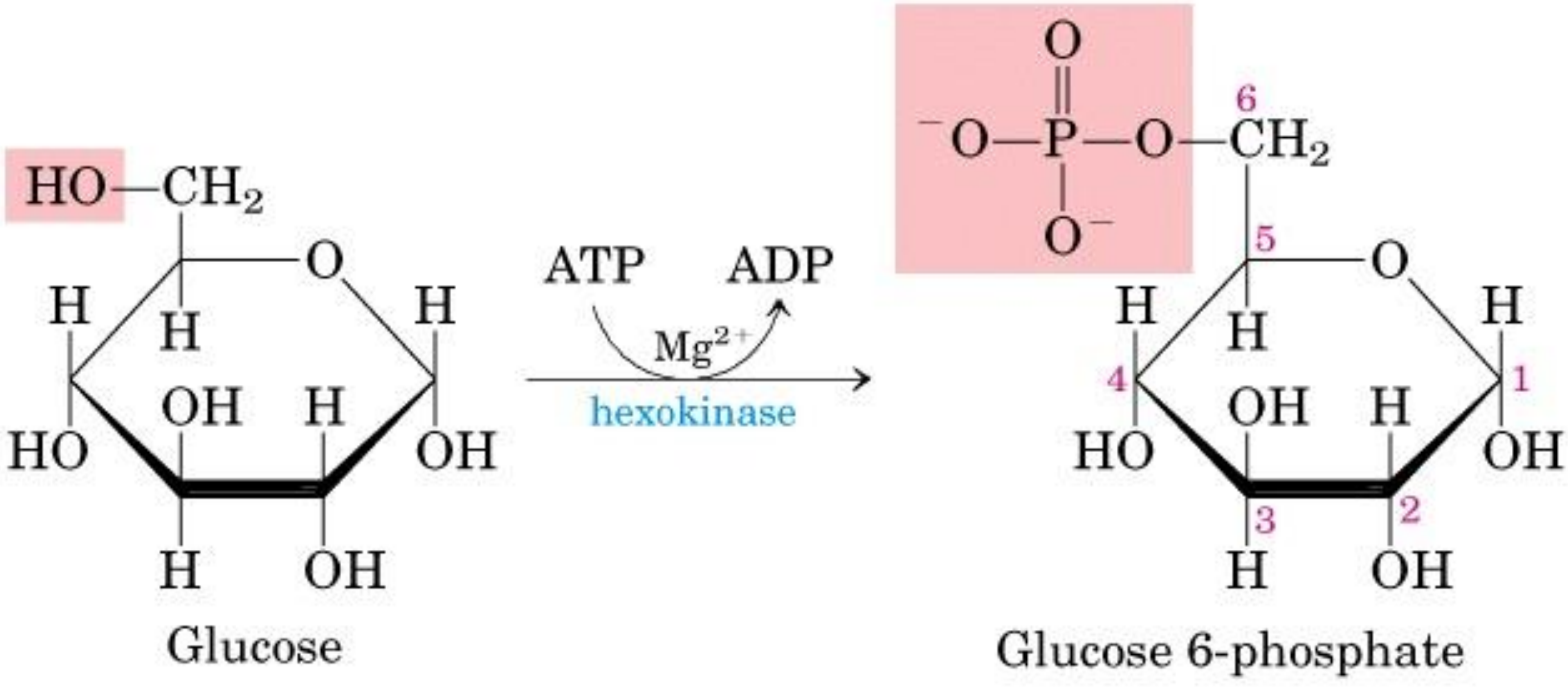



Glucose
ATP
ADP
Hexokin
Fructose bisphosphate aldose
Dihydroxyacetone phosphate
Triose phosphate isomerase
Glyceraldehyde 3-phosphate
Glyceraldehyde 3-phosphate dehydrogenase
$NAD^+ + P_i$
$NADH + H^+$
2X
1,3-Bisphosphoglycerate
phosphoglycerate kinase
3-Phosphoglycerate
phosphoglycerate mutase
2-Phosphoglycerate
Enolase
Phosphoenolpyruvate (PEP)
pyruvate kinase
Pyruvate
The More I Think
The More Confused I Get

Steps of glycolysis

1- Hexokinase reaction: phosphorylation of glucose

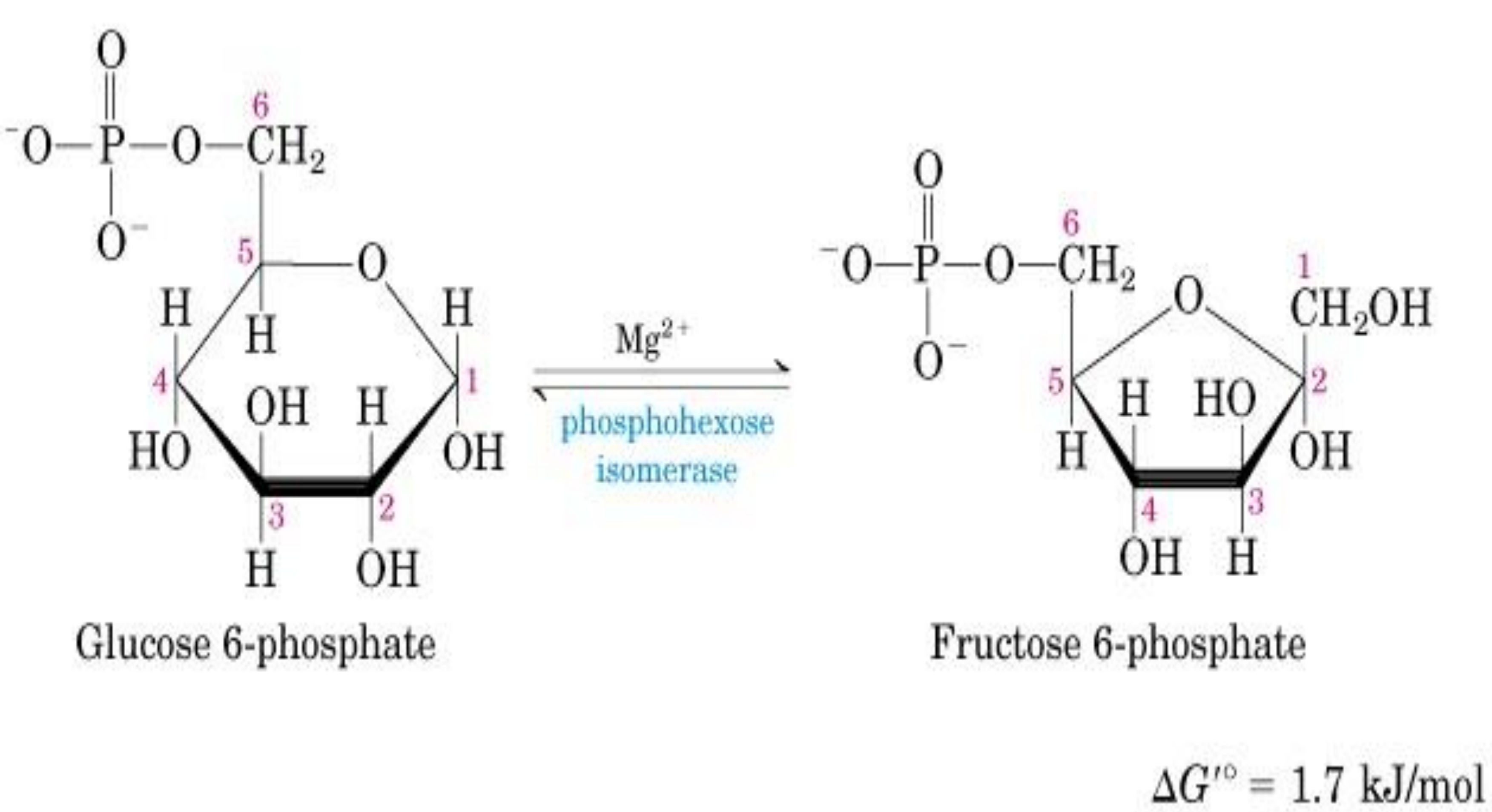
- This enzyme is present in most cells. In liver Glucokinase is the main hexokinase which prefers glucose as substrate.
- It requires Mg-ATP complex as substrate. Un-complexed ATP is a potent competitive inhibitor of this enzyme.



$\Delta G'^{\circ} = -16.7$ kJ/mol

2-Phosphoglucose Isomerase: Isomerization of G6P to Fructose 6-P.

- This enzyme catalyzes the reversible isomerization of G6P (an aldohexose) to F6P (a ketohexose).
- This enzyme requires Mg^{++} for its activity.
- It is specific for G6P and F6P.

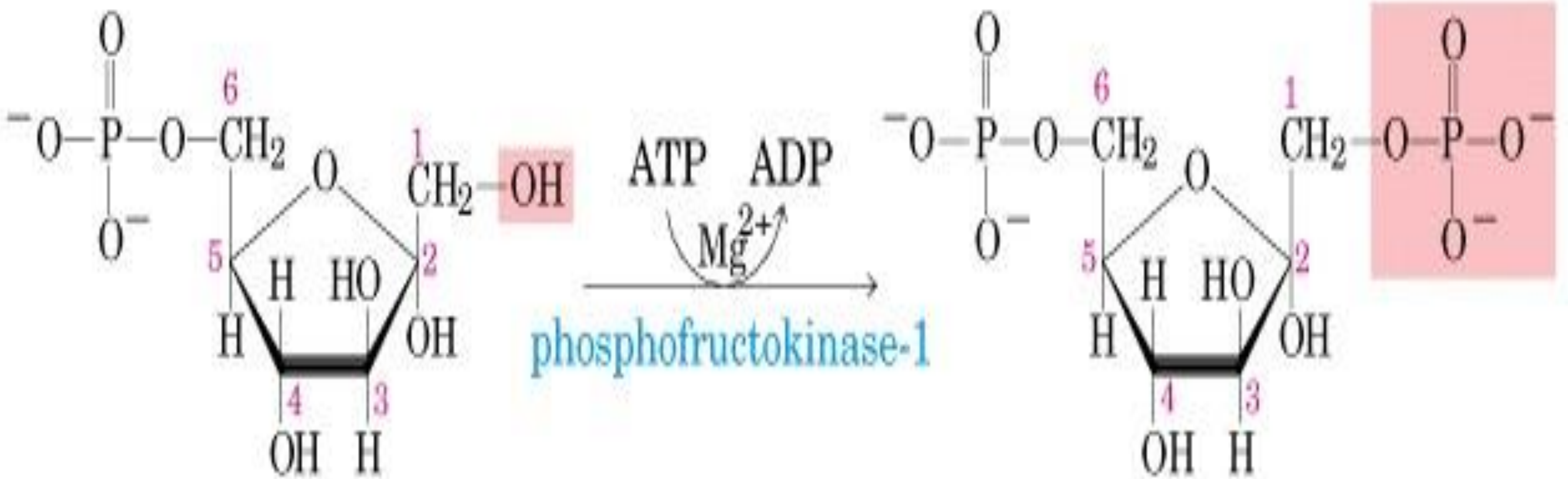

Mg^{2+}
phosphohexose isomerase
Glucose 6-phosphate
Fructose 6-phosphate
$\Delta G'^{\circ}$ = 1.7 kJ/mol

3-Phosphofructokinase-1 Reaction

- Transfer of phosphoryl group from ATP to C-1 of F6P to produce Fructose 1,6 bisphosphate.

- This step is an important irreversible, regulatory step.

- The enzyme Phosphofructokinase-1 is one of the most complex regulatory enzymes



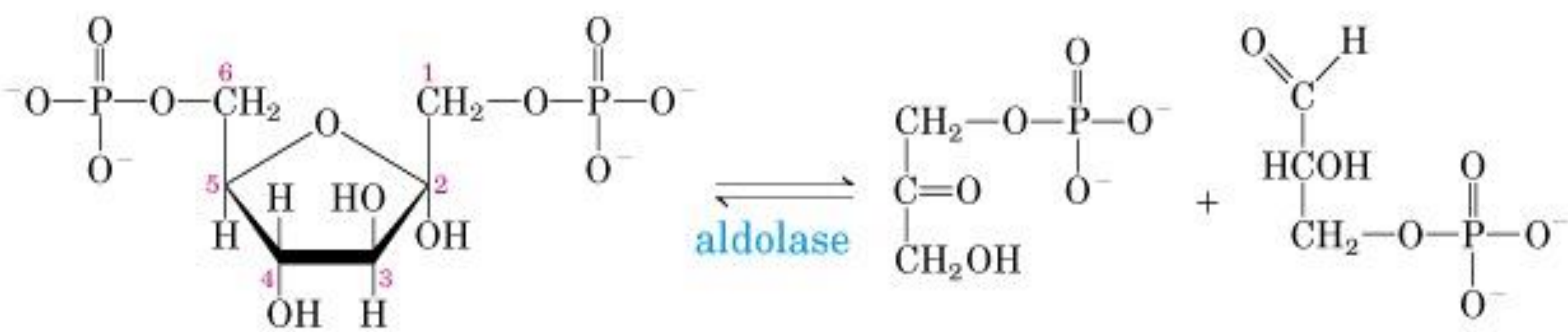
Fructose 6-phosphate

Fructose 1,6-bisphosphate

$\Delta G'^{\circ} = -14.2$ kJ/mol

4. Aldolase Reaction:

- Cleavage of Fructose 1,6 bisphosphate into glyceraldehyde 3 phosphate (an aldose) and dihydroxy acetone phosphate (a ketose).
- This enzyme catalyses the cleavage of F1,6 bisphosphate by aldol condensation mechanism



Fructose 1,6-bisphosphate

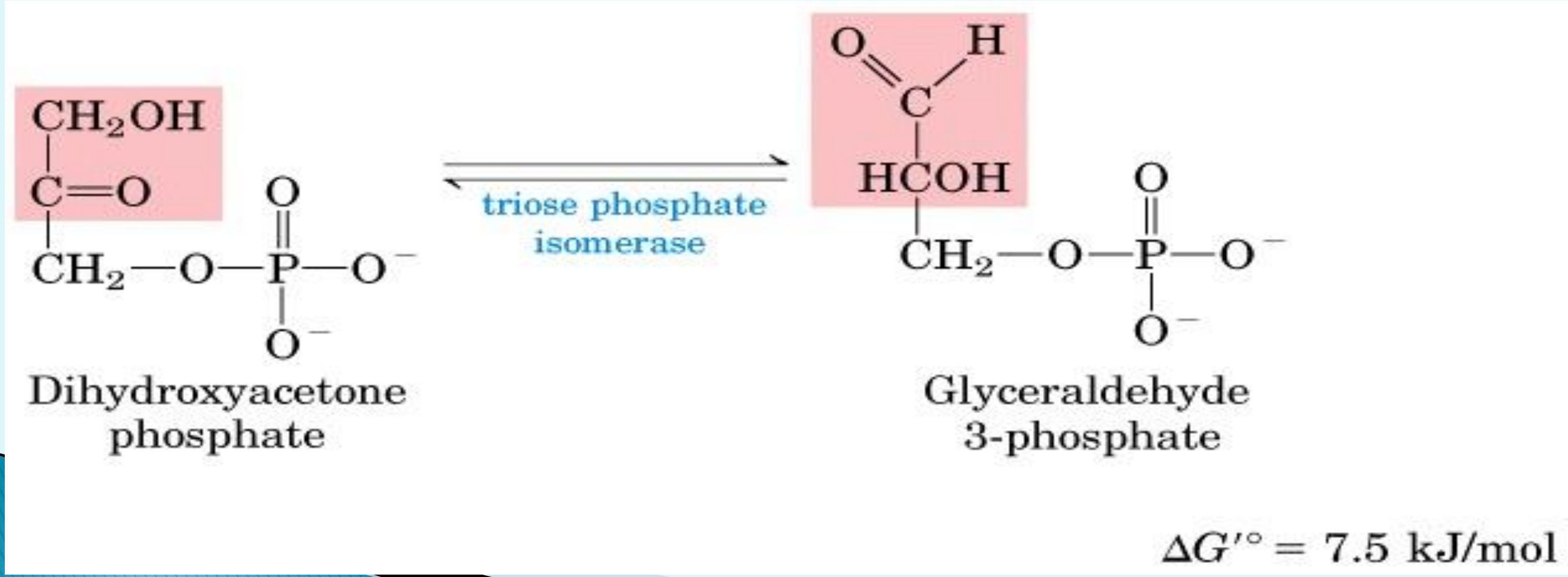
Dihydroxyacetone phosphate

Glyceraldehyde 3-phosphate

$\Delta G'^{\circ} = 23.8 kJ/mol$

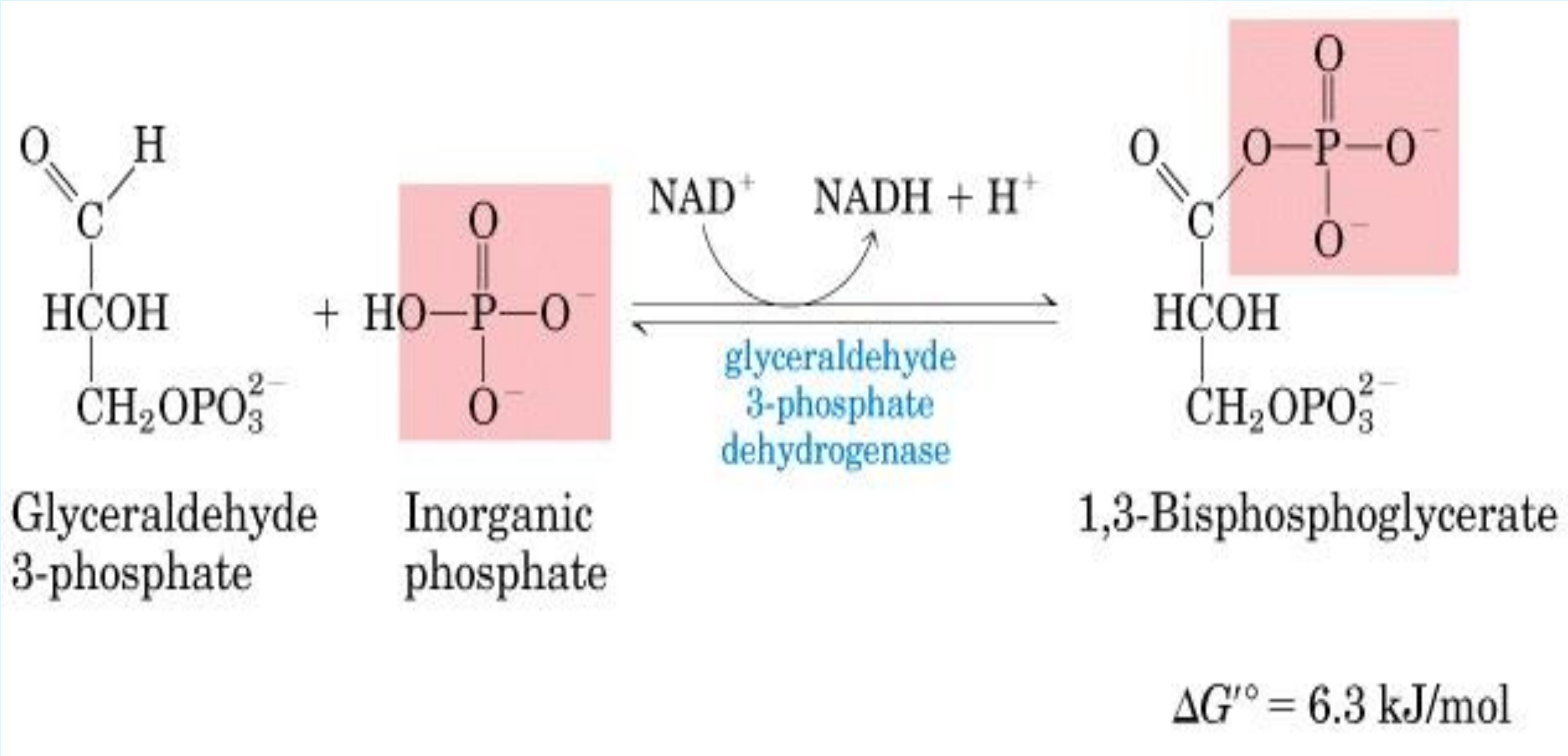
5. Triose phosphate mutase reaction

- Conversion of Dihydroxyacetone phosphate to glyceraldehyde 3 Phosphate.
- This a reversible reaction catalysed by acid-base catalysis.



6. Glyceraldehyde-3-phosphate dehydrogenase reaction (GAPDH):

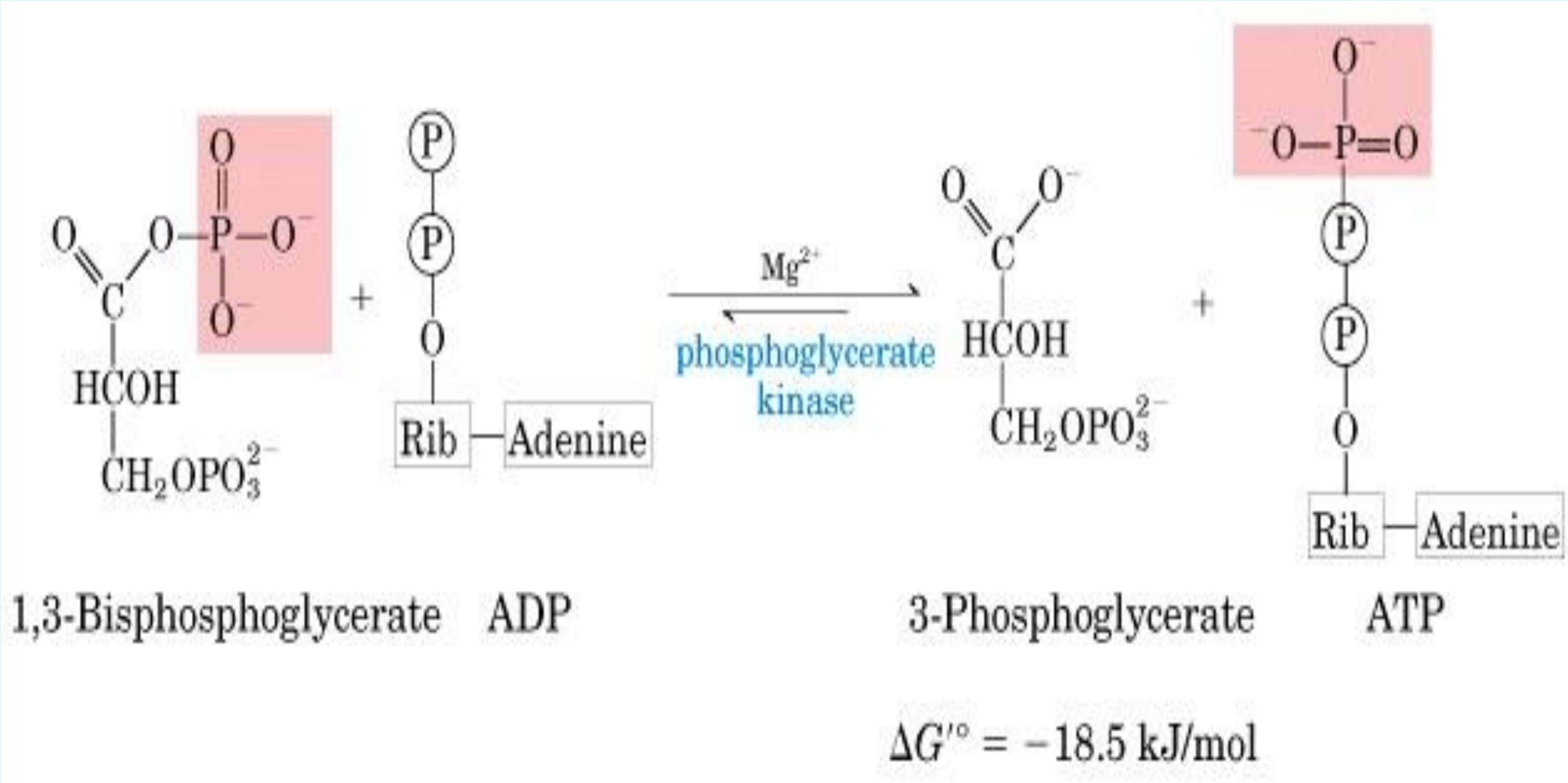
- Conversion of GAP to Bisphosphoglycerate.
- This is the first reaction of energy yielding step. Oxidation of aldehyde derives the formation of a high energy acyl phosphate derivative.
- An inorganic phosphate is incorporated in this reaction without any expense of ATP



NAD+
NADH + H+
HCOH
CH2OPO3 2−
+ HO—P—O−
glyceraldehyde
3-phosphate
dehydrogenase
Glyceraldehyde
3-phosphate
Inorganic
phosphate
1,3-Bisphosphoglycerate
ΔG′° = 6.3 kJ/mol

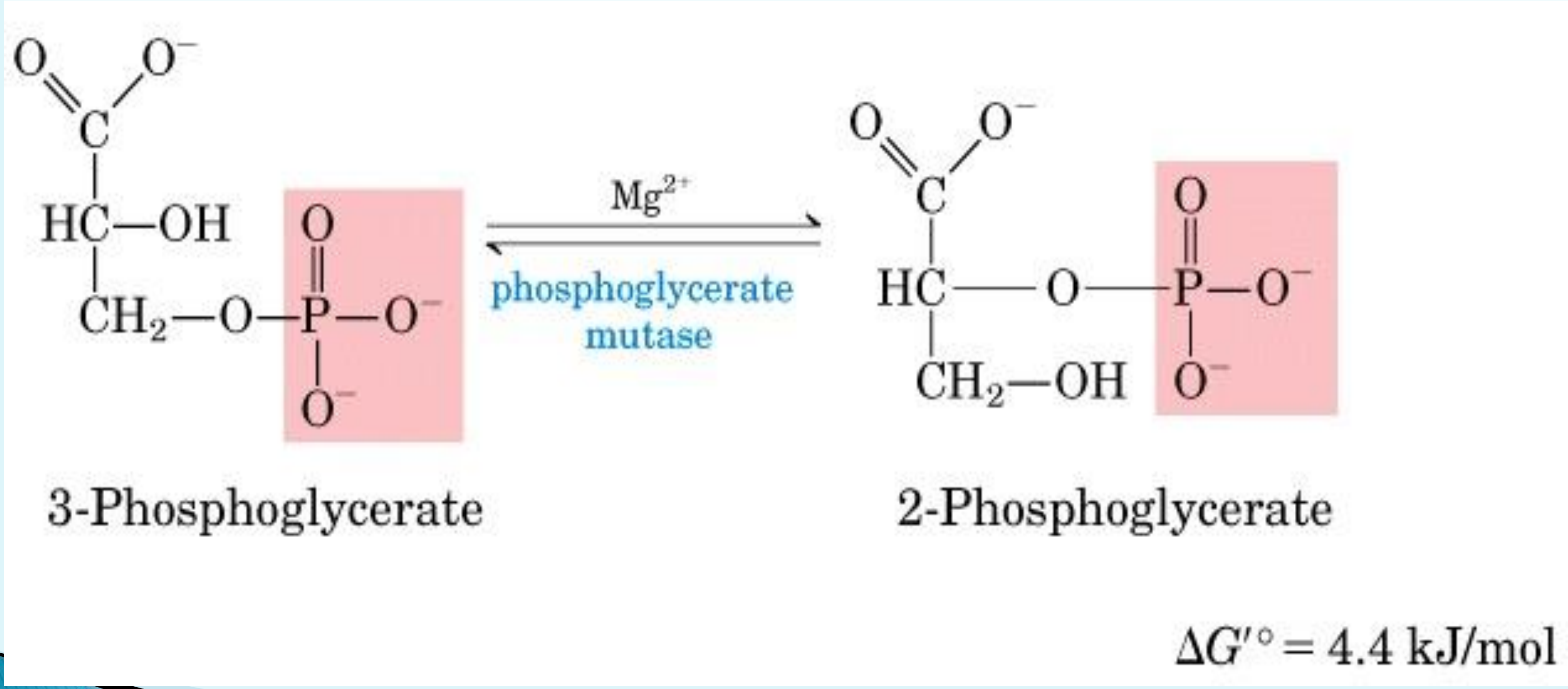
7. Phosphoglycerate kinase Reaction:

- Transfer of phosphoryl group from 1,3 bisphosphoglycerate to ADP generating ATP.
- The name of this enzyme indicates its function for reverse reaction.
- This step generates ATP by substrate – level phosphorylation.


Mg²⁺
phosphoglycerate kinase
HCOH
Rib
Adenine
1,3-Bisphosphoglycerate
ADP
3-Phosphoglycerate
ATP
ΔG′° = −18.5 kJ/mol

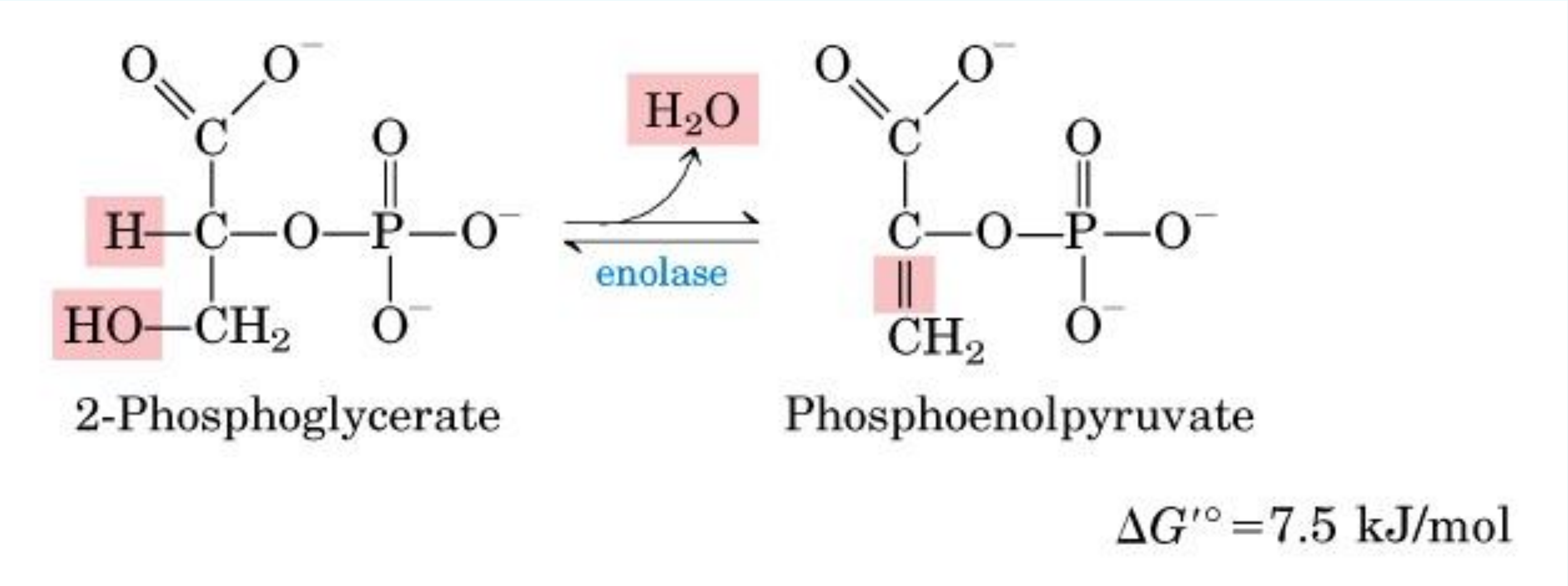
8. Phosphoglycerate Mutase Reaction:

- Conversion of 3-phosphoglycerate to 2-phosphoglycerate (2-PG).



9. Enolase Reaction:

- Dehydration of 2-phosphoglycerate (2-PG) to phosphoenolpyruvate (PEP).
- The second rate limiting step involves elimination of OH group generating PEP.

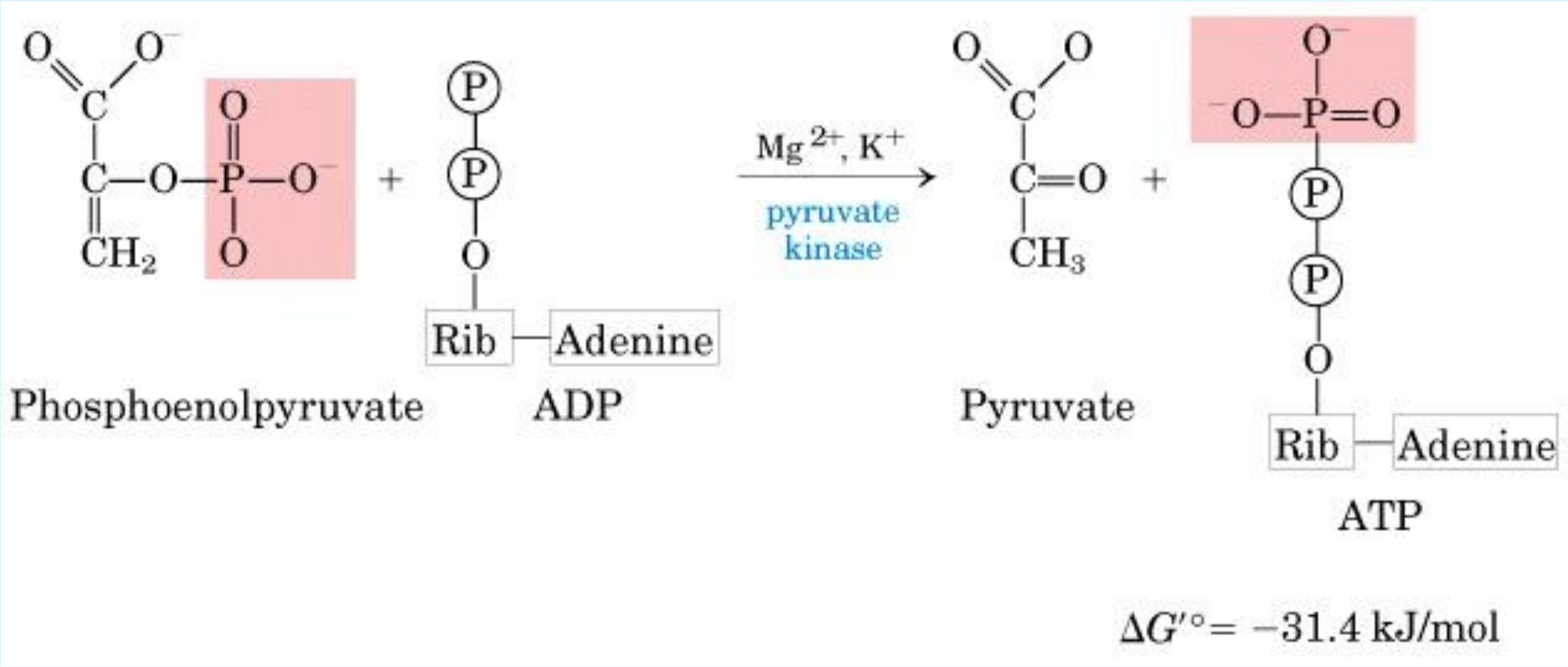


10. Pyruvate Kinase Reaction:

- Transfer of phosphoryl group from PEP to ADP generating ATP and Pyruvate.

- This enzyme couple the free enrgy of PEP hydrolysis to the synthesis of ATP

- This enzyme requires Mg^{++} and K^{+}


Mg 2+, K+
pyruvate
kinase
Rib
Adenine
Phosphoenolpyruvate
ADP
Pyruvate
ATP
ΔG′° = −31.4 kJ/mol

Energetics and products of Glycolysis:

From one molecule of Glucose:
1Gl+2ATP+2NAD$^+$+ 4ADP+ 4Pi = 2pyruvate+2NADH+4ATP+ 2ADP+ 2Pi

After balancing: 1Gl + 2NAD$^+$+ 2ADP + 2Pi = 2pyruvate+2ATP + 2NADH

2 molecules of ATP generated can directly be used for doing work or synthesis. The 2 NADH molecules are oxidized in mitochondria under aerobic condition and the free energy released is enough to synthesize 6 molecules of ATP by oxidative phosphorylation.

Under the aerobic condition, pyruvate is catabolized further in mitochondria through pyruvate dehydrogenase and cytric acid cycle where all the carbon atoms are oxidized to CO2. The free energy released is used in the synthesis of ATP, NADH and FADH2.

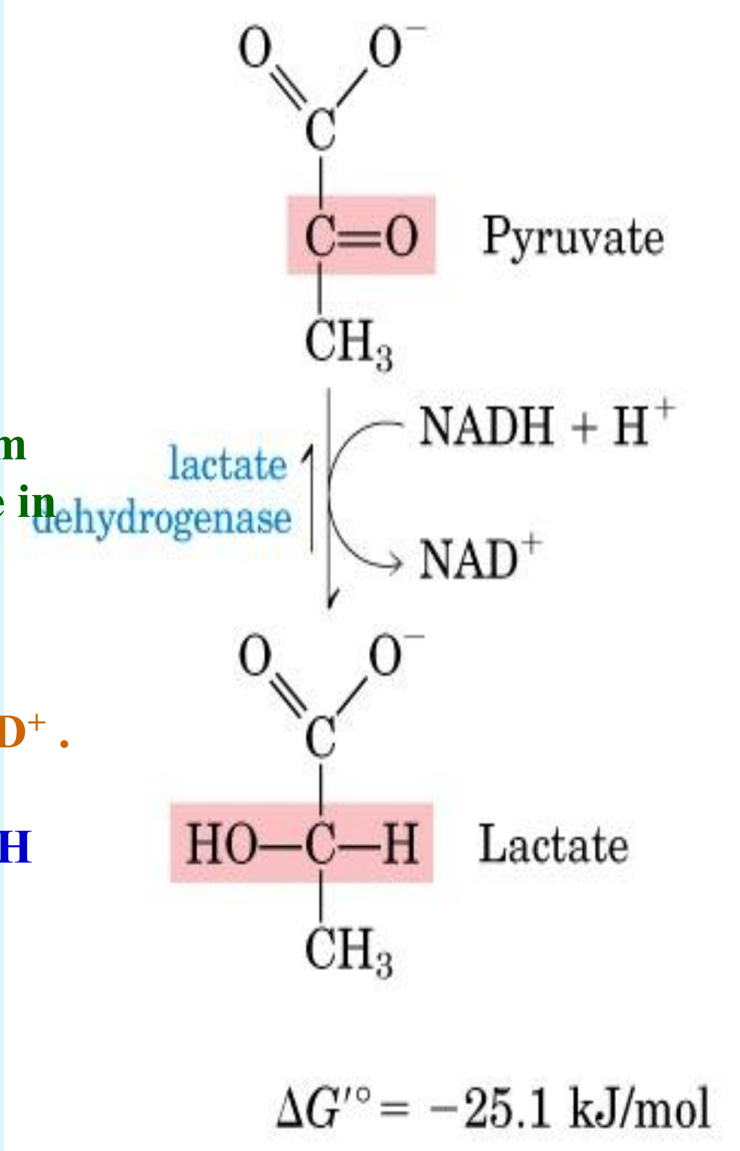
Under anaerobic condition: Pyruvate is converted to Lactate in homolactic fermentation or in ethanol in alcohalic fermentation.

Homolactic Fermentation:

In an anaerobic condition or in the need of sudden need of high amount of ATP, glycolysis is the main source for generation of ATP.
NAD^+ is one of the crucial cofactor required for GAPDH reaction. In order to regenerate NAD^+ from the reduced form (NADH), this reaction takes place in muscle cells.

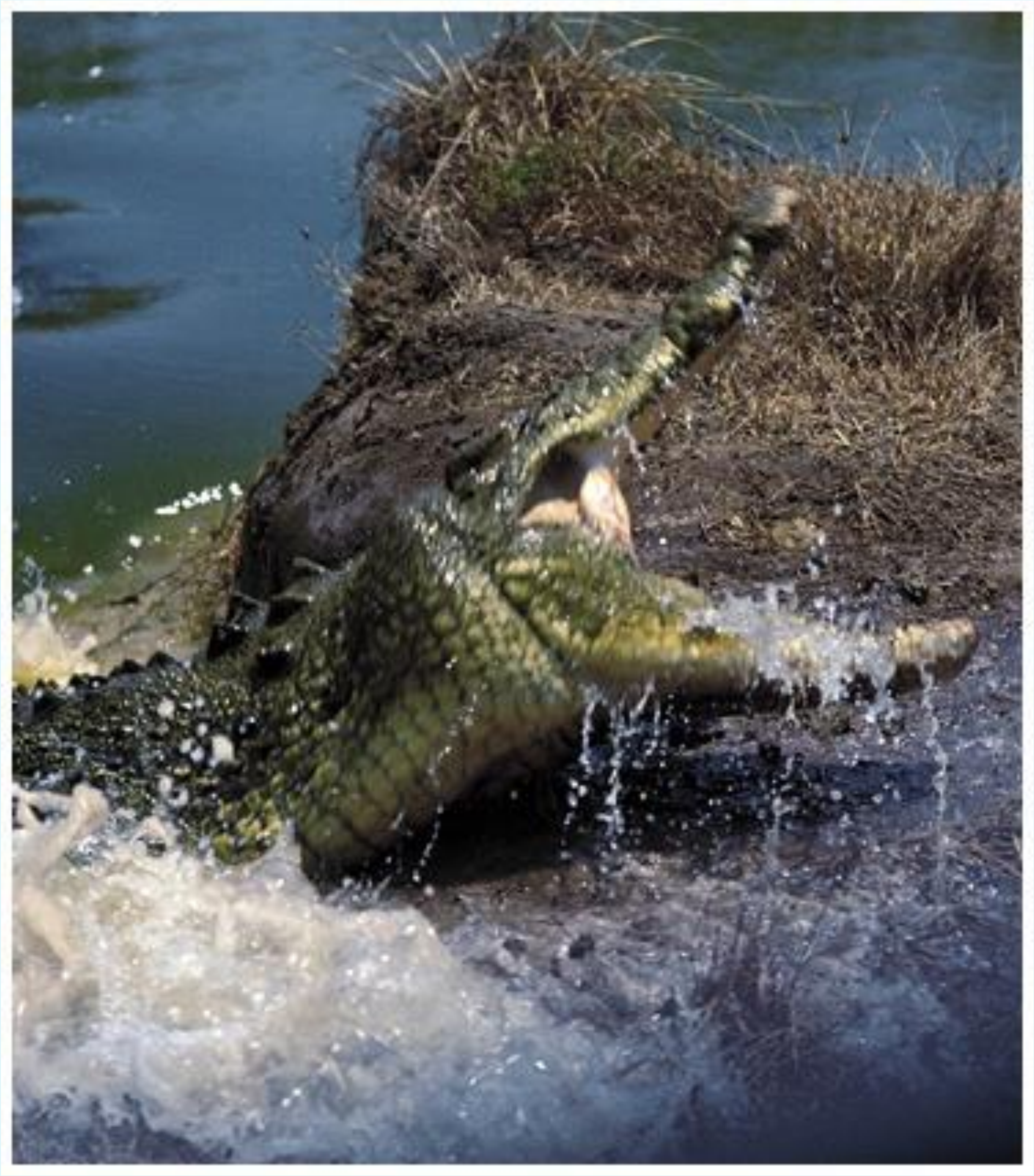
Lactate dehydrogenase (LDH) reduces pyruvate to lactate using NADH and thereby oxidizing it to NAD^+ .

Other than regenerating NAD^+ for running GAPDH reaction, LDH reaction is a waste of energy, and its product lactic acid brings the pH lower and causes fatigue.



Glycolysis can generate sudden burst of ATP without oxygen, using glucose and glycogen storage of muscle and liver.

NAD^+ is regenerated by lactic fermentation to carry out GAPDH reaction of glycolysis.



Pathways for Pyruvate

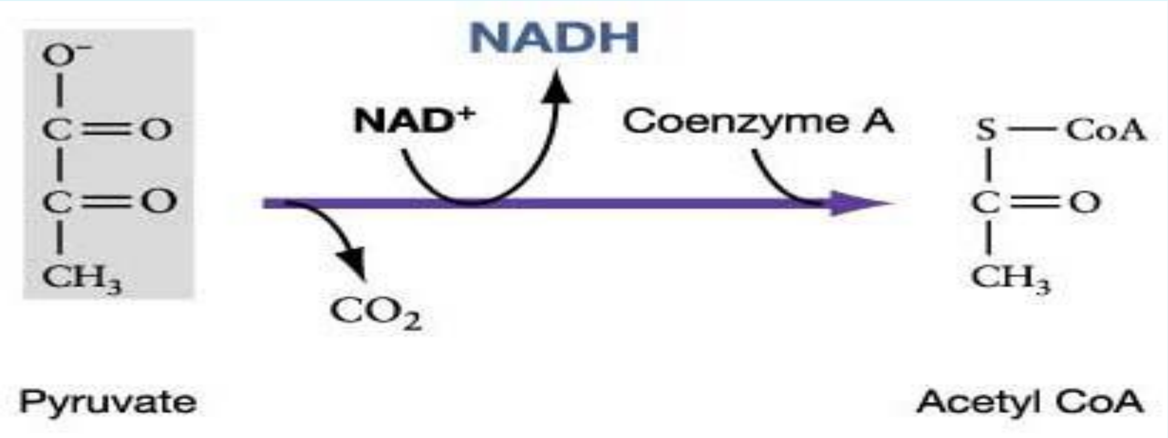
Pathways for Pyruvate

- The pyruvate produced from glucose during glycolysis can be further metabolized in three possible ways
- For **aerobic** organisms, when oxygen is plentiful the pyruvate is converted to acetyl coenzyme A (acetyl CoA)
- For aerobic organisms, when oxygen is scarce, and for some **anaerobic** organisms, the pyruvate is reduced to lactate
- For some anaerobic organisms (like yeast), the pyruvate is fermented to ethanol

Conversion of Pyruvate to Acetyl CoA

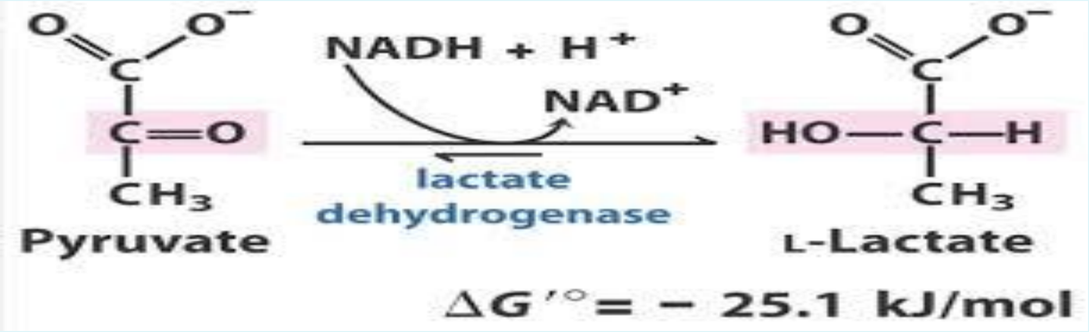
- Under aerobic conditions, pyruvate from glycolysis is decarboxylated to produce acetyl CoA, which enters the citric acid cycle as well as other metabolic pathways

  - the enzyme involved is **pyruvate dehydrogenase complex** and the coenzyme **NAD**$^+$ is also required
- This pathway provides the most energy from glucose



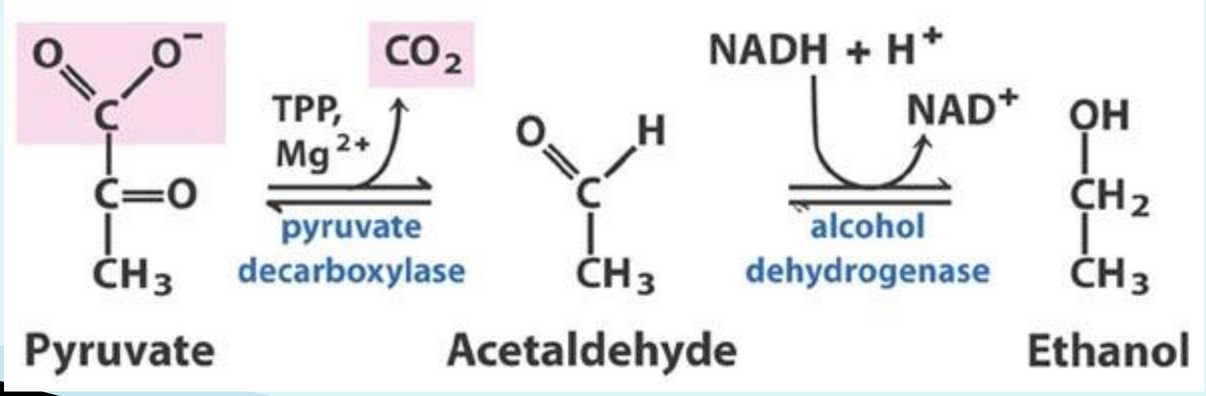
Conversion of Pyruvate to Lactate

- For aerobic organisms under anaerobic conditions, pyruvate is reduced to lactate, which replenishes NAD^+ to continue glycolysis
- During strenuous exercise, muscle cells quickly use up their stored oxygen, creating anaerobic conditions
  - **lactate** accumulates, leading to muscle fatigue and soreness
- Anaerobic bacteria can also produce lactate, which is how we make pickles and yogurt (among other things)

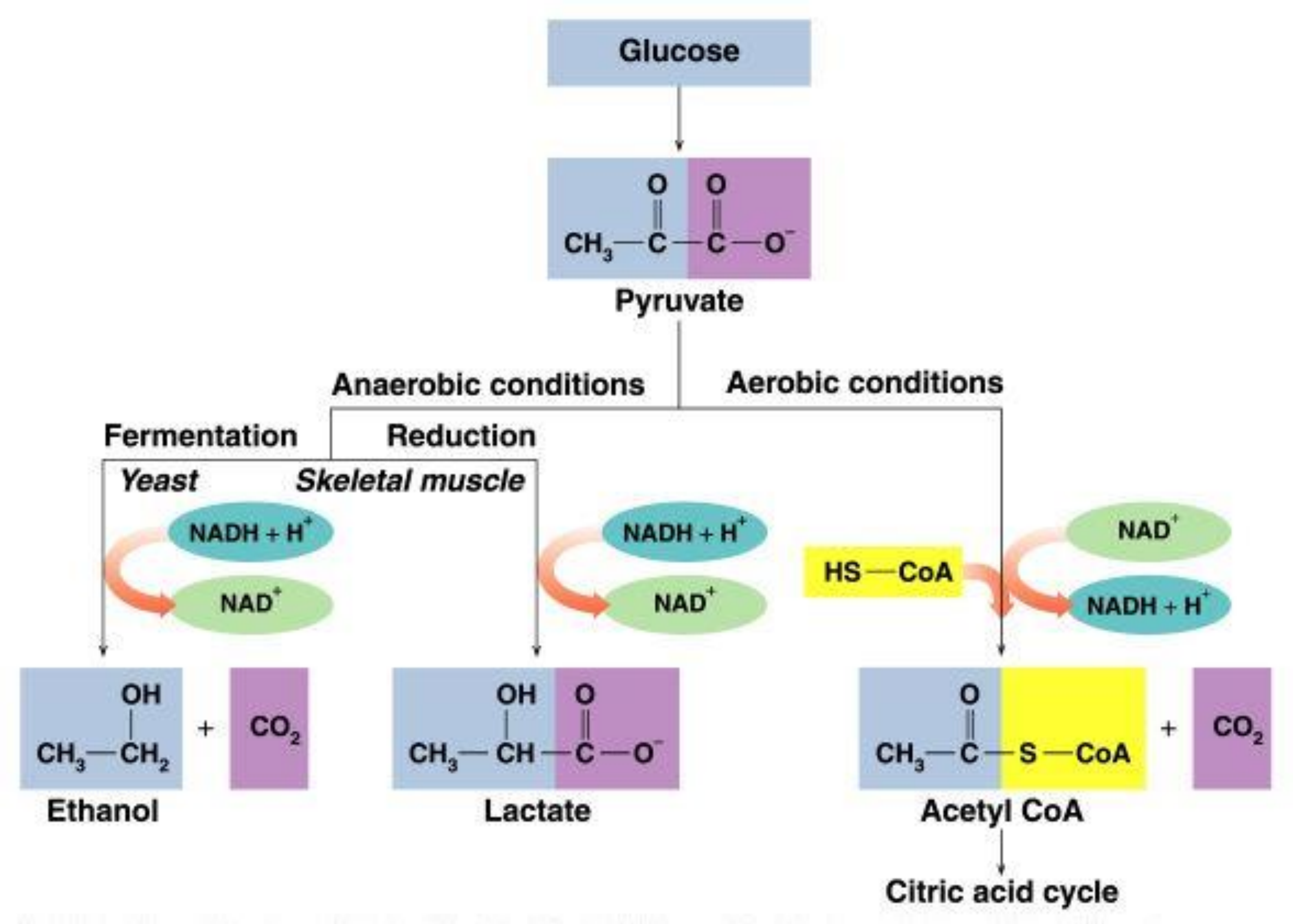


Conversion of Pyruvate to Ethanol

- Anaerobic microorganisms such as yeast, convert pyruvate to **ethanol** by fermentation
  - pyruvate is decarboxylated to acetaldehyde, which is reduced to ethanol
  - NAD^+ is regenerated to continue glycolysis
- The CO_2 produced during fermentation make the bubbles in beer and champagne, and also makes bread rise
- Alcoholic beverages produced by fermentation can be up to around 15% ethanol
  - above that concentration the yeast die



Overview of Pyruvate Pathways

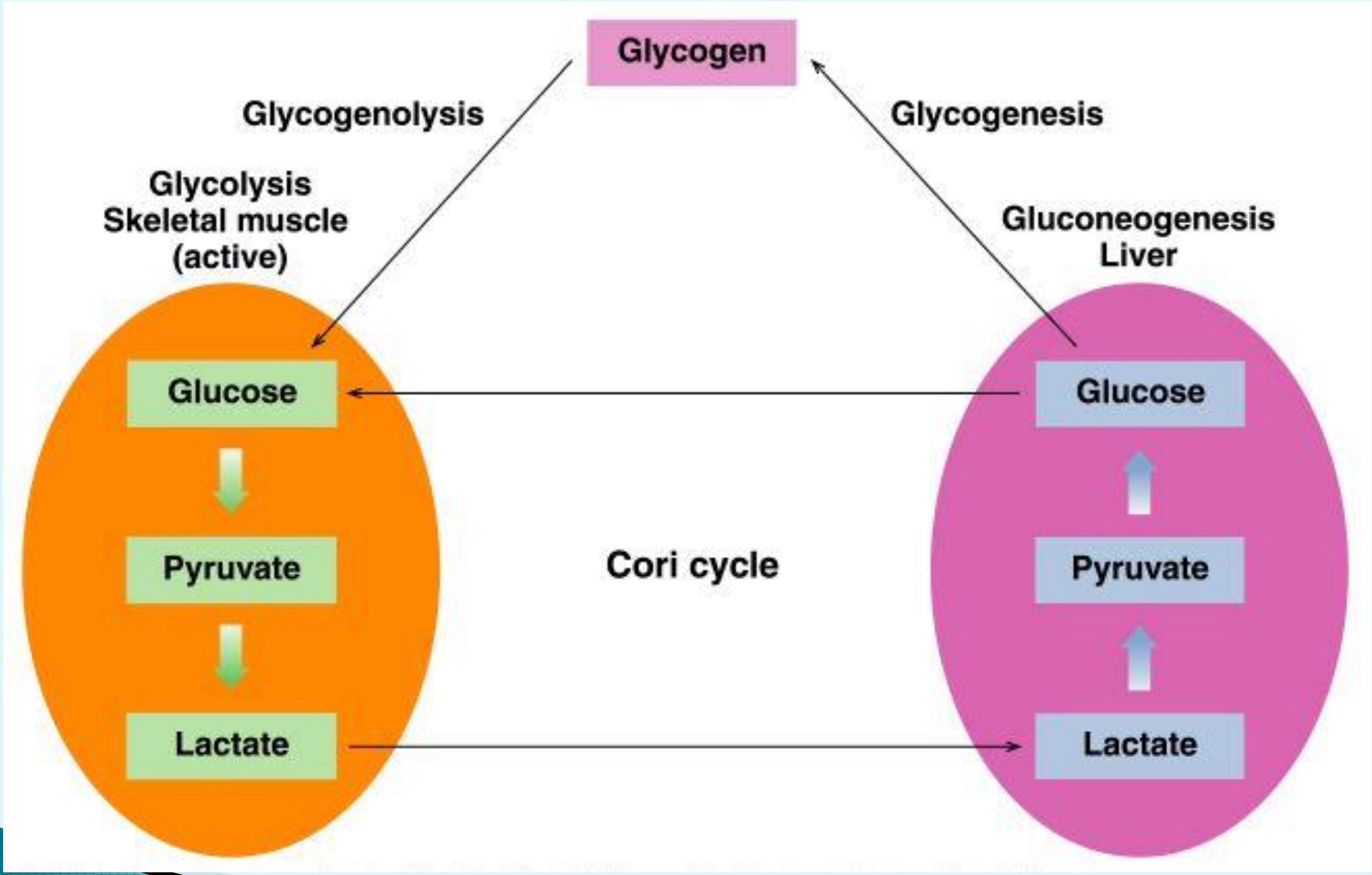


Cori Cycle

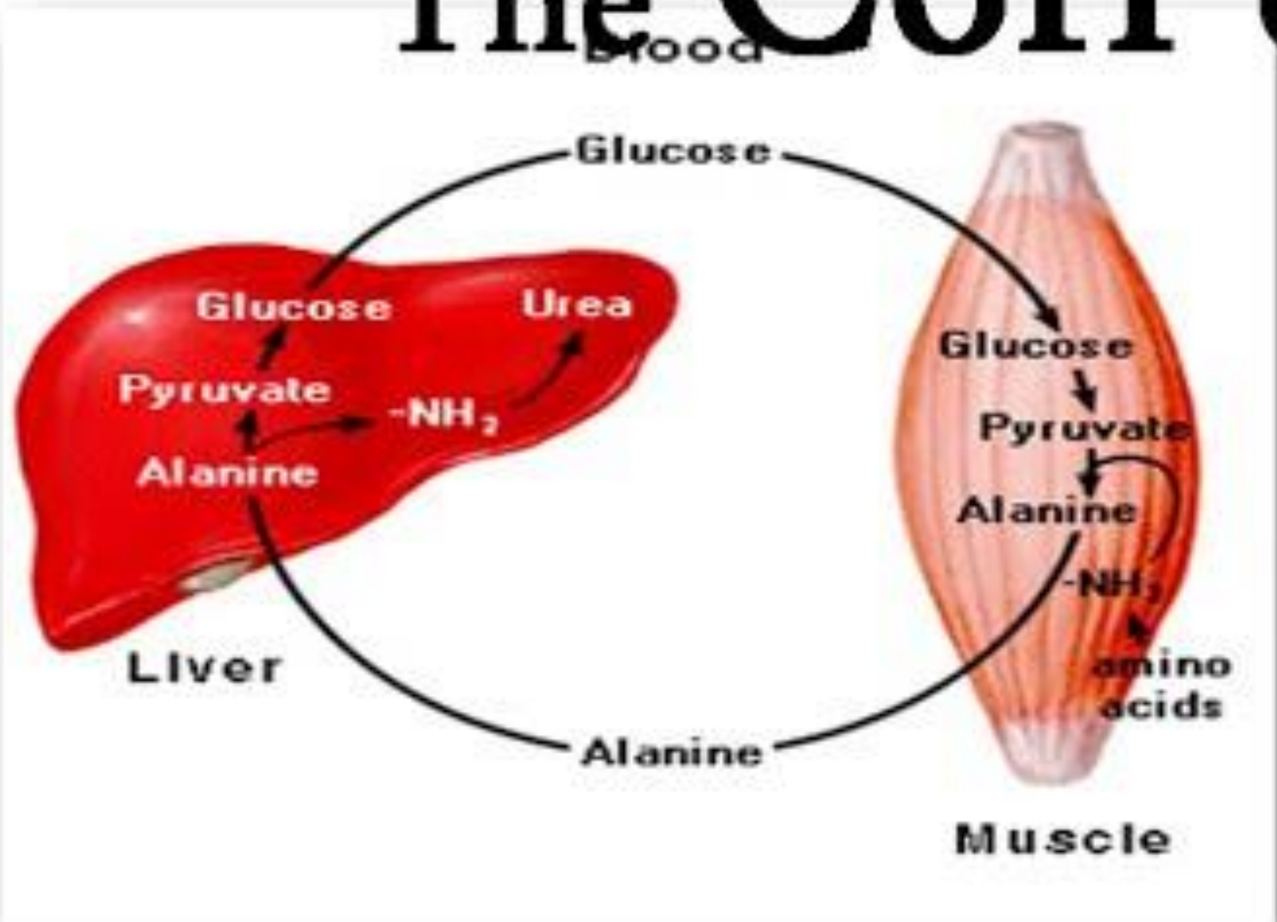
Cori Cycle

- When anaerobic conditions occur in active muscle, glycolysis produces lactate
- The lactate moves through the blood stream to the liver, where it is oxidized back to pyruvate.
- Gluconeogenesis converts pyruvate to glucose, which is carried back to the muscles
- The **Cori cycle** is the flow of lactate and glucose between the muscles and the liver

Cori Cycle diagram



The Cori cycle




thank you!