

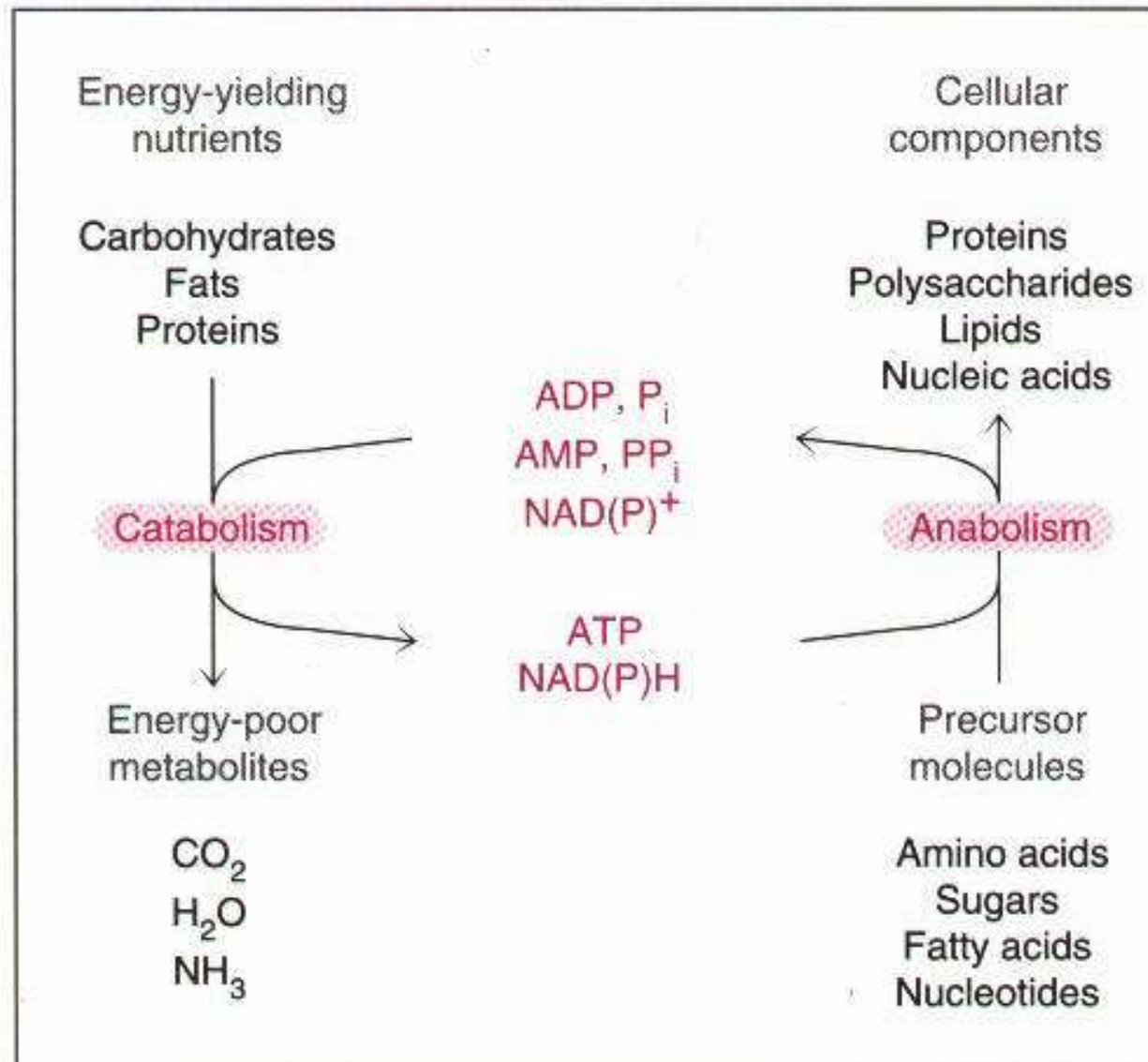
Topic-**Overview of Metabolism**

Department- Botany

Semester-IV

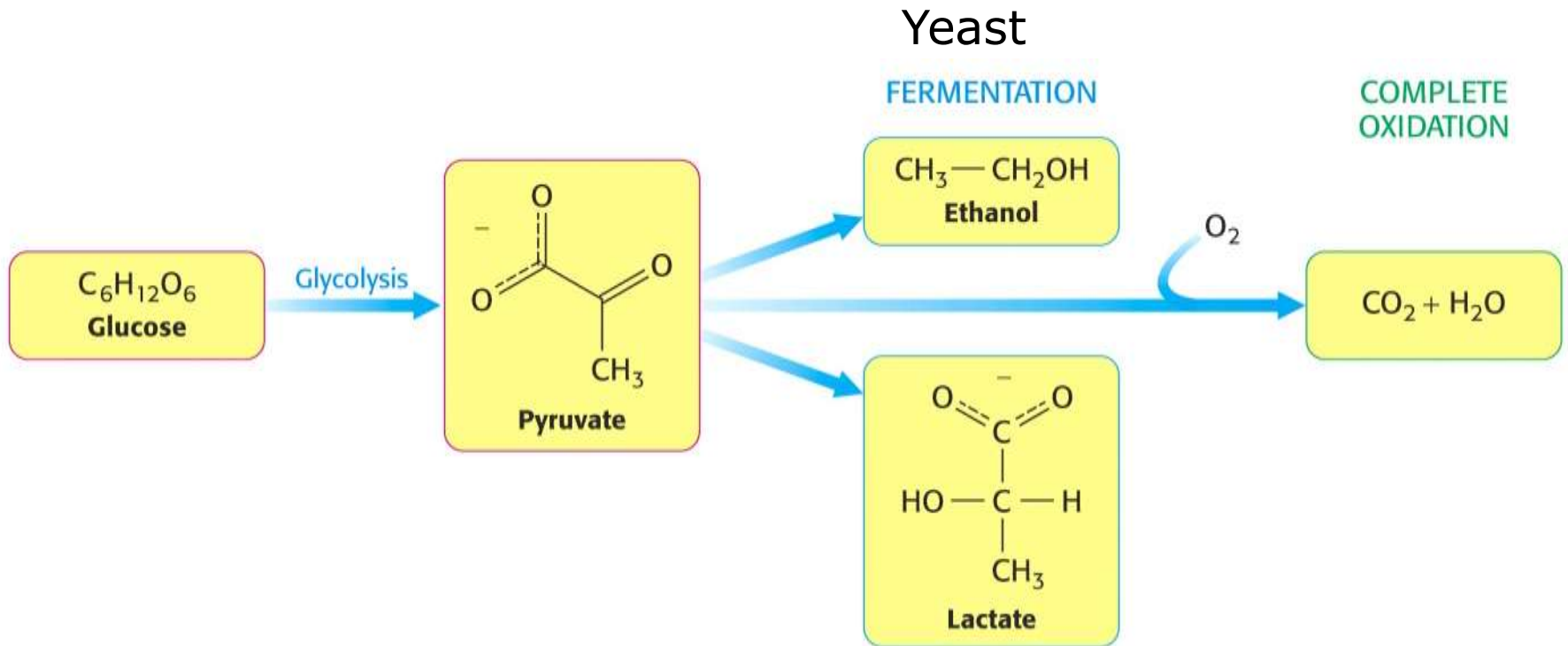
Presented by- **Papiya Dey**

# Overview of Metabolism



**FIGURE 7-1. Overview of metabolism.** The exergonic reactions of catabolism sustain ATP, NADH, and NADPH formation. ATP and NADPH provide energy and reducing equivalents for the endergonic reactions of anabolism.

# The Fate of Glucose



The fate of glucose is varies with physiological conditions, tissues, and organisms.

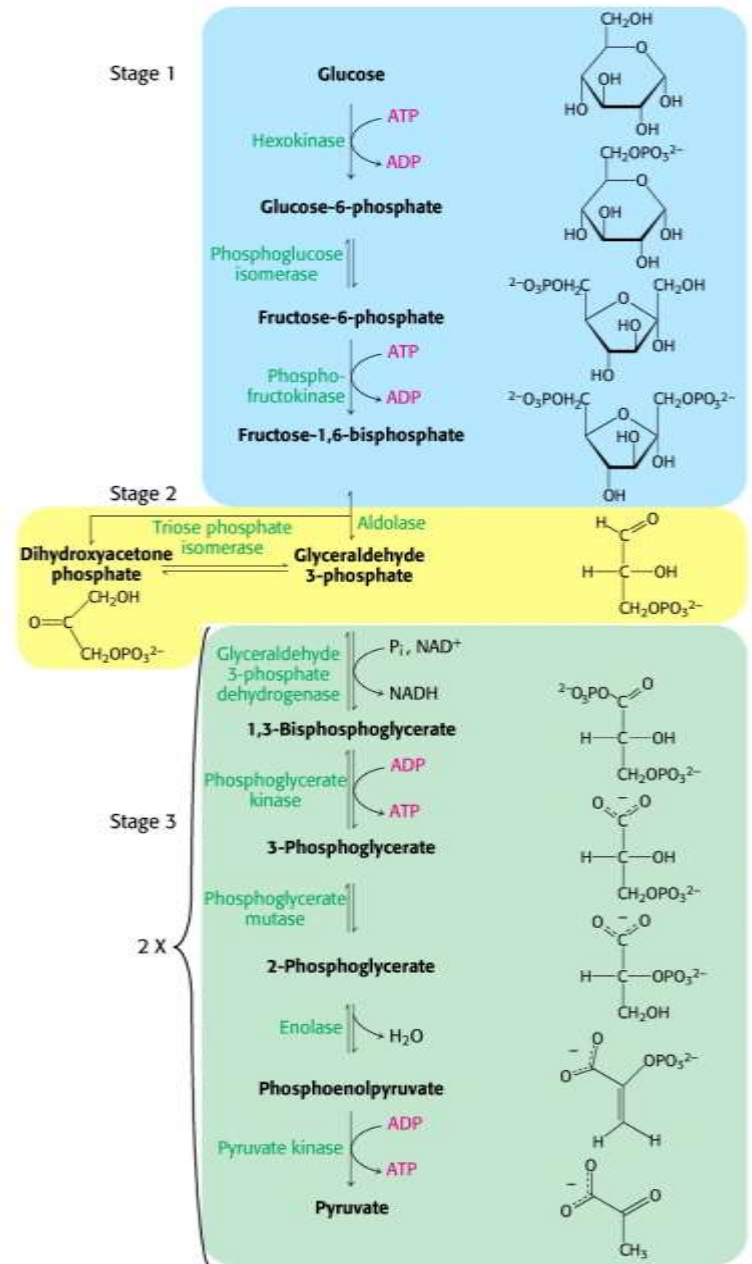
Exercising muscle  
**BIG PICTURE**

# Glycolysis

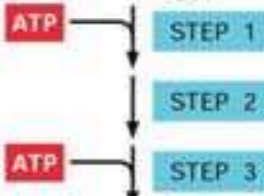
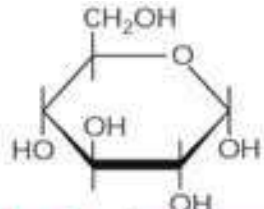
Stage 1 - Investment of ATP. Glucose is phosphorylated. The negative charge concentrates glucose in the cell and glucose becomes less stable.

Stage 2 - The 6 carbon sugar is split to two 3-carbon fragments.

Stage 3 - Energy yielding phase. The oxidation of the 3-carbon fragments yields ATP

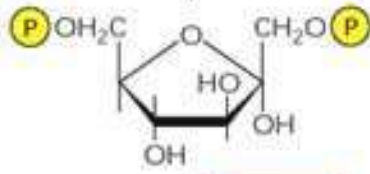


one molecule of glucose



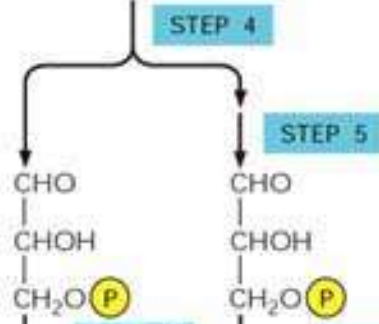
energy investment to be recouped later

fructose 1,6-bisphosphate

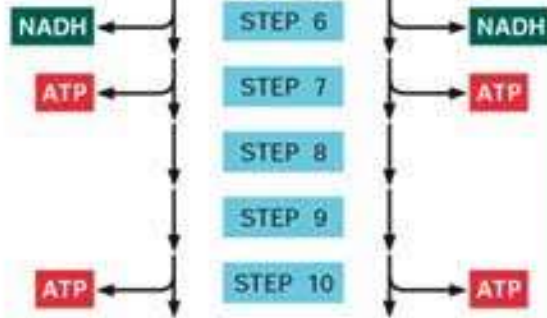


cleavage of six-carbon sugar to two three-carbon sugars

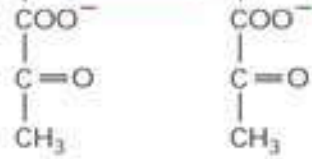
two molecules of glyceraldehyde 3-phosphate

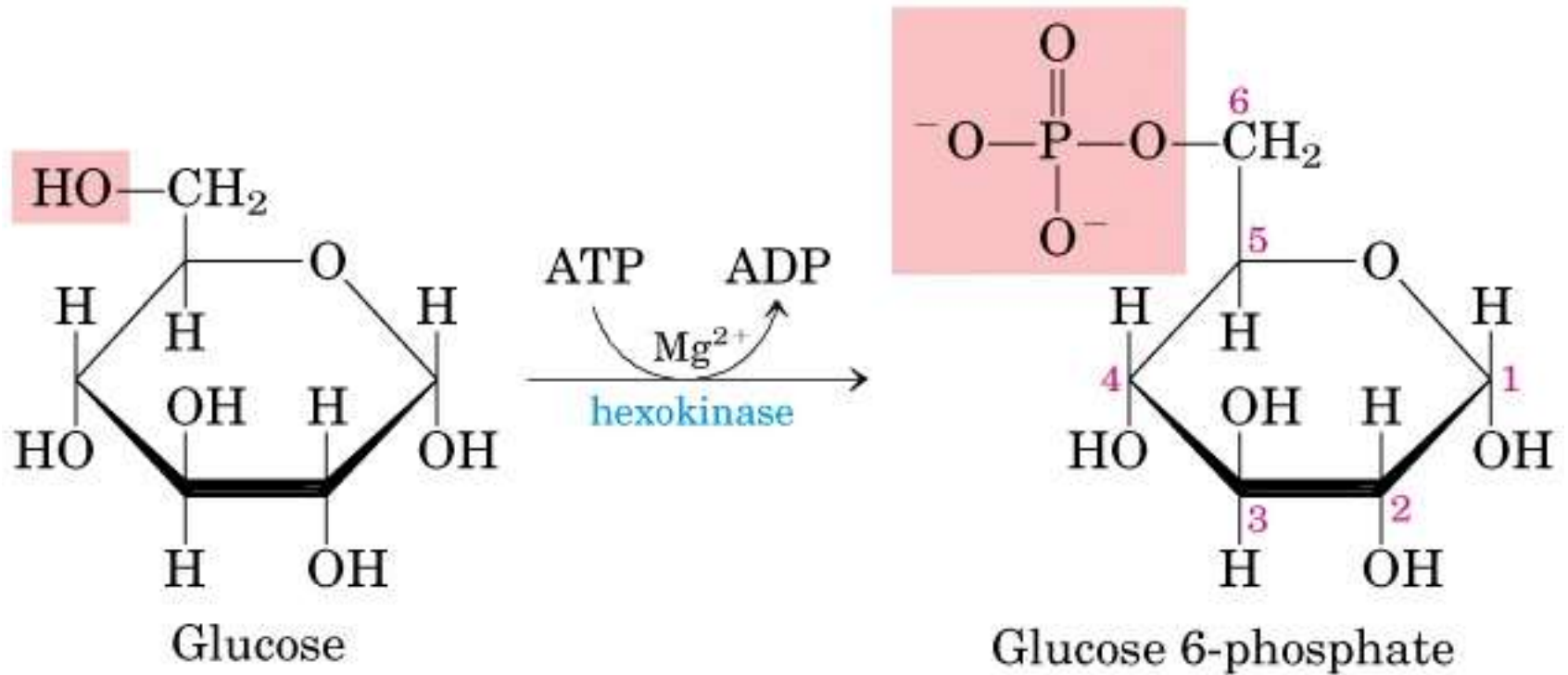


energy generation



two molecules of pyruvate





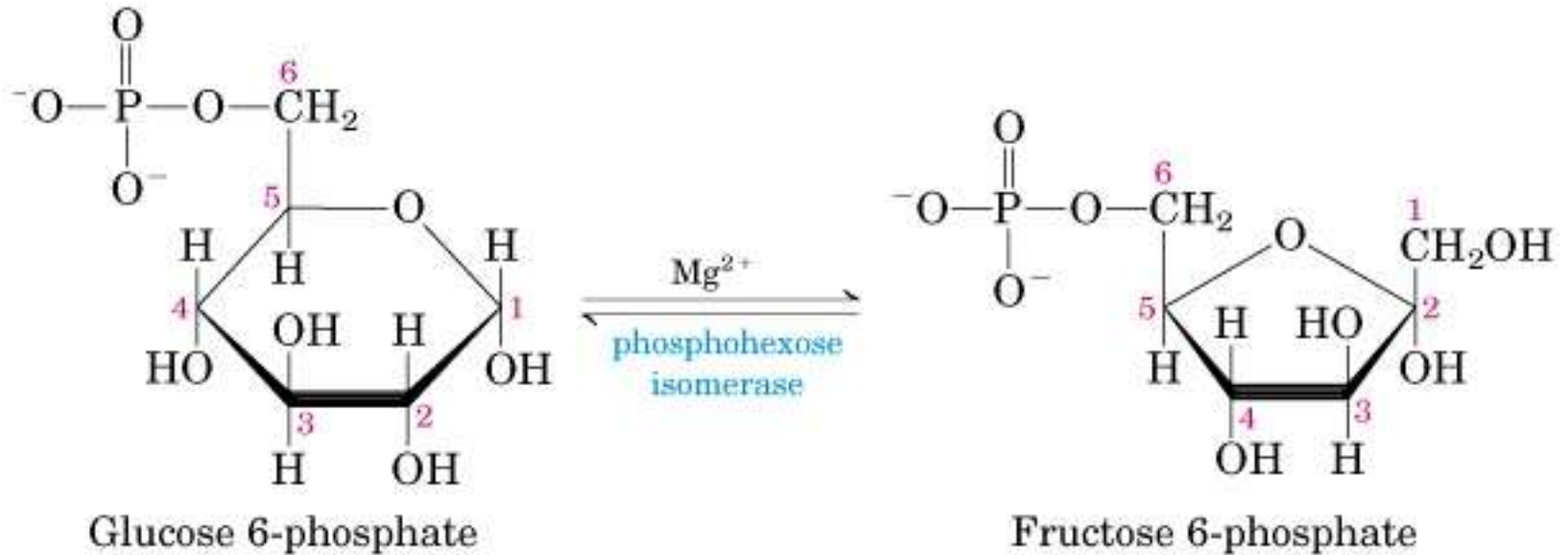
$$\Delta G'^{\circ} = -16.7 \text{ kJ/mol}$$

$$\Delta G^{\circ} = -4.0 \text{ kcal mol}^{-1}$$

Phosphoryl transfer reaction. Kinases transfer phosphate from ATP to an acceptor. Hexokinase has a more general specificity in that it can transfer phosphate to other sugars such as mannose.

# Phosphoglucose Isomerase

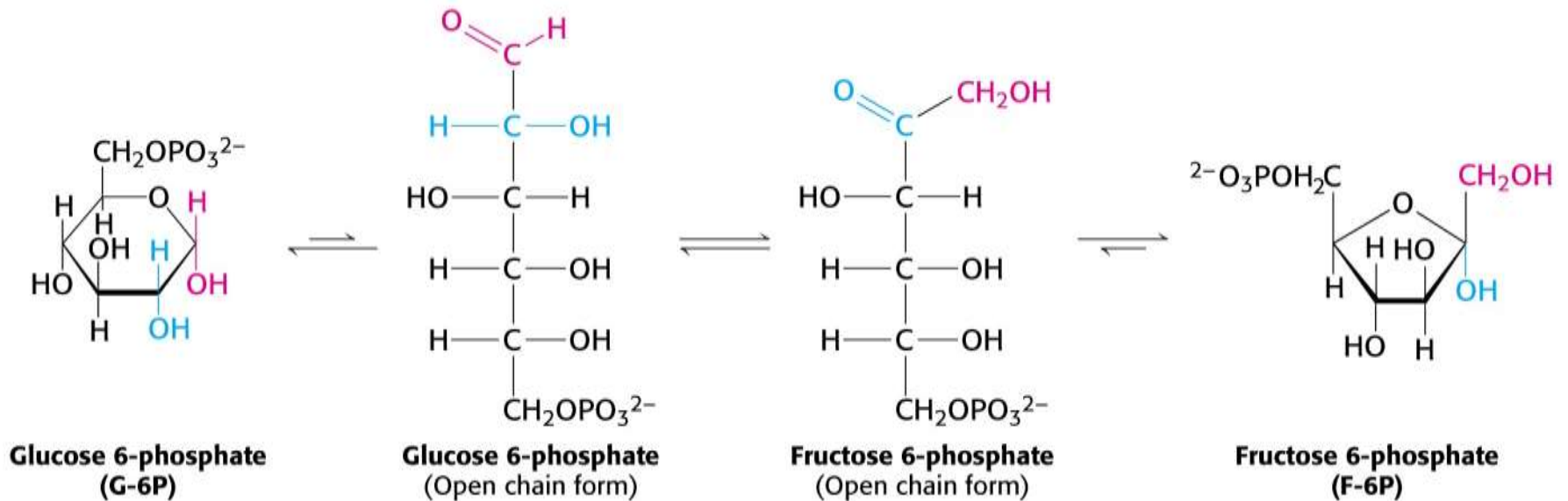
The conversion of an aldose to a ketose.



$$\Delta G'^{\circ} = 1.7 \text{ kJ/mol}$$

$$\Delta G^{\circ} = .40 \text{ kcal mol}^{-1}$$

# Phosphoglucose Isomerase

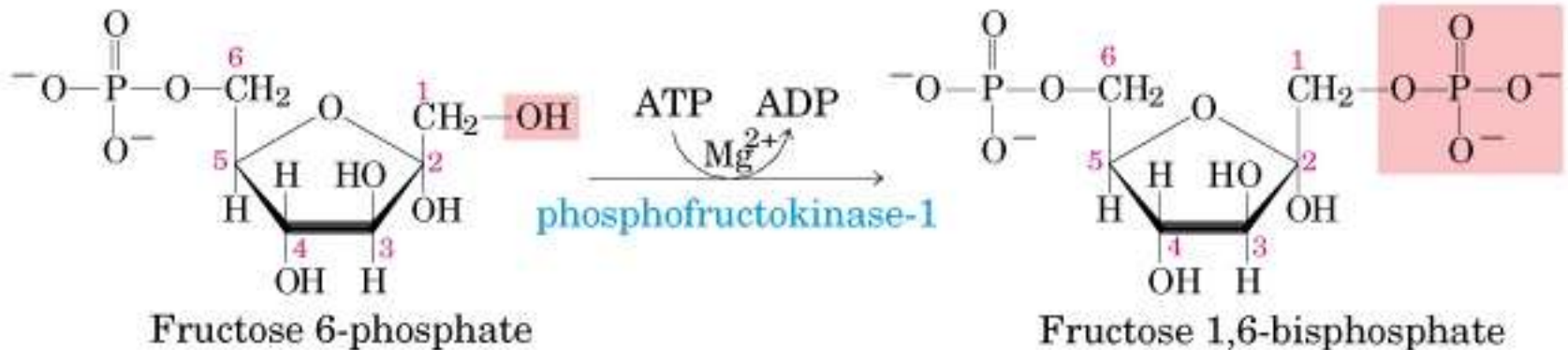


The enzyme opens the ring, catalyzes the isomerization, and promotes the closure of the five member ring.

# Phosphofructokinase-1

## PFK

The 2<sup>nd</sup> investment of an ATP in glycolysis.



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

$$\Delta G^{\circ} = -3.4 \text{ kcal mol}^{-1}$$

PFK is an important allosteric enzyme regulating the rate of glucose catabolism and plays a role in integrating metabolism.

*Bis* means two phosphate groups on two different carbon atoms. *Di* means two phosphate groups linked together on the same carbon atom.

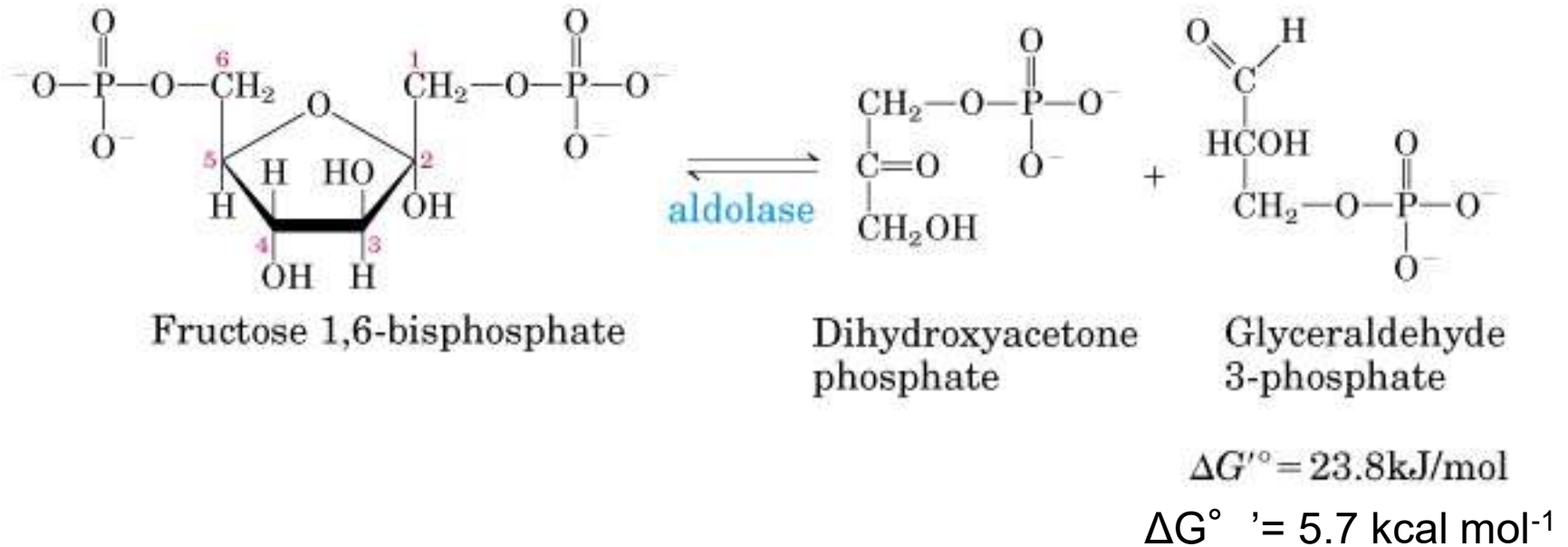
How this enzyme regulates metabolism will be discussed in down stream and in future lectures .

# Phosphofructokinase-1

- The PFK reaction is the first unique and irreversible step in the glycolytic pathway.
- It is the “committed” in the pathway.
- In general, the enzyme catalyzing the committed step in a metabolic pathway is the most important control component in the pathway.

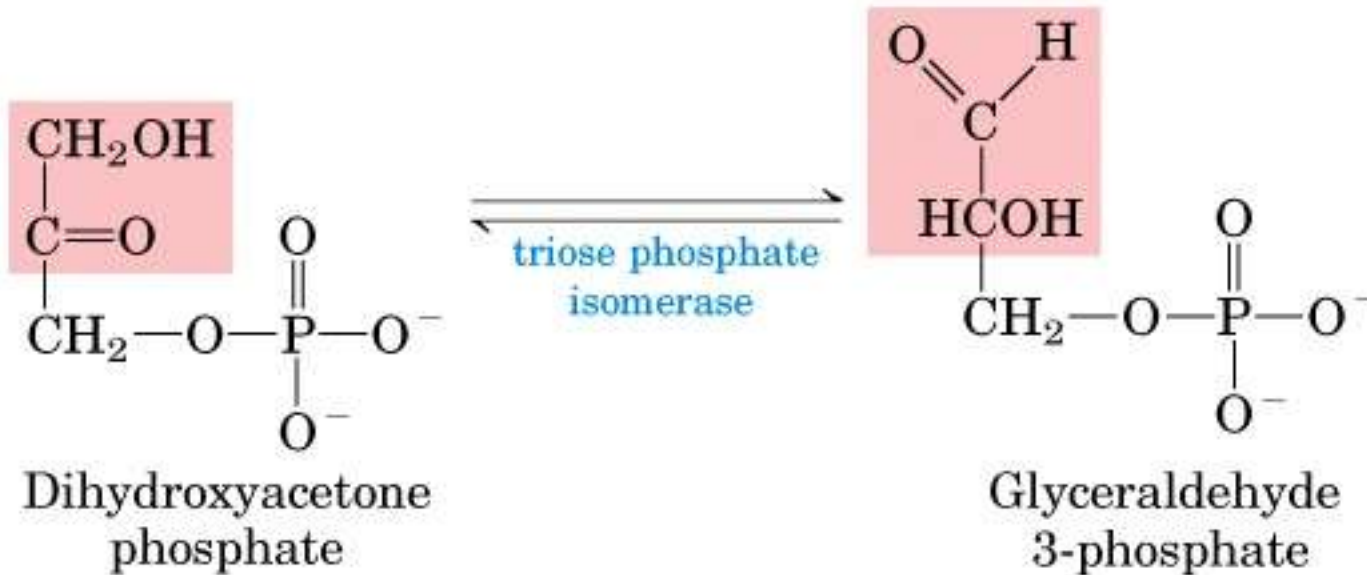
2nd stage

# ALDOLASE



Reverse aldol condensation; converts a 6 carbon atom sugar to 2 molecules, each containing 3 carbon atoms.

# Triose phosphate isomerase



$$\Delta G'^{\circ} = 7.5 \text{ kJ/mol}$$

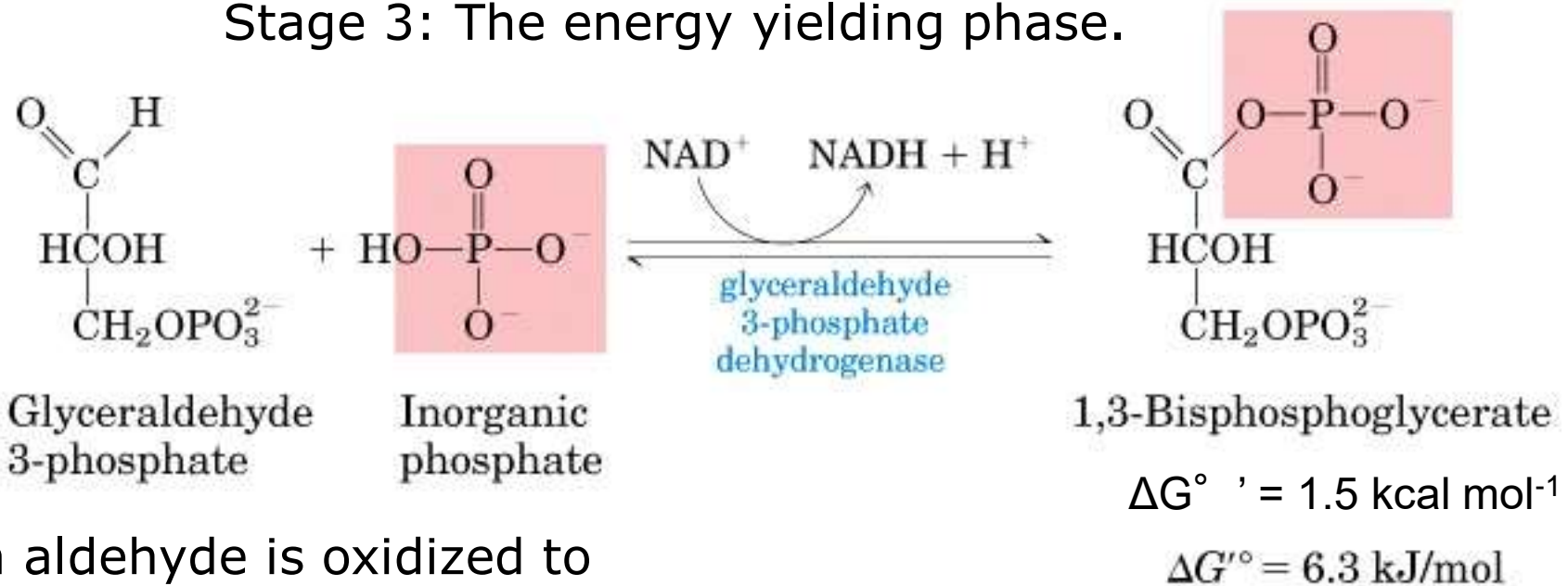
$$\Delta G^{\circ} = 1.8 \text{ kcal mol}^{-1}$$

All the DHAP is converted to glyceraldehyde 3-phosphate. Although, the reaction is reversible it is shifted to the right since glyceraldehyde 3-phosphate is a substrate for the next reactions of glycolysis. Thus, both 3-carbon fragments are subsequently oxidized.

# The fate of glyceraldehyde 3-phosphate

## Glyceraldehyde 3-phosphate DH

Stage 3: The energy yielding phase.



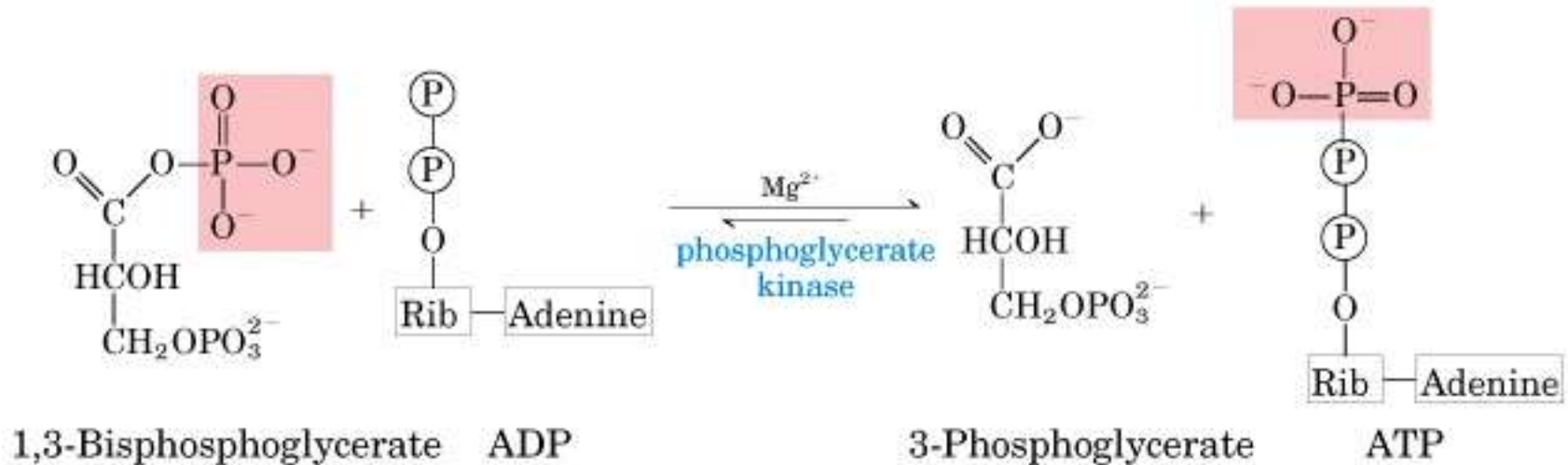
An aldehyde is oxidized to carboxylic acid and inorganic phosphate is transferred to form acyl-phosphate. NAD<sup>+</sup> is reduced to NADH.

1,3-BPG has a high phosphoryl-transfer potential. It is a mixed anhydride.

Notice, under anaerobic conditions NAD<sup>+</sup> must be re-supplied.

# Phosphoglycerate Kinase

## Substrate-level phosphorylation



ATP is produced from P<sub>i</sub> and ADP at the expense of carbon oxidation from the glyceraldehyde 3-phosphate DH reaction.

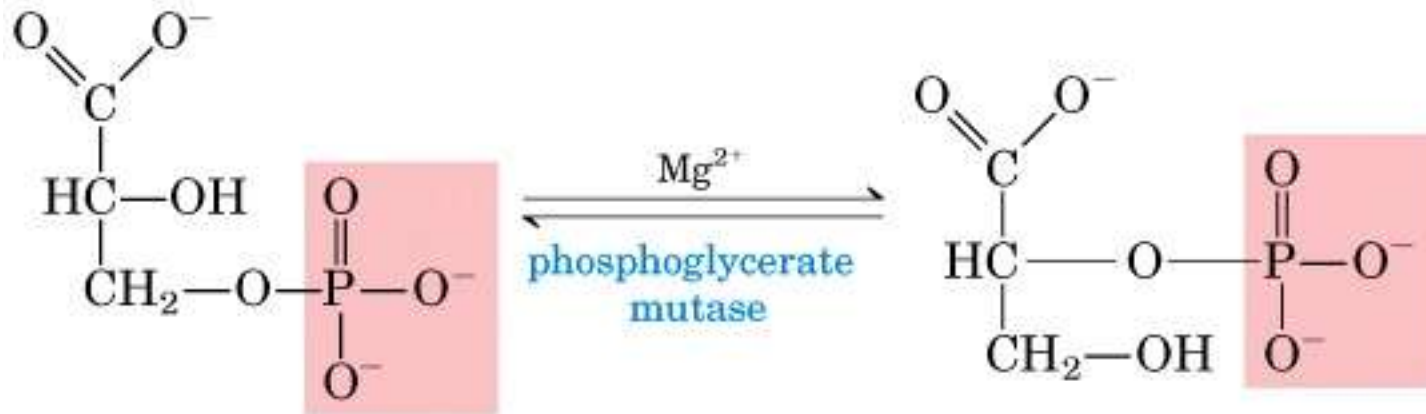
$$\Delta G'^{\circ} = -18.5 \text{ kJ/mol}$$

$$\Delta G^{\circ} = -4.5 \text{ kcal mol}^{-1}$$

Remember: 2 molecules of ATP are produced per glucose.

**At this point 2ATPs were invested and 2ATPs are produced.**

# Phosphoglycerate mutase



3-Phosphoglycerate

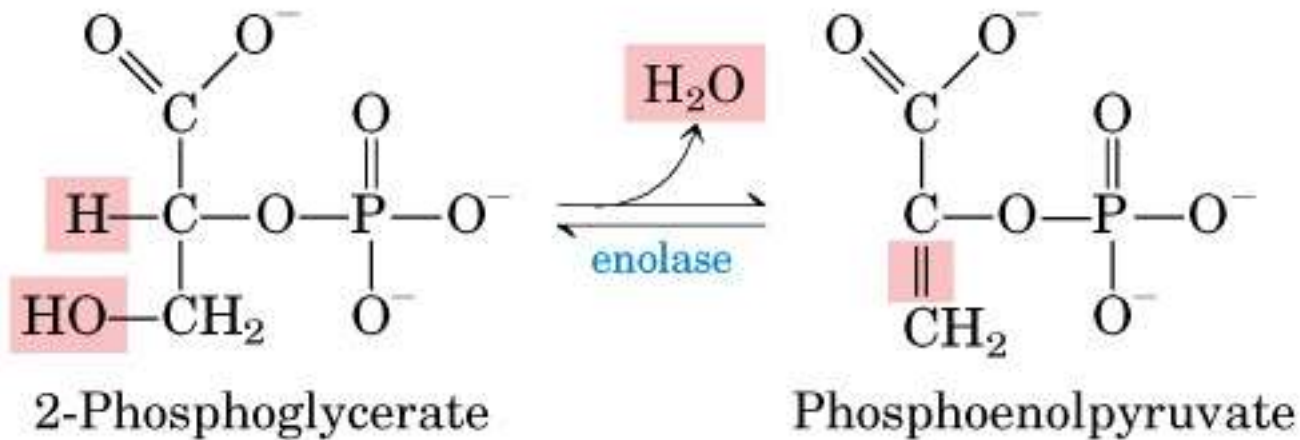
2-Phosphoglycerate

Phosphate shift

$$\Delta G'^{\circ} = 4.4 \text{ kJ/mol}$$

$$\Delta G^{\circ} = 1.1 \text{ kcal mol}^{-1}$$

# Enolase



Dehydration reaction

$$\Delta G'^{\circ} = 7.5 \text{ kJ/mol}$$

$$\Delta G^{\circ} = .4 \text{ kcal mol}^{-1}$$

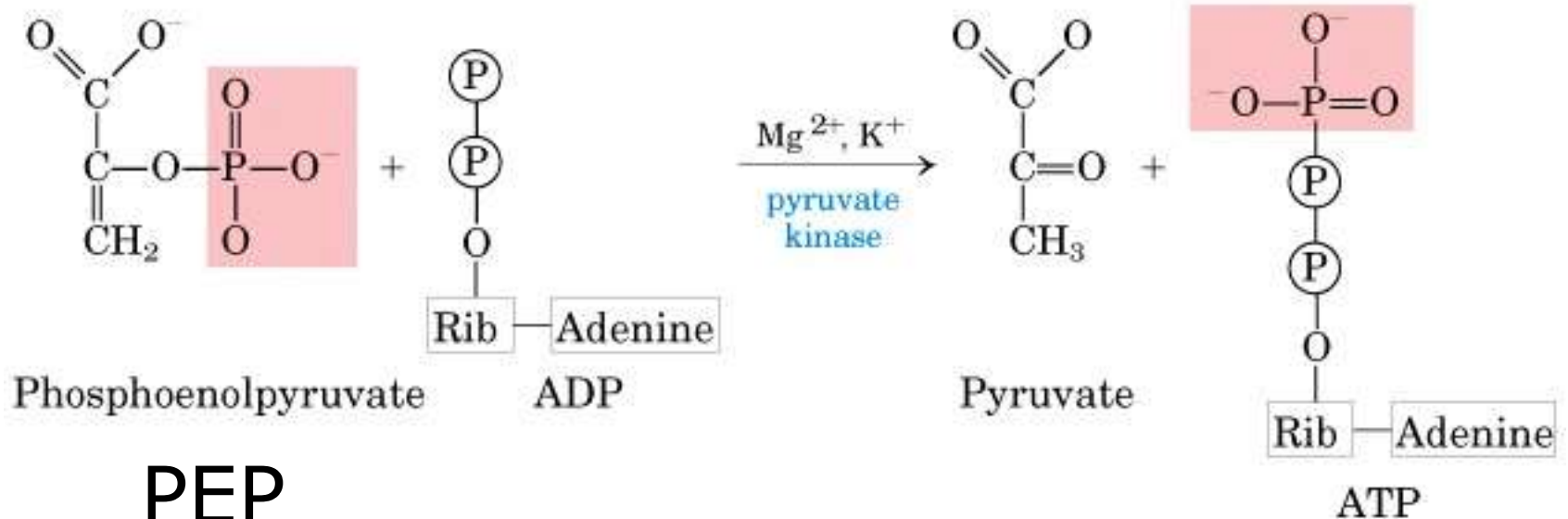
PEP

# Pyruvate Kinase

2<sup>nd</sup> example of substrate level phosphorylation.

The net yield from glycolysis is 2 ATP

unstable Enol form → more stable keto form



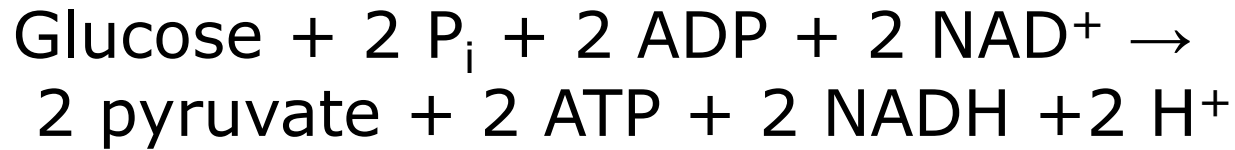
PEP

$$\Delta G^{\circ} = -7.5 \text{ kcal mol}^{-1}$$

$$\Delta G'^{\circ} = -31.4 \text{ kJ/mol}$$

- Substrate level phosphorylation is the synthesis of ATP from ADP that is not linked to the electron transport system.

# The Conversion of Glucose to Pyruvate



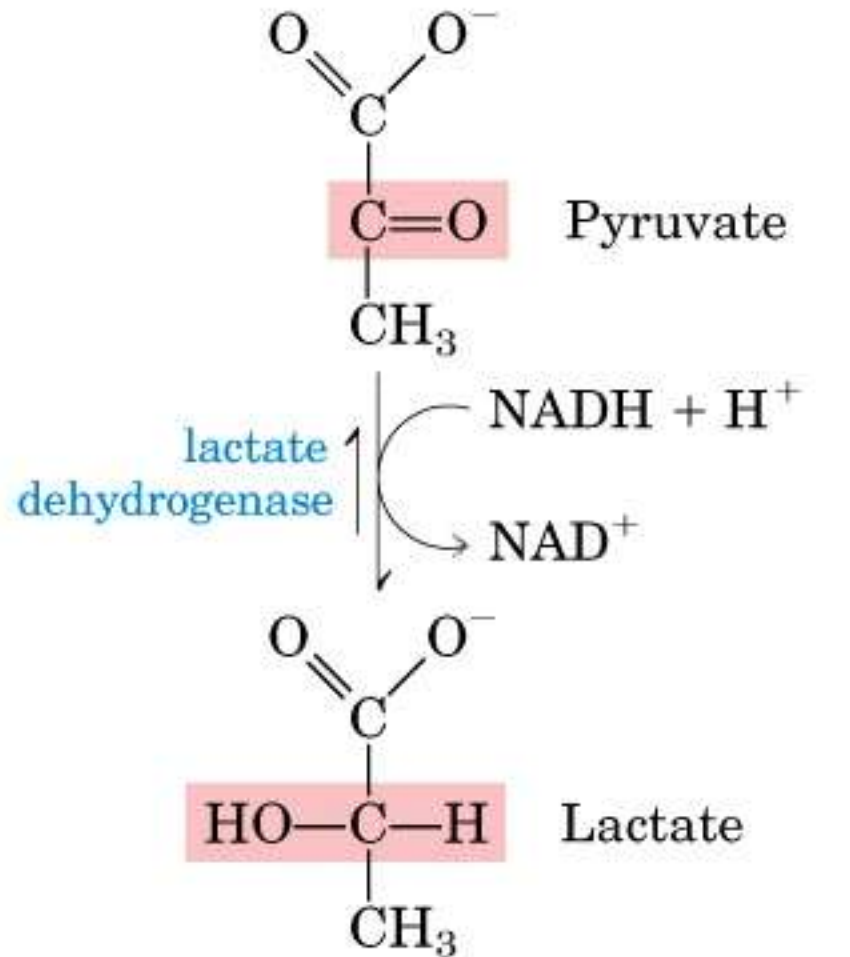
The Energy released from the anaerobic conversion of glucose to pyruvate is  $-47\text{kcal mol}^{-1}$ .

Under aerobic conditions much more chemical bond energy can be extracted from pyruvate.

The question still remains: How is  $\text{NAD}^+$  supplied under anaerobic conditions? Or how is redox balance maintained?

Under anaerobic conditions pyruvate is converted to lactate. Exercising muscle is an example.

The  $\text{NAD}^+$  that is consumed in the glyceraldehyde 3-phosphate reaction is produced in the lactate DH reaction. The redox balance is maintained. The activities of glyceraldehyde 3-phosphate DH and Lactate DH are linked metabolically.



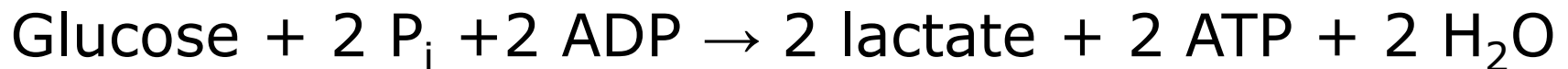
What happens to the lactate after a run?

$$\Delta G'^{\circ} = -25.1 \text{ kJ/mol}$$

## Remember!

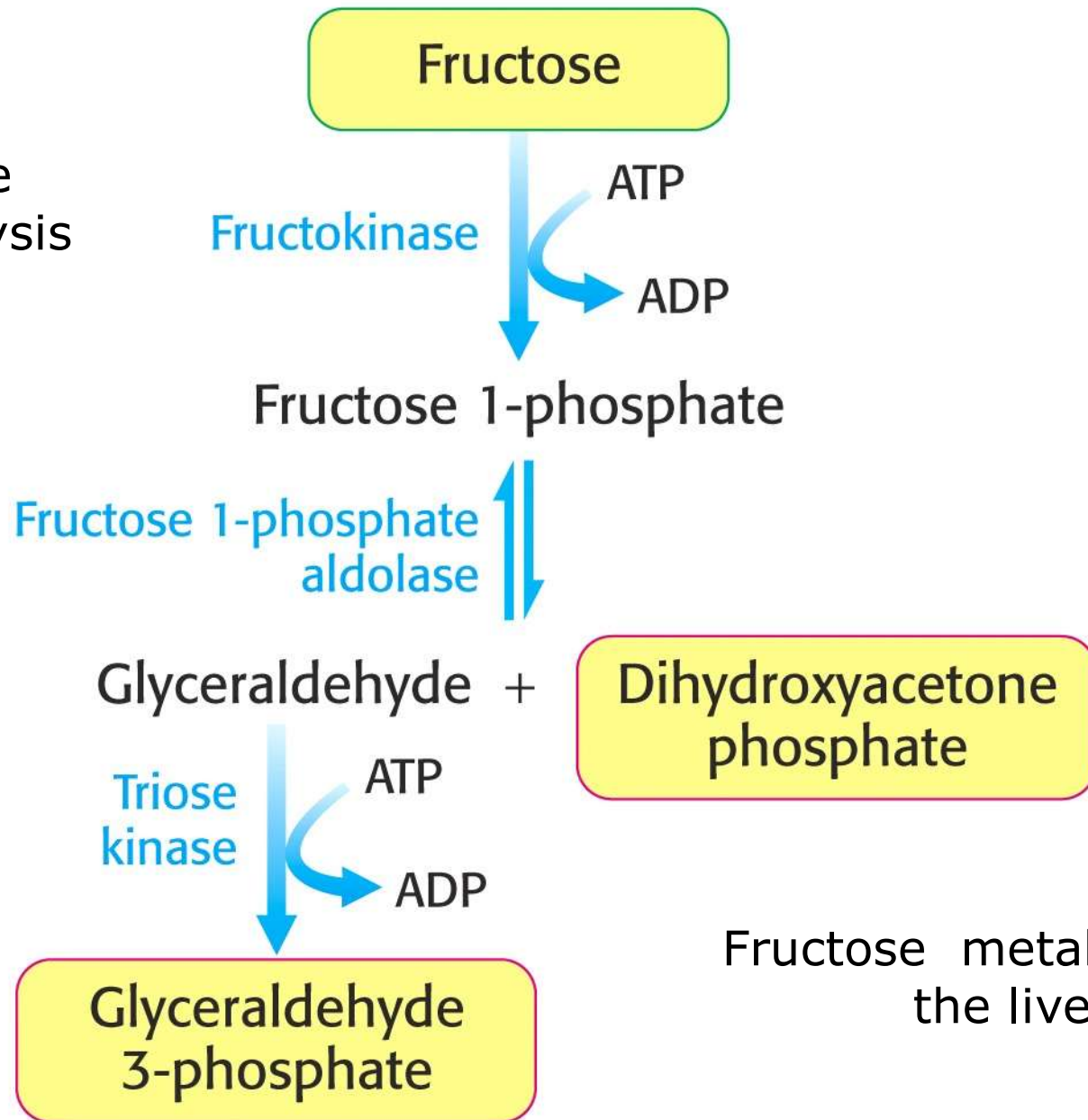
The  $\text{NAD}^+$  that is consumed in the glyceraldehyde 3-phosphate reaction is produced in the lactate DH reaction. Thus, redox balance is maintained.

The  $\text{NADH}$  that is produced in the glyceraldehyde 3-phosphate reaction is consumed in the lactate DH reaction. Thus, redox balance is maintained.



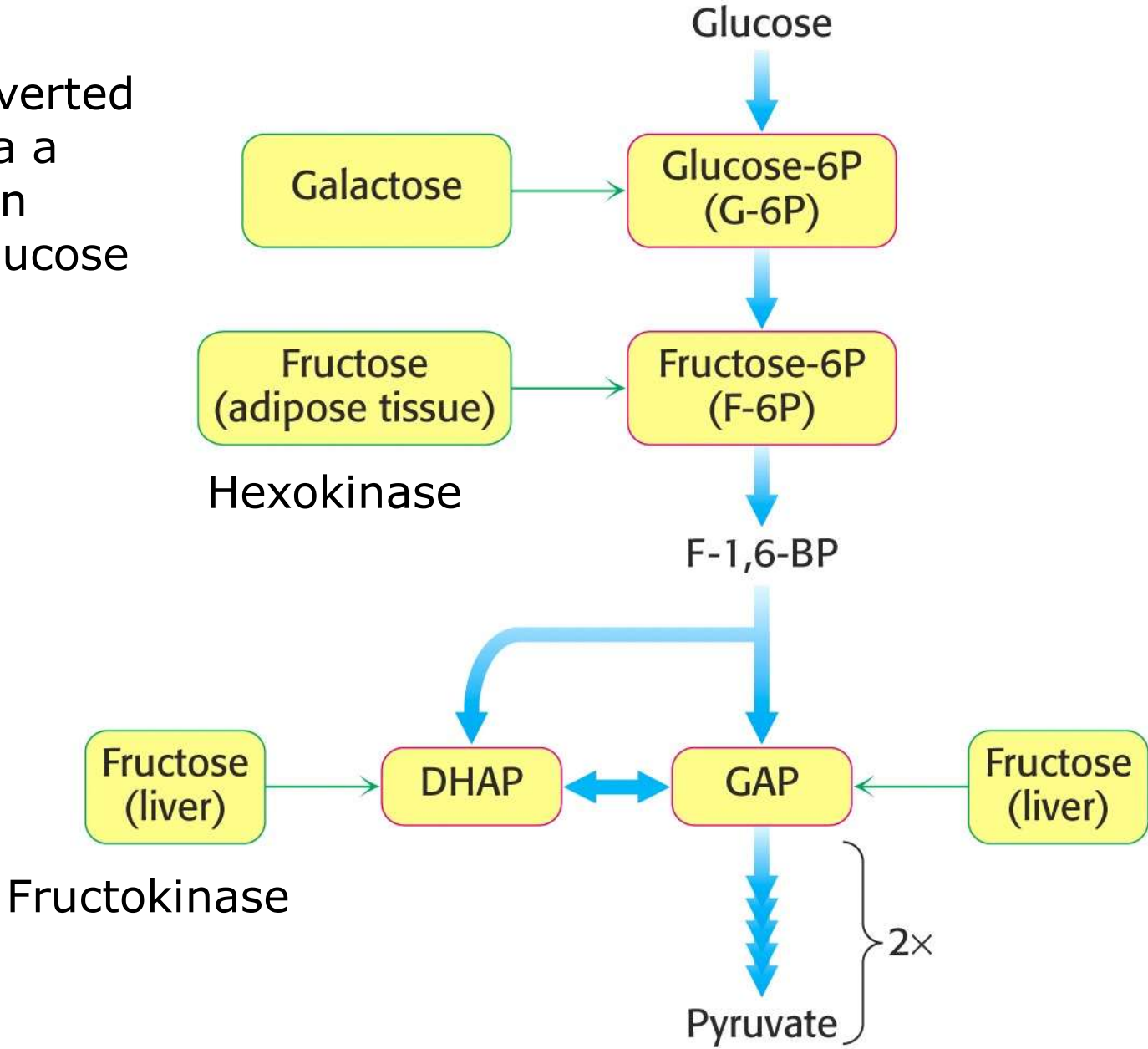
Fructose and galactose feed into  
the glycolytic pathway

In the liver,  
when fructose  
enters glycolysis  
the PFK  
reaction is  
bypassed.

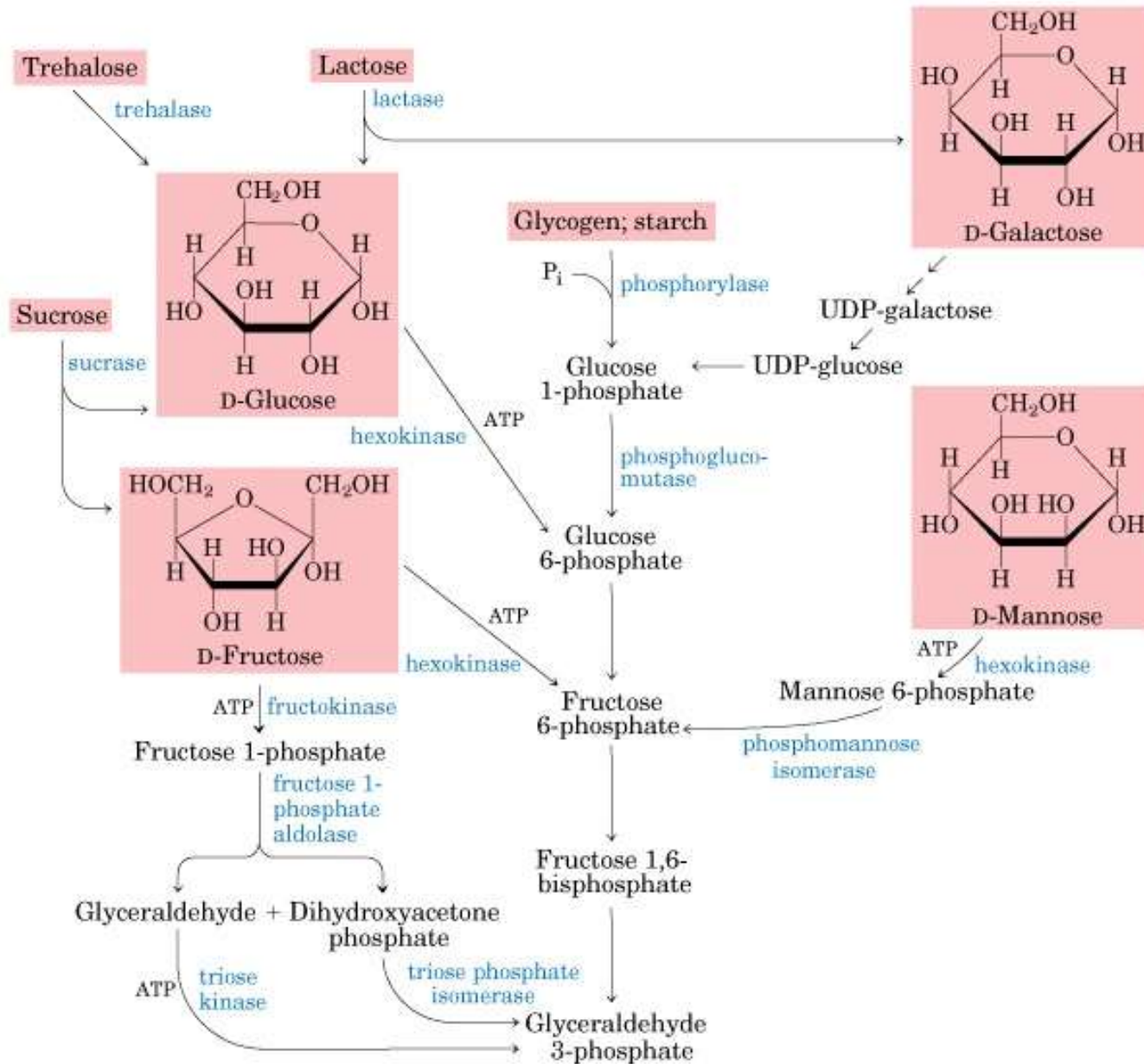


Fructose metabolism in  
the liver

Galactose is converted to glucose-6P via a four step reaction involving UDP-glucose



# In Summary



# Gluconeogenesis

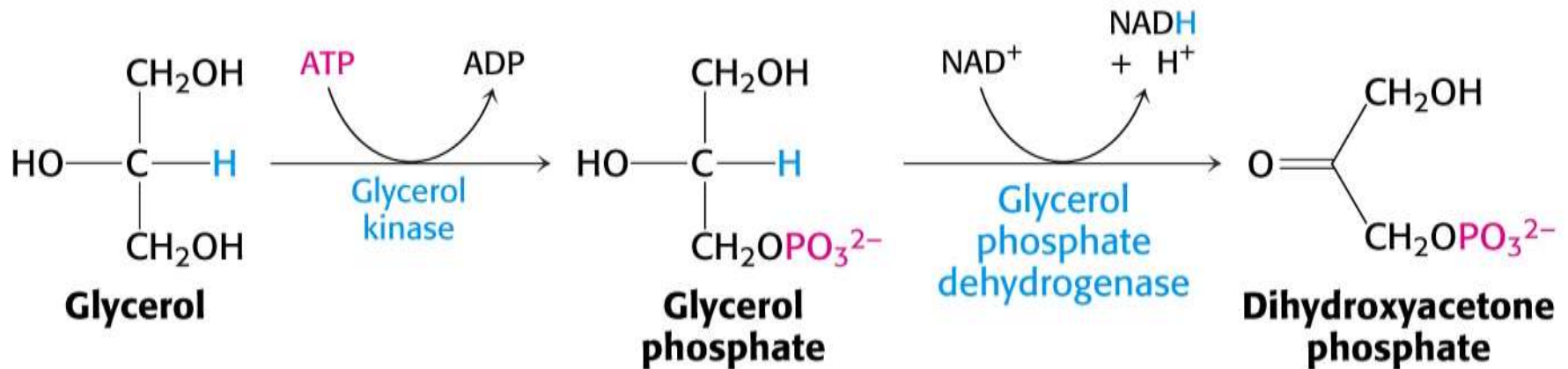
- Gluconeogenesis is the synthesis of glucose from non-carbohydrate precursors.
- Glucose stores are depleted during periods of starvation or fasting beyond a day.
- Since the brain relies on glucose (120g/d) as a source of energy, glucose must be synthesized from molecules other than carbohydrates.

PYRUVATE → GLUCOSE

# Gluconeogenesis

## PYRUVATE → GLUCOSE

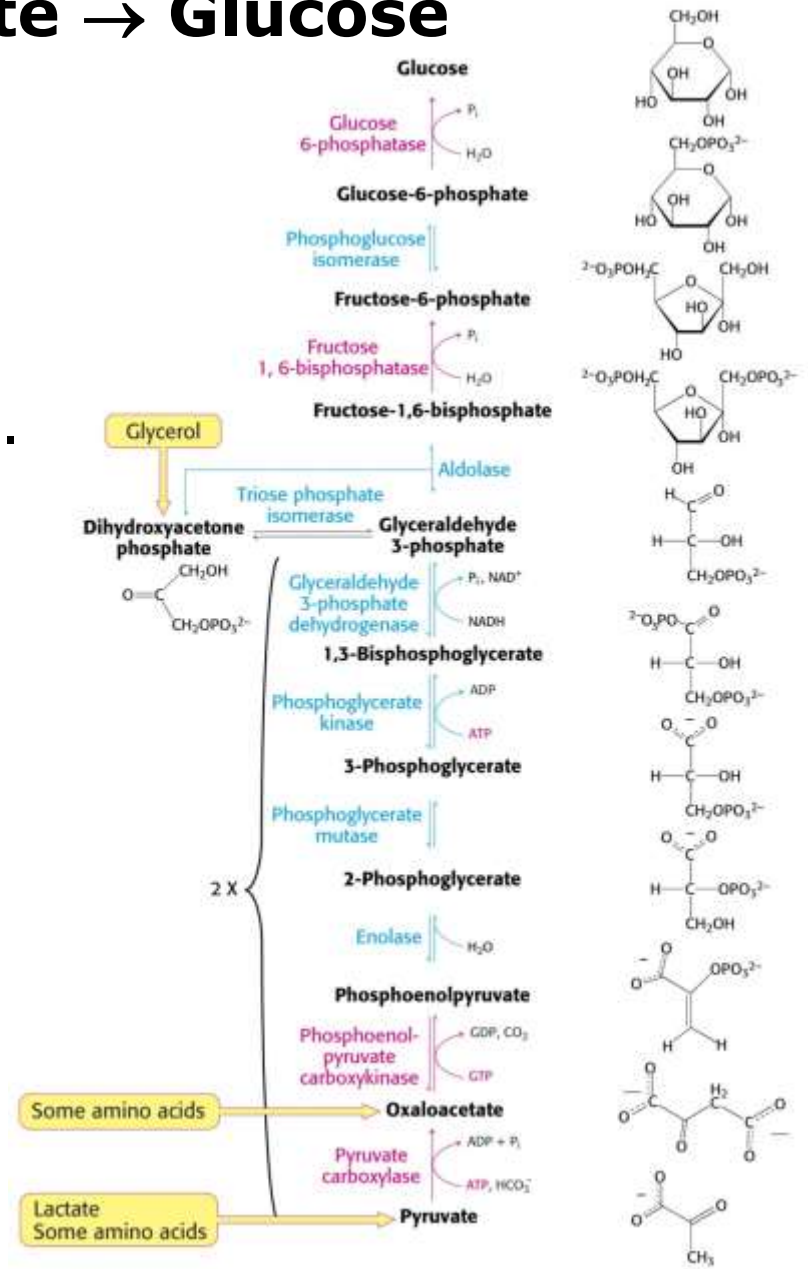
- So any molecule that can be converted to pyruvate is considered glucogenic
- Lactate and alanine are glucogenic.
- Glycerol is also glucogenic.



# Gluconeogenesis: Pyruvate → Glucose

The enzymes in red belong to the gluconeogenic pathway. These reactions overcome the high negative free energy of the irreversible reactions of glycolysis.

The enzymes in blue are held in common between the two pathways.



# Gluconeogenesis

The irreversible glycolytic enzymes are: hexokinase ( $\Delta G = -8 \text{ kcal mol}^{-1}$ ) phosphofructokinase ( $\Delta G = -5.3 \text{ kcal mol}^{-1}$ ) pyruvate kinase ( $\Delta G = -4.0 \text{ kcal mol}^{-1}$ ).

The enzymes of gluconeogenesis are:

pyruvate carboxylase (ATP)

phosphoenolpyruvate carboxykinase (GTP)

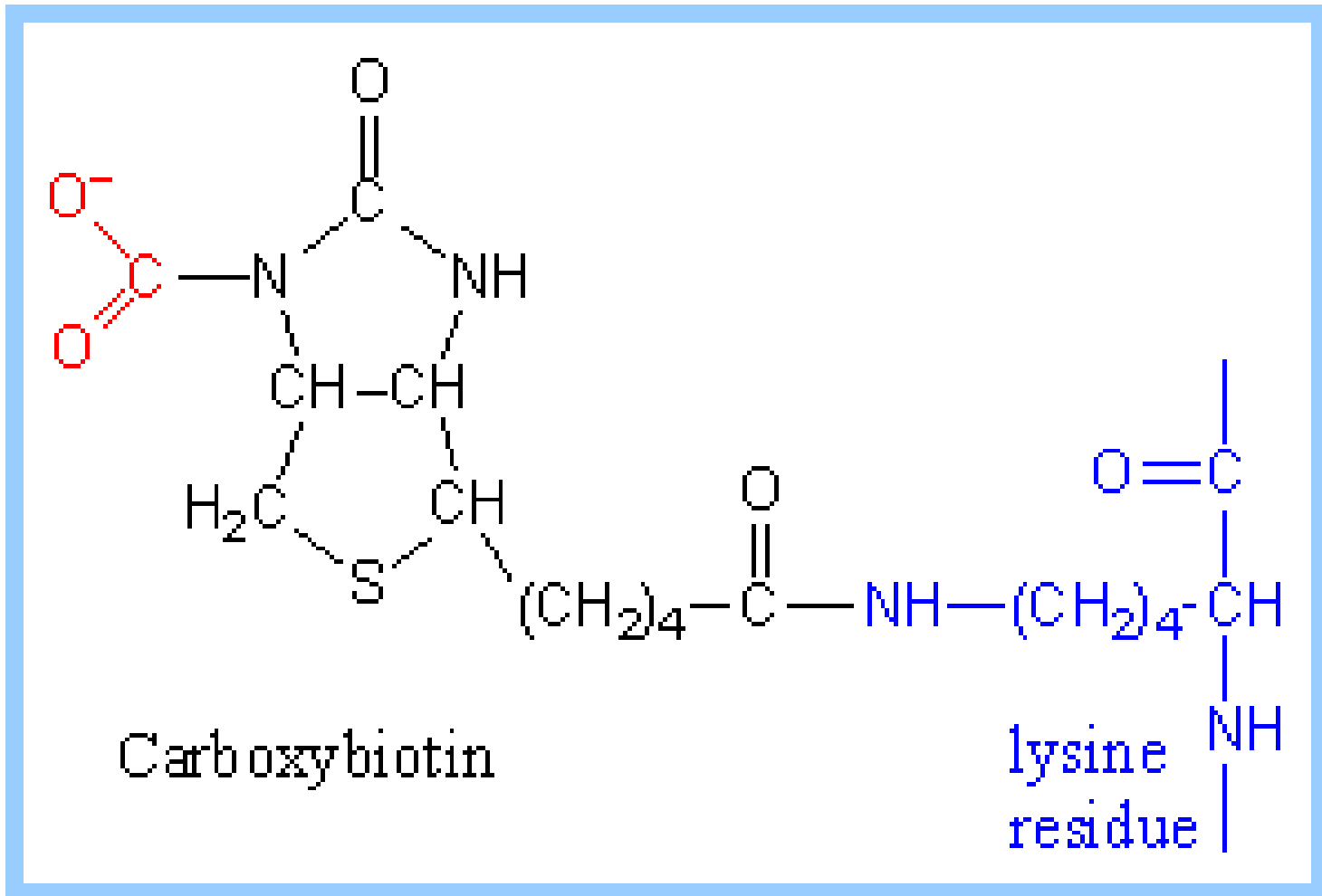
fructose 1,6-bisphosphatase

glucose 6-phosphatase

# Pyruvate Carboxylase

- $\text{Pyruvate} + \text{CO}_2 + \text{ATP} + \text{H}_2\text{O} \rightarrow$   
oxaloacetate + ADP +  $\text{P}_i$  +  $2 \text{H}^+$
- Pyruvate Carboxylase fixes  $\text{CO}_2$ . Enzymes which fix  $\text{CO}_2$  require the cofactor BIOTIN. Biotin is a vitamin and is always involved in  $\text{CO}_2$  fixation.
- This reaction takes place in the mitochondrial matrix.  
–

# Biotin



Notice there are no components of ATP in the structure of biotin.

# Phosphoenolpyruvate Carboxykinase

- Oxaloacetate + GTP  $\rightarrow$   
phosphoenolpyruvate + GDP + CO<sub>2</sub>
- This reaction takes place in the cytosol
- PEP is now synthesized and the sum of the two reaction is:
- Pyruvate + ATP + GTP + H<sub>2</sub>O  $\rightarrow$   
PEP + ADP + GDP + P<sub>i</sub> + H<sup>+</sup>.

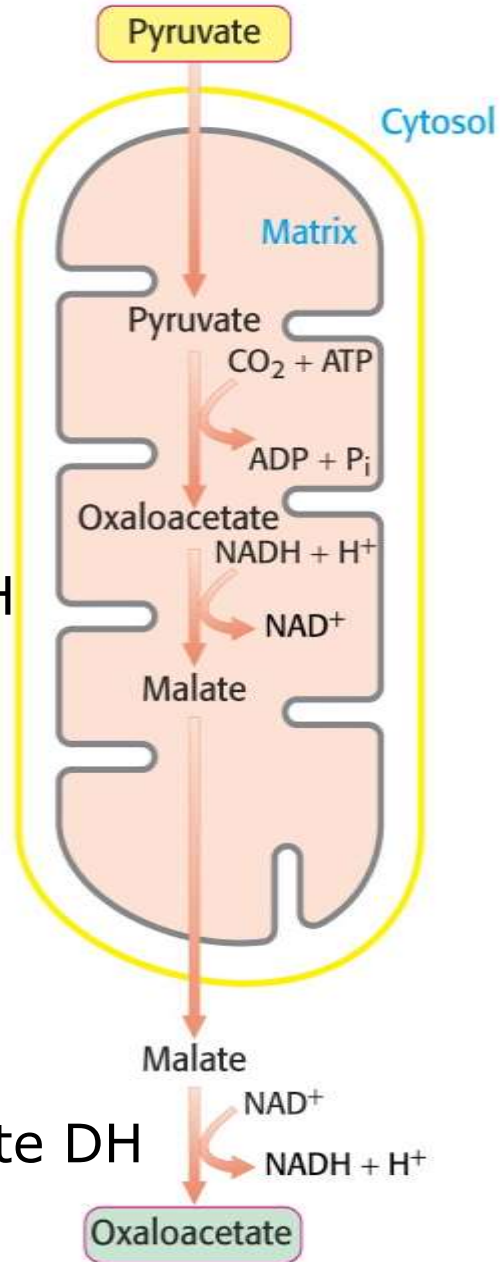
Pyruvate is carboxylated in the mitochondria.  
Pyruvate Carboxylase

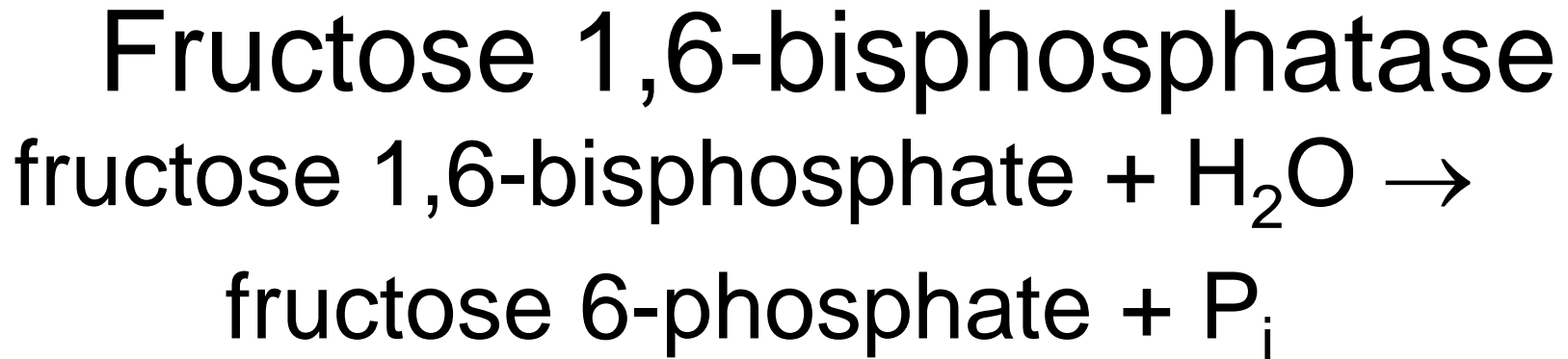
Oxaloacetate can't pass out of  
the mitochondria.

Oxaloacetate decarboxylated and  
phosphorylated in the cytosol.  
Phosphoenolpyruvate Carboxykinase

malate DH

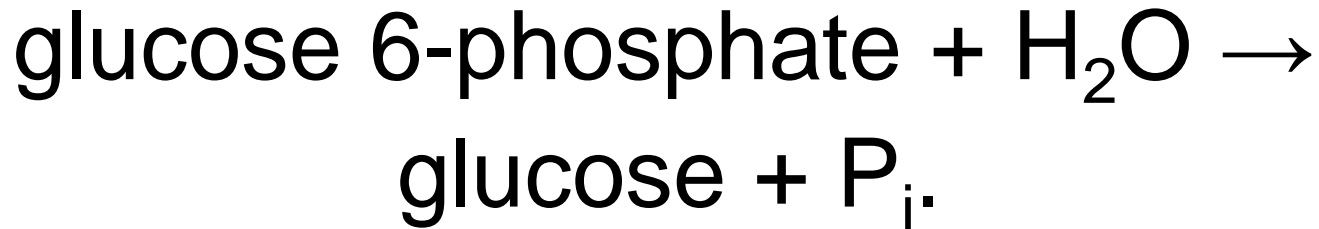
malate DH





- Fructose 1,6-bisphosphatase is an allosteric enzyme and regulates gluconeogenesis.
- fructose 6-phosphate is easily converted to glucose 6-phosphate.

# Glucose 6-phosphatase



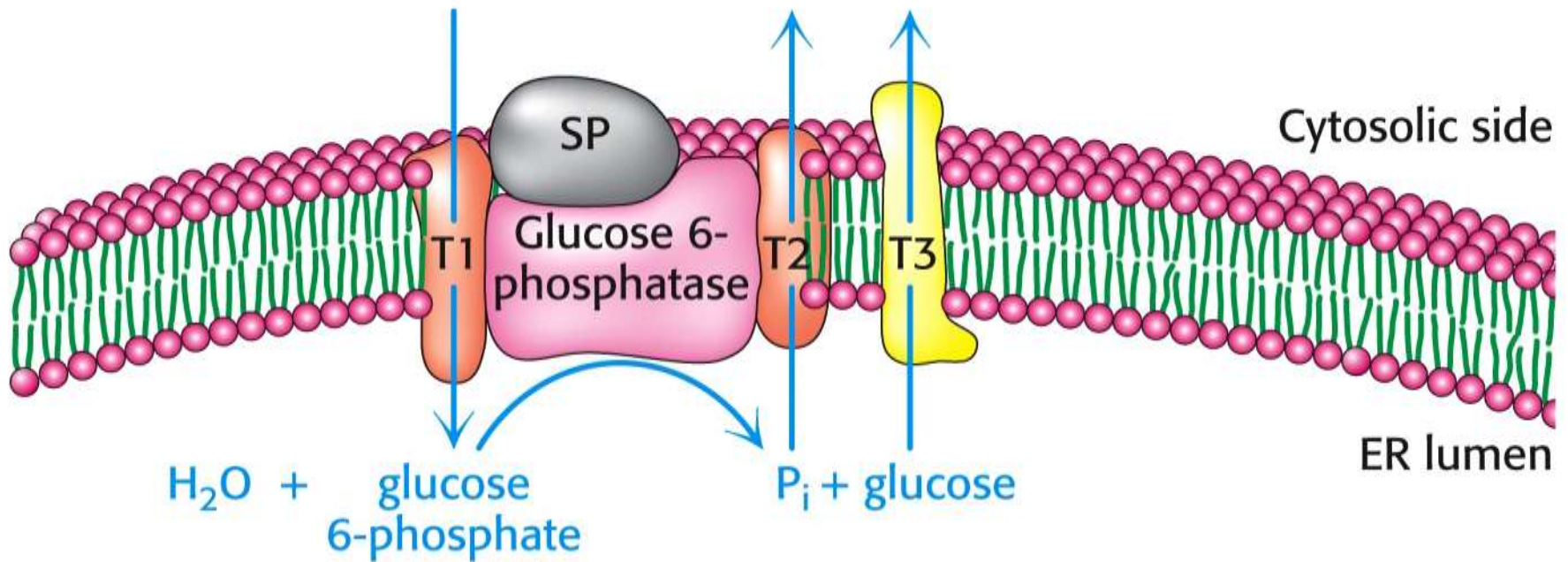
Liver can send glucose to blood to maintain homeostasis.

Glucose 6-phosphate is also a precursor to glycogen.

# glucose 6-P

- Glucose 6-P is valuable; a precursor for glycogen synthesis.
- Glucose 6-phosphatase is present only in tissues responsible for maintaining blood glucose levels, liver and kidney.
- In liver, glucose 6-phosphatase is highly regulated.

# In Liver



Lumen of the ER

It takes 5 proteins to convert glucose 6-phosphate to glucose.

# Gluconeogenesis

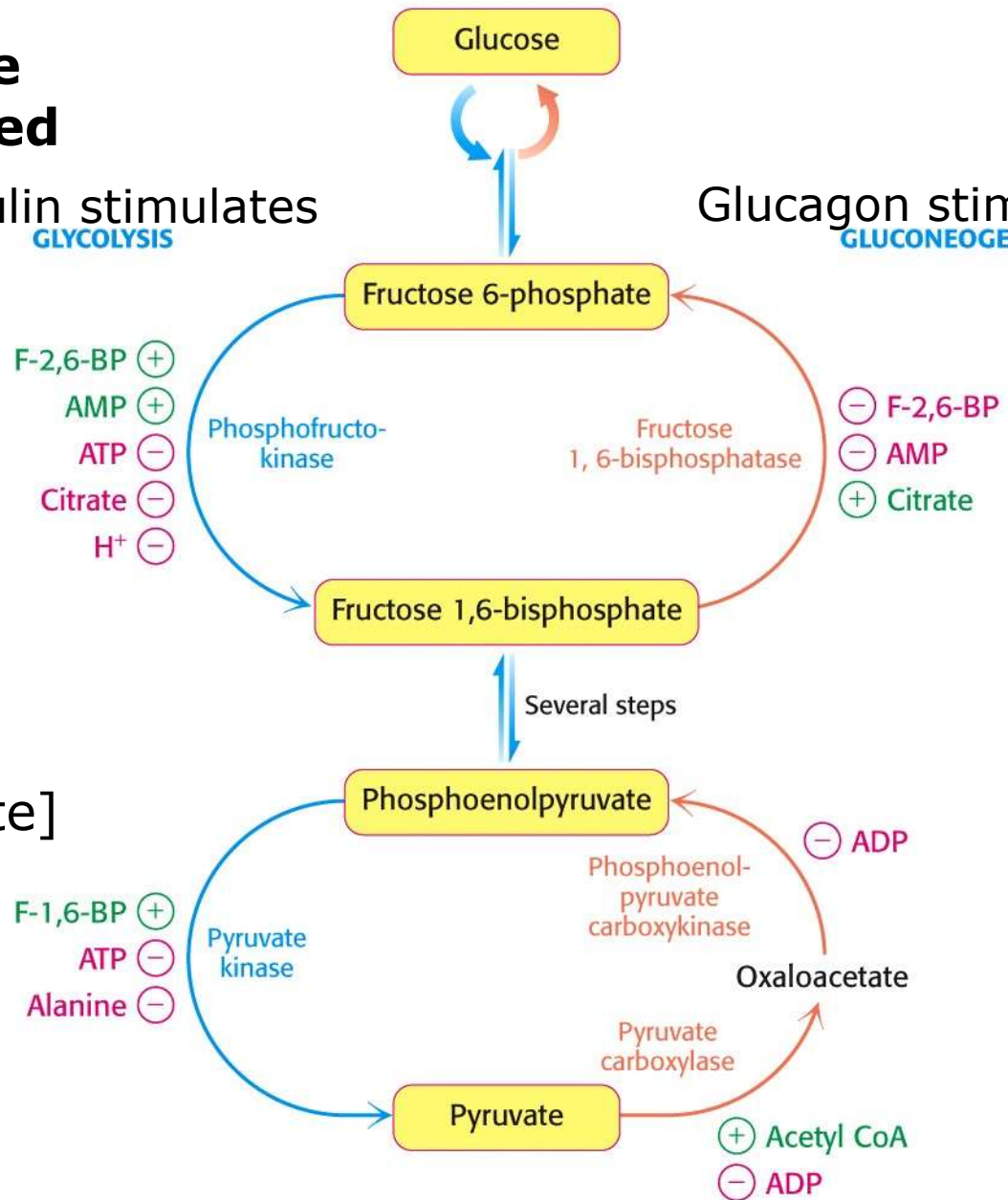
## Stoichiometry

- $2\text{pyruvate} + 4\text{ATP} + 2\text{GTP} + 2\text{NADH} + 6\text{H}_2\text{O} \rightarrow$   
 $\text{glucose} + 4\text{ADP} + 2\text{GDP} + 6\text{P}_i + 2\text{NAD}^+ + 2\text{H}^+$ ;  
 $G^\circ ' = -9\text{kcal mol}^{-1}$ .
  - Just the reverse of glycolysis,  $G^\circ ' = 20\text{kcal mol}^{-1}$ .
- Note: it takes 6 nucleotide triphosphate molecules to synthesize glucose. Only 2 nucleotide triphosphate molecules are generated from glycolysis.
- So it takes four extra high phosphoryl-transfer potential molecules to drive the unfavorable gluconeogenesis pathway.

# Glycolysis and gluconeogenesis are reciprocally regulated

Insulin stimulates  
GLYCOLYSIS

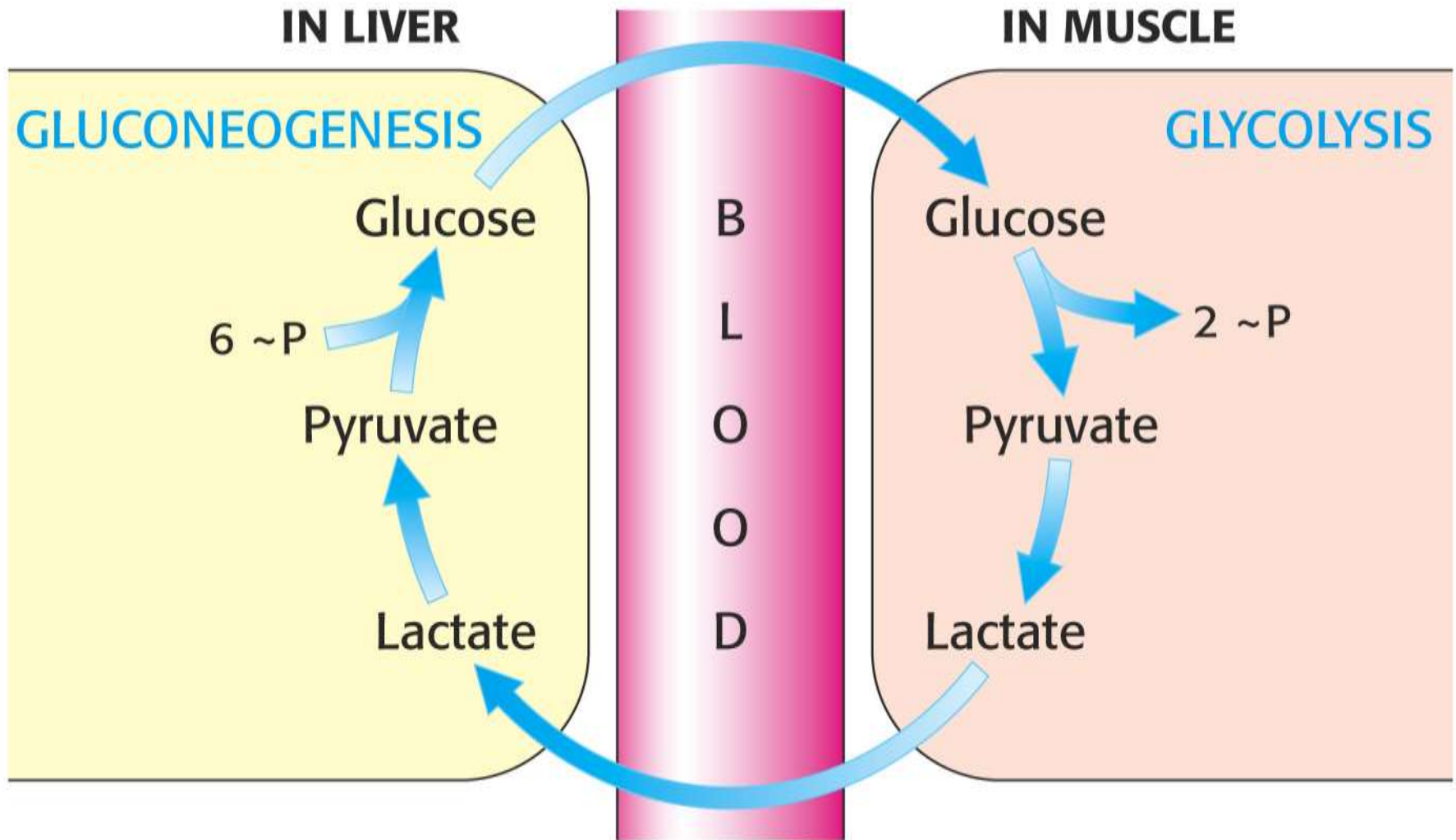
Glucagon stimulates  
GLUCONEOGENESIS



A high [AMP] indicates that the energy charge is low and signals the need for ATP.

High [ATP] and [citrate] indicate the energy charge is high and intermediates are abundant.

# The Cori Cycle



**Lactate from active muscle is converted to glucose in liver.**

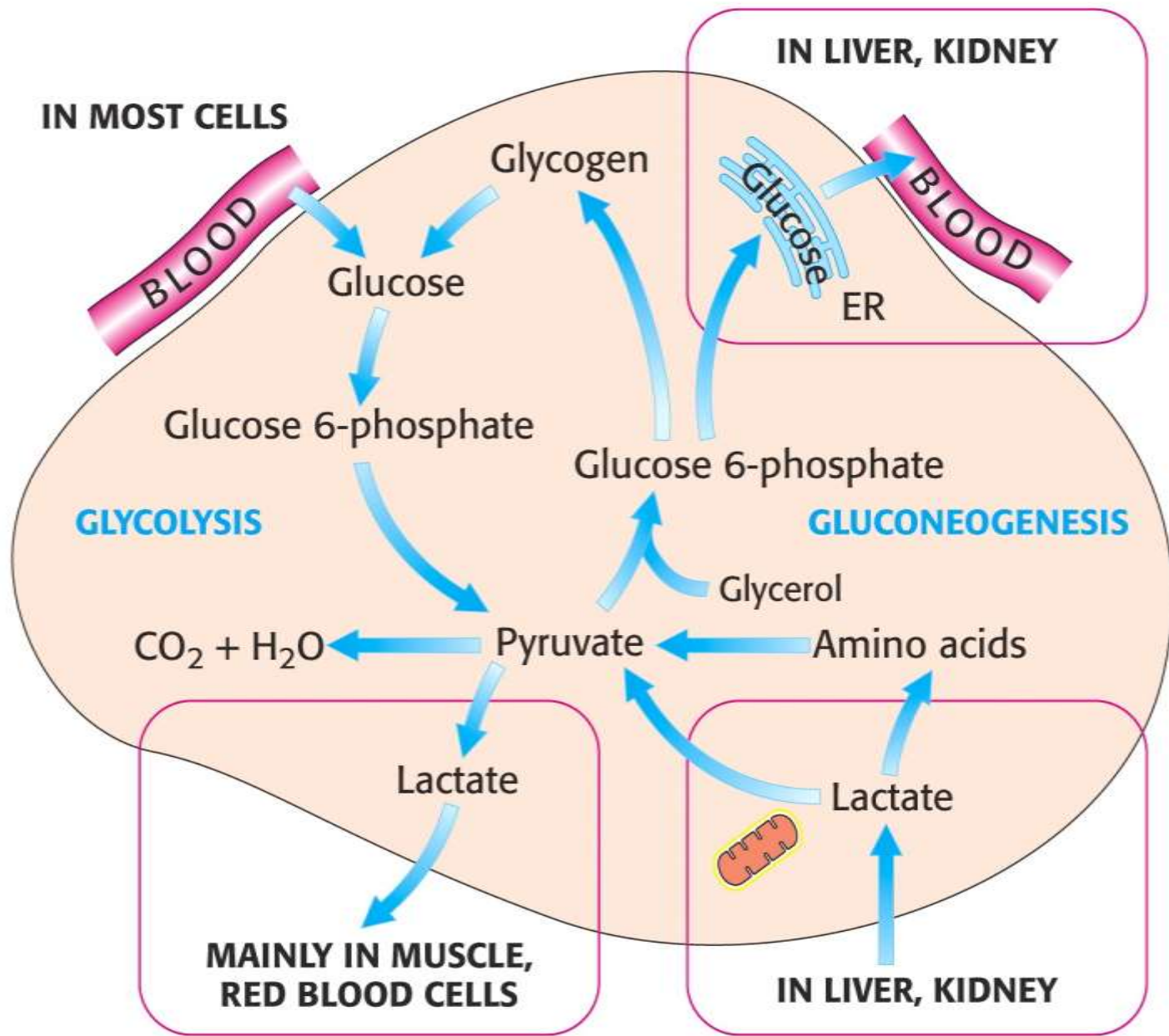
Carl and Gerty Cori  
Nobel Prize in Physiology and medicine  
1947



“for their discovery of the course of the catalytic conversion of glycogen”

# Lactate and alanine are glucogenic

- In muscle alanine is produced from pyruvate by transamination.  
$$\text{pyruvate} + \text{glutamate} \rightleftharpoons \text{alanine} + \alpha\text{-ketoglutarate}$$
- In the liver alanine is converted back to pyruvate.
- In active muscle lactate builds up, passes through the blood and is converted to pyruvate in the liver.
- Thus, part of the metabolic burden of active muscle is shifted to the liver.



*Thank  
you!*

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