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Chem 352 - Lecture 8
Carbohydrate Metabolism
Part I: Glycolysis

2-1

Introduction

Carbohydrate metabolism involves a collection of pathways.

- Glycolysis
  - Hexoses → 3-Carbon molecules
- Gluconeogenesis
  - 3-Carbon molecules → Hexoses
- Fermentation (anaerobic)
- Citric Acid Cycle (aerobic)
  - Oxidation all the way to CO_2 + H_2O
- Pentose-Phosphate pathway
  - Hexose → Pentose

2-2

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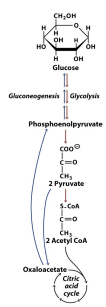

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3-1

The Glycolytic Reactions

- There are 10 reactions, which lead from glucose to pyruvate.
  - These reactions couple the lysis (splitting) and oxidation of hexose to the synthesis of 2 ATP's from ADP and P_i.

$$\text{Glucose} + 2\,NAD^+ + 2\,ADP + 2\,P_i \longrightarrow$$
$$2\,\text{Pyruvate} + 2\,NADH + H^+ + 2\,ATP + 2\,H_2O$$

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The Glycolytic Reactions

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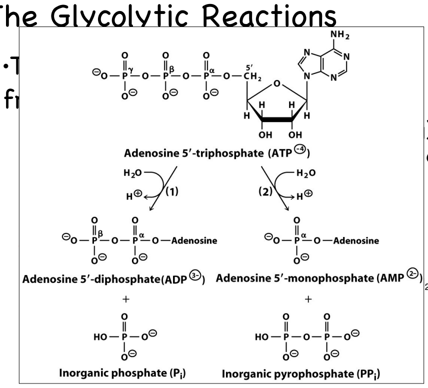

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The Glycolytic Reactions

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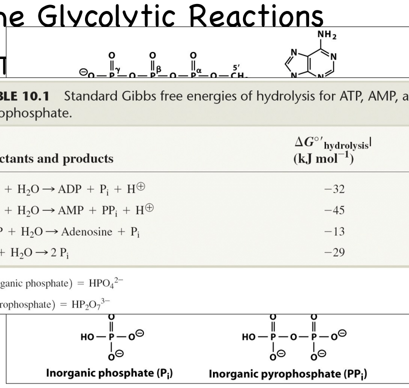

TABLE 10.1 Standard Gibbs free energies of hydrolysis for ATP, AMP, and pyrophosphate.

Reactants and products	$\Delta G^{\circ\prime}_{hydrolysis}$ (kJ mol^{-1})
$ATP + H_2O \rightarrow ADP + P_i + H^{\oplus}$	−32
$ATP + H_2O \rightarrow AMP + PP_i + H^{\oplus}$	−45
$AMP + H_2O \rightarrow \text{Adenosine} + P_i$	−13
$PP_i + H_2O \rightarrow 2\,P_i$	−29

P_i (inorganic phosphate) = HPO_4^{2-}
PP_i (pyrophosphate) = $HP_2O_7^{3-}$

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The Glycolytic Reactions

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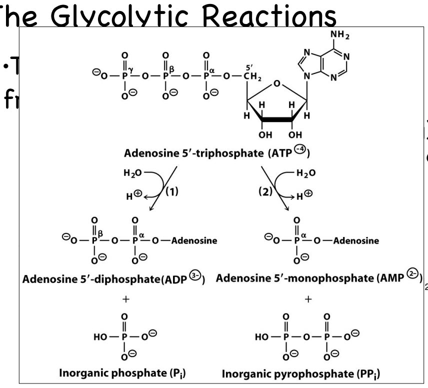

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The Glycolytic Reactions

- There are 10 reactions, which lead from glucose to pyruvate.
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$$\text{Glucose} + 2\,NAD^{+} + 2\,ADP + 2\,P_i \longrightarrow 2\,\text{Pyruvate} + 2\,NADH + H^{+} + 2\,ATP + 2\,H_2O$$

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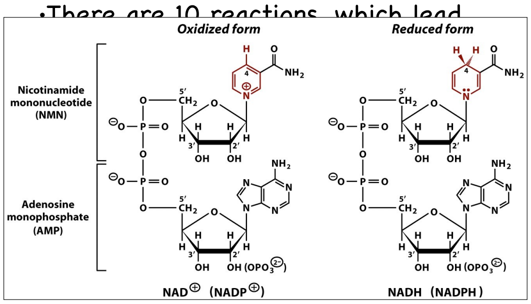
The Glycolytic Reactions

- There are 10 reactions, which lead



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The Glycolytic Reactions

- There are 10 reactions, which lead

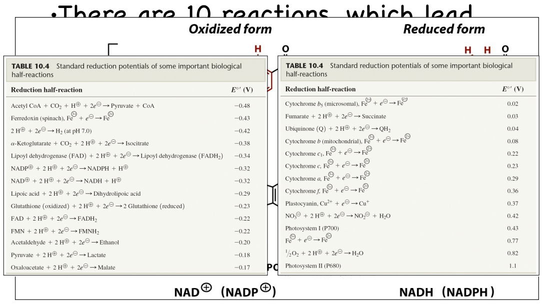

TABLE 10.4 Standard reduction potentials of some important biological half-reactions

Reduction half-reaction	$E^{\circ\prime}$ (V)
Acetyl CoA + CO_2 + $H^{\oplus}$ + $2e^{\ominus}$ → Pyruvate + CoA	−0.48
Ferredoxin (spinach), Fe^{3+} + $e^{\ominus}$ → Fe^{2+}	−0.43
$2\,H^{\oplus} + 2e^{\ominus} \rightarrow H_2$ (at pH 7.0)	−0.42
α-Ketoglutarate + CO_2 + $2\,H^{\oplus}$ + $2e^{\ominus}$ → Isocitrate	−0.38
Lipoyl dehydrogenase (FAD) + $2\,H^{\oplus}$ + $2e^{\ominus}$ → Lipoyl dehydrogenase ($FADH_2$)	−0.34
$NADP^{\oplus}$ + $2\,H^{\oplus}$ + $2e^{\ominus}$ → NADPH + $H^{\oplus}$	−0.32
$NAD^{\oplus}$ + $2\,H^{\oplus}$ + $2e^{\ominus}$ → NADH + $H^{\oplus}$	−0.32
Lipoic acid + $2\,H^{\oplus}$ + $2e^{\ominus}$ → Dihydrolipoic acid	−0.29
Glutathione (oxidized) + $2\,H^{\oplus}$ + $2e^{\ominus}$ → 2 Glutathione (reduced)	−0.23
FAD + $2\,H^{\oplus}$ + $2e^{\ominus}$ → $FADH_2$	−0.22
FMN + $2\,H^{\oplus}$ + $2e^{\ominus}$ → $FMNH_2$	−0.22
Acetaldehyde + $2\,H^{\oplus}$ + $2e^{\ominus}$ → Ethanol	−0.20
Pyruvate + $2\,H^{\oplus}$ + $2e^{\ominus}$ → Lactate	−0.18
Oxaloacetate + $2\,H^{\oplus}$ + $2e^{\ominus}$ → Malate	−0.17

TABLE 10.4 Standard reduction potentials of some important biological half-reactions

Reduction half-reaction	$E^{\circ\prime}$ (V)
Cytochrome b_5 (microsomal), Fe^{3+} + $e^{\ominus}$ → Fe^{2+}	0.02
Fumarate + $2\,H^{\oplus}$ + $2e^{\ominus}$ → Succinate	0.03
Ubiquinone (Q) + $2\,H^{\oplus}$ + $2e^{\ominus}$ → QH_2	0.04
Cytochrome *b* (mitochondrial), Fe^{3+} + $e^{\ominus}$ → Fe^{2+}	0.08
Cytochrome c_1, Fe^{3+} + $e^{\ominus}$ → Fe^{2+}	0.22
Cytochrome *c*, Fe^{3+} + $e^{\ominus}$ → Fe^{2+}	0.23
Cytochrome *a*, Fe^{3+} + $e^{\ominus}$ → Fe^{2+}	0.29
Cytochrome *f*, Fe^{3+} + $e^{\ominus}$ → Fe^{2+}	0.36
Plastocyanin, Cu^{2+} + $e^{\ominus}$ → Cu^{+}	0.37
$NO_3^{\ominus}$ + $2\,H^{\oplus}$ + $2e^{\ominus}$ → $NO_2^{\ominus}$ + H_2O	0.42
Photosystem I (P700)	0.43
Fe^{3+} + $e^{\ominus}$ → Fe^{2+}	0.77
$\frac{1}{2}O_2$ + $2\,H^{\oplus}$ + $2e^{\ominus}$ → H_2O	0.82
Photosystem II (P680)	1.1

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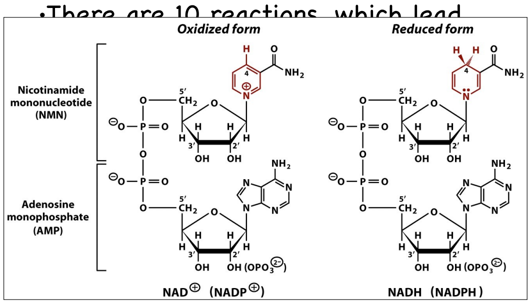
The Glycolytic Reactions

- There are 10 reactions, which lead



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4

The Glycolytic Reactions

TABLE 11.1 The reactions and enzymes of glycolysis

1. Glucose + ATP $\longrightarrow$ Glucose 6-phosphate + ADP + $H^\oplus$	Hexokinase, glucokinase
2. Glucose 6-phosphate $\rightleftharpoons$ Fructose 6-phosphate	Glucose-6-phosphate isomerase
3. Fructose 6-phosphate + ATP $\longrightarrow$ Fructose 1,6-bisphosphate + ADP + $H^\oplus$	Phosphofructokinase-1
4. Fructose 1,6-bisphosphate $\rightleftharpoons$ Dihydroxyacetone phosphate + Glyceraldehyde 3-phosphate	Aldolase
5. Dihydroxyacetone phosphate $\rightleftharpoons$ Glyceraldehyde 3-phosphate	Triose phosphate isomerase
6. Glyceraldehyde 3-phosphate + $NAD^\oplus$ + P_i $\rightleftharpoons$ 1,3-Bisphosphoglycerate + NADH + $H^\oplus$	Glyceraldehyde 3-phosphate dehydrogenase
7. 1,3-Bisphosphoglycerate + ADP $\rightleftharpoons$ 3-Phosphoglycerate + ATP	Phosphoglycerate kinase
8. 3-Phosphoglycerate $\rightleftharpoons$ 2-Phosphoglycerate	Phosphoglycerate mutase
9. 2-Phosphoglycerate $\rightleftharpoons$ Phosphoenolpyruvate + H_2O	Enolase
10. Phosphoenolpyruvate + ADP + $H^\oplus$ $\longrightarrow$ Pyruvate + ATP	Pyruvate kinase

$$\text{Glucose} + 2\,NAD^+ + 2\,ADP + 2\,P_i \longrightarrow$$

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5-2

The Glycolytic Reactions

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2x	10. Phosphoenolpyruvate + ADP + $H^\oplus$ $\longrightarrow$ Pyruvate + ATP	Pyruvate kinase

$$\text{Glucose} + 2\,NAD^+ + 2\,ADP + 2\,P_i \longrightarrow$$

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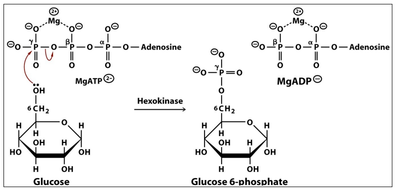
The Glycolytic Reactions

• Reaction 1: Hexokinase



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The Glycolytic Reactions

Clicker Questions:

There are four different hexokinase enzymes (I - IV) with differing K_M values:

Hexokinase	K_M
I, II, III	10^{-4} - 10^{-6} M
IV	10^{-2} M

Hexokinase IV, also known as glucokinase, is found in the liver. When the different tissues line up to take glucose from the blood, where is the liver in this lineup?

A. First in line
B. Last in line
C. Somewhere in the middle

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The Glycolytic Reactions

• Reaction 1: Hexokinase

- Different tissues have different **isoforms** of hexokinase.
  - The liver hexokinase, also called glucokinase, has the highest K_M, which reflects this organs role in regulating blood glucose levels
- This reaction has a high negative ΔG.
- Except for the liver, once phosphorylated, glucose cannot leave the cell.

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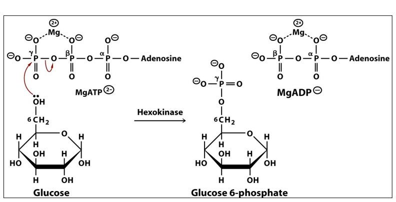
The Glycolytic Reactions

• Reaction 1: Hexokinase



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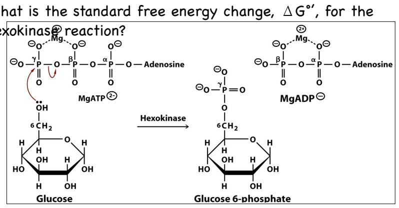
The Glycolytic Reactions

•Reaction 1: Hexokinase

Problem:

What is the standard free energy change, $\Delta G°'$, for the hexokinase reaction?



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The Glycolytic Reactions

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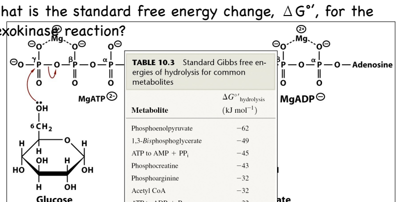

TABLE 10.3 Standard Gibbs free energies of hydrolysis for common metabolites

Metabolite	$\Delta G°'_{hydrolysis}$ (kJ mol^{-1})
Phosphoenolpyruvate	−62
1,3-Bisphosphoglycerate	−49
ATP to AMP + PP_i	−45
Phosphocreatine	−43
Phosphoarginine	−32
Acetyl CoA	−32
ATP to ADP + P_i	−32
Pyrophosphate	−29
Glucose 1-phosphate	−21
Glucose 6-phosphate	−14
Glycerol 3-phosphate	−9

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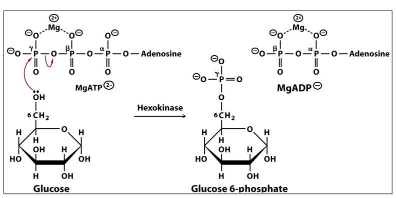
The Glycolytic Reactions

•Reaction 1: Hexokinase



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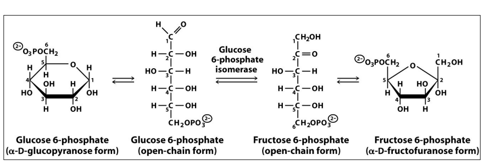
The Glycolytic Reactions

•Reaction 2: Glucose 6-Phosphate Isomerase



The Glycolytic Reactions

- Reaction 2: Glucose 6-Phosphate Isomerase
  - In the cell, this reaction occurs near equilibrium

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The Glycolytic Reactions

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  - In the cell, this reaction occurs near equilibrium

Clicker Question:

If a reaction occurs near equilibrium, what does this say about the actual ΔG for the reaction?

A. $\Delta G > 0$

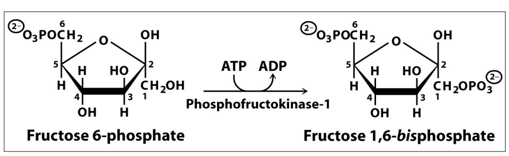
B. $\Delta G \approx 0$

C. $\Delta G < 0$

11-2

The Glycolytic Reactions

- Reaction 3: Phosphofructokinase 1



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The Glycolytic Reactions

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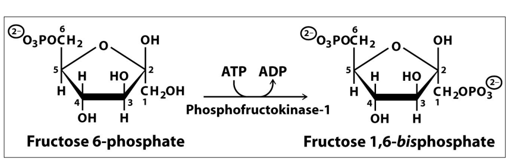

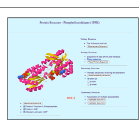

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The Glycolytic Reactions

- Reaction 3: <u>Phosphofructokinase 1</u>
  - This enzyme catalyzes the first committed step in glycolysis.
  - PFK-1 is regulated by numerous allosteric effectors.

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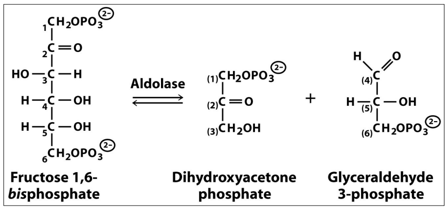
The Glycolytic Reactions

- Reaction 4: Aldolase



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The Glycolytic Reactions

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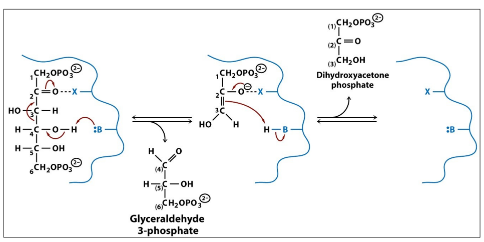

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The Glycolytic Reactions

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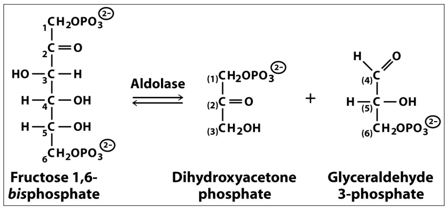

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The Glycolytic Reactions

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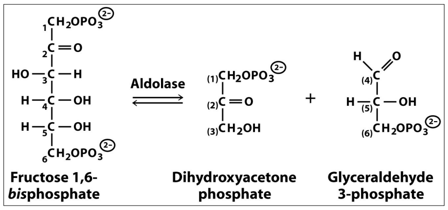

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The Glycolytic Reactions

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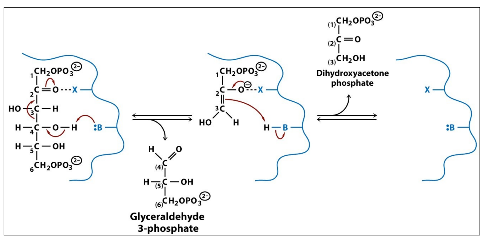

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The Glycolytic Reactions

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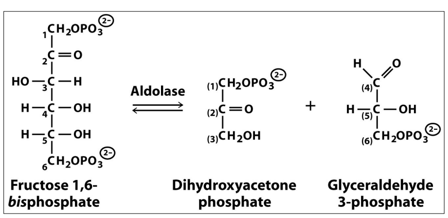

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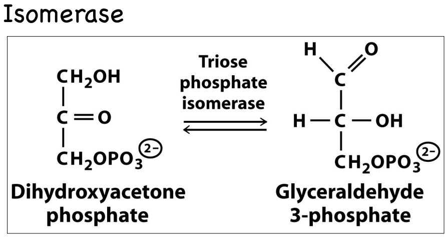
The Glycolytic Reactions

- Reaction 5: Triose-Phosphate Isomerase



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The Glycolytic Reactions

- Reaction 5: Triose-Phosphate Isomerase
  - This reaction also occurs near equlibrium
  - The reaction mechanism involves an endiol intermediate.

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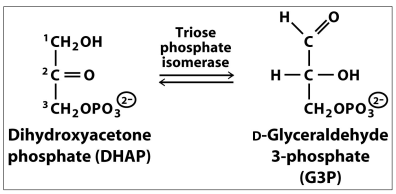
Chemical Modes of Enzymatic Catalysis

- Acid/Base catalysis
  - Triose phosphate isomerase illustrates both general acid and bases catalysis.



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Chemical Modes of Enzymatic Catalysis

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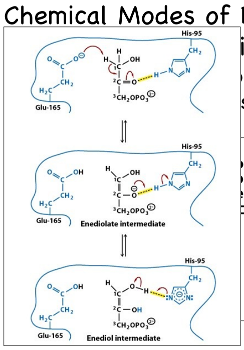

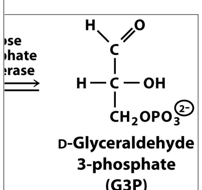

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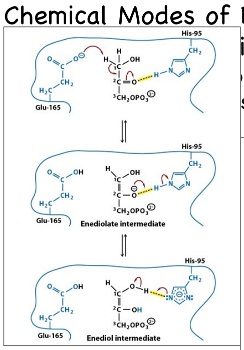

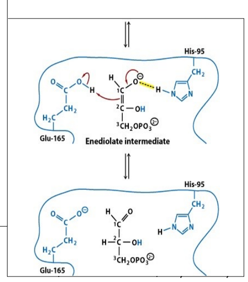

The Glycolytic Reactions

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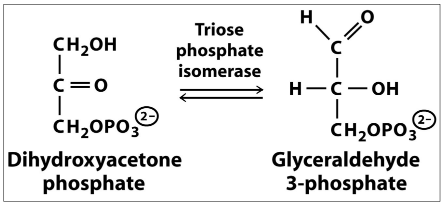

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The Glycolytic Reactions

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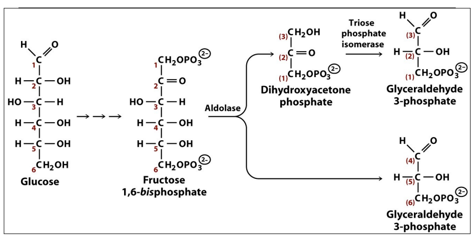

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The Glycolytic Reactions

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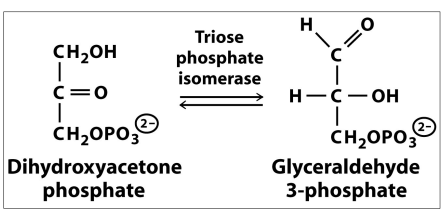

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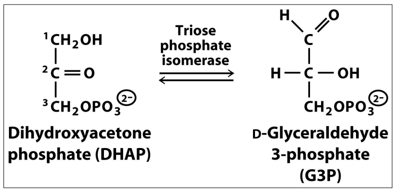

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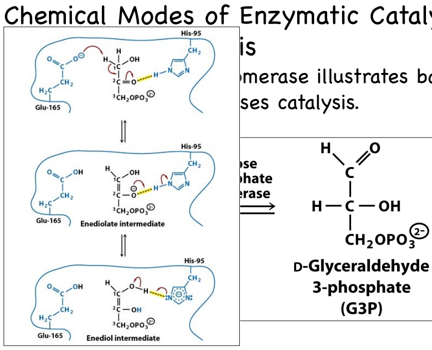

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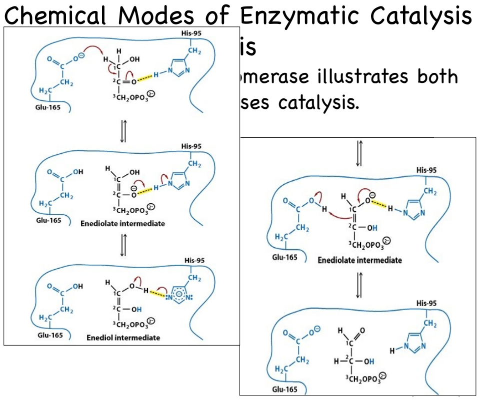
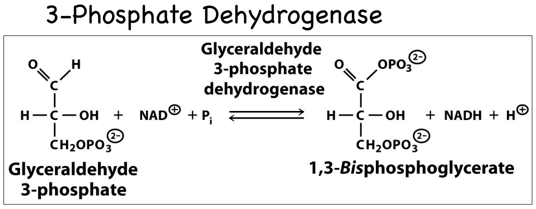


21-3

The Glycolytic Reactions

- Reaction 6: Glyceraldehyde 3-Phosphate Dehydrogenase



22

23

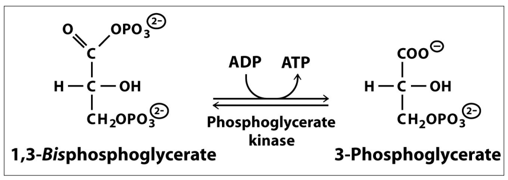
The Glycolytic Reactions

- Reaction 6: Glyceraldehyde 3-Phosphate Dehydrogenase
  - This reaction also takes place near equilibrium because the 1,3-bisphosphoglycerate is rapidly depleated.
  - NAD^+ levels in the cell are typically low, so regeneration of NAD^+, is critical for this step in glycolysis.

24-1

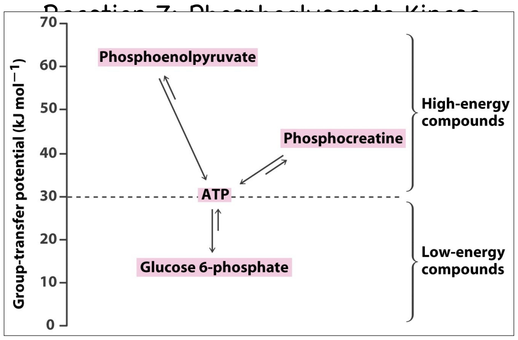
The Glycolytic Reactions

- Reaction 7: Phosphoglycerate Kinase



24-2

The Glycolytic Reactions



24-3

The Glycolytic Reactions

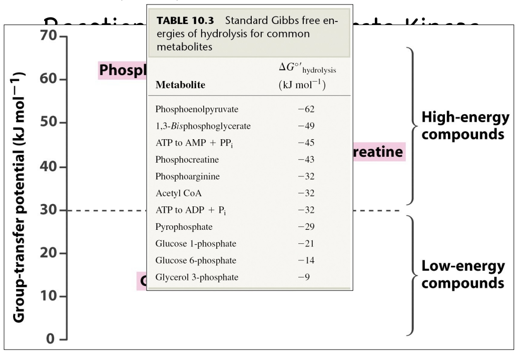
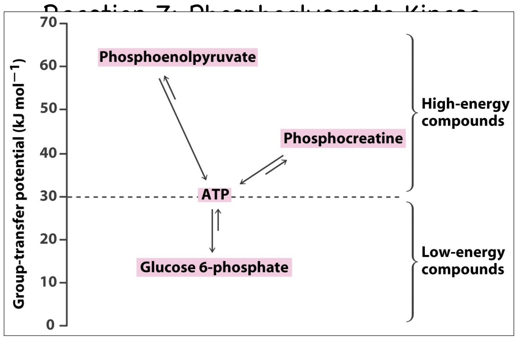


TABLE 10.3 Standard Gibbs free energies of hydrolysis for common metabolites

Metabolite	$\Delta G^{\circ\prime}_{hydrolysis}$ (kJ mol^{-1})
Phosphoenolpyruvate	−62
1,3-*Bis*phosphoglycerate	−49
ATP to AMP + PP_i	−45
Phosphocreatine	−43
Phosphoarginine	−32
Acetyl CoA	−32
ATP to ADP + P_i	−32
Pyrophosphate	−29
Glucose 1-phosphate	−21
Glucose 6-phosphate	−14
Glycerol 3-phosphate	−9

24-4

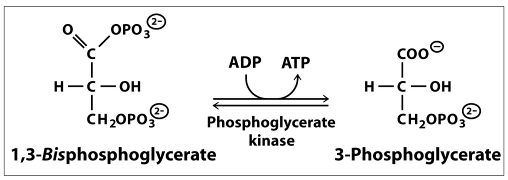
The Glycolytic Reactions



24-5

The Glycolytic Reactions

- Reaction 7: Phosphoglycerate Kinase



25

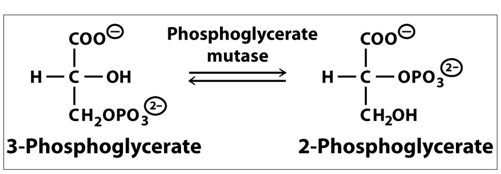
The Glycolytic Reactions

- Reaction 7: Phosphoglycerate Kinase
  - This enzyme is named for the reverse reaction.
  - This reaction is an example of **substrate-level phosphorylation**.

26

The Glycolytic Reactions

- Reaction 8: Phosphoglycerate Mutase



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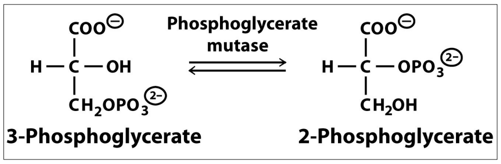
The Glycolytic Reactions

- Reaction 8: Phosphoglycerate Mutase



27-2

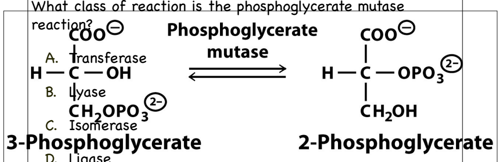
The Glycolytic Reactions

- Reaction 8: Phosphoglycerate Mutase

Clicker Questions:

What class of reaction is the phosphoglycerate mutase reaction?

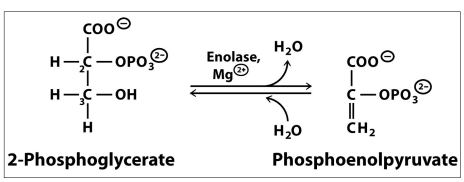
A. Transferase
B. Lyase
C. Isomerase
D. Ligase
E. Oxidoreductase



28

The Glycolytic Reactions

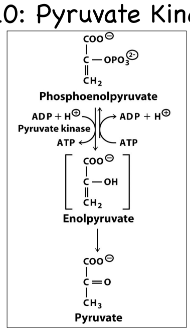
- Reaction 9: Enolase



29-1

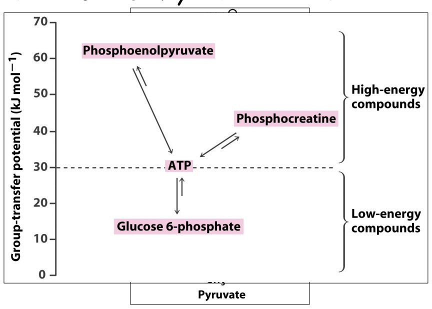
The Glycolytic Reactions

- Reaction 10: Pyruvate Kinase



The Glycolytic Reactions

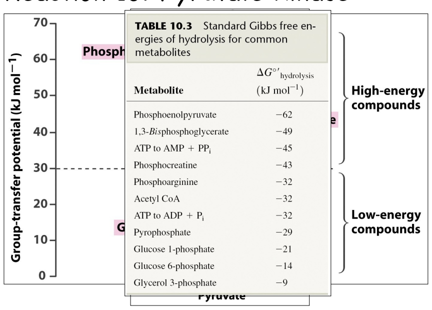
- Reaction 10: Pyruvate Kinase



29-2

The Glycolytic Reactions

- Reaction 10: Pyruvate Kinase



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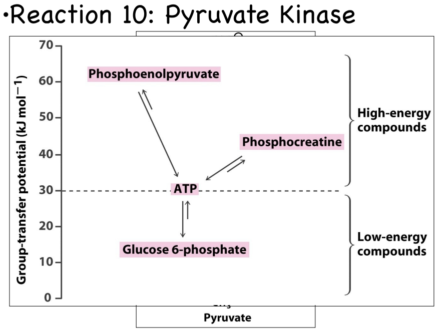
29-3

The Glycolytic Reactions

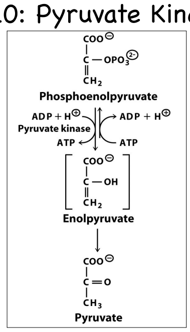
- Reaction 10: Pyruvate Kinase



29-4

The Glycolytic Reactions

- Reaction 10: Pyruvate Kinase

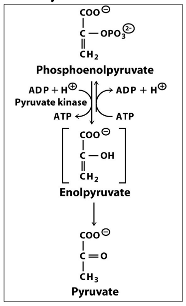


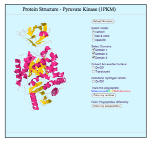
29-5

29-6

The Glycolytic Reactions

- Reaction 10: Pyruvate Kinase





30

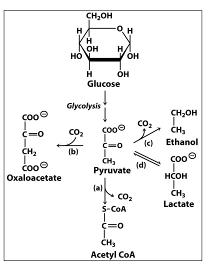
The Glycolytic Reactions

- Reaction 10: Pyruvate Kinase
  - Like phospglycerate kinase, this enzyme is named for the reverse reaction.
  - This reaction is another example of **substrate-level phosphorylation**.

31-1

The Fates of Pyruvate

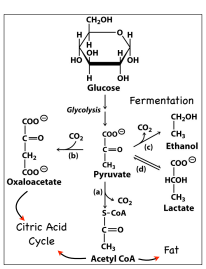
- Pyruvate represents one of the major intersections in metabolism.



31-2

The Fates of Pyruvate

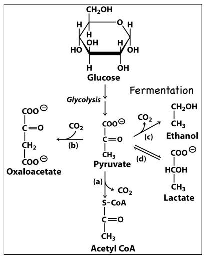
- Pyruvate represents one of the major intersections in metabolism.



32-1

The Fates of Pyruvate

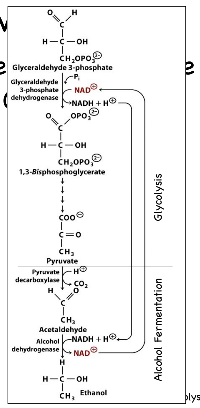
- Fermenatation is used to regenerate oxidized NAD^+ when O_2 cannot be utilized to do this.



32-2

The Fates of Pyruv

- Fermenatation is use
oxidized NAD^+ when (
utilized to do this.



32-3

The Fates of Pyruv

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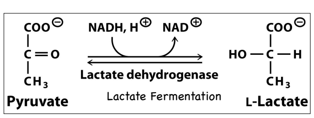

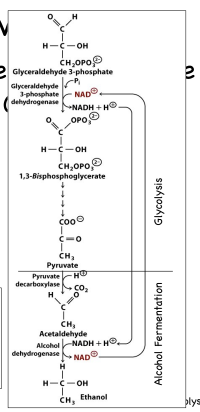

33-1

Coenzymes and Vitamins (Chapter 7.7)

- Pyruvate decarboxylase uses the coenzyme thiamine pyrophosphate (TPP).
  - thiamine pyrophosphate is synthesized from vitamin B_1 (thiamine)

33-2

TABLE 7.2 Major coenzymes

Coenzyme	Vitamin source	Major metabolic roles	Mechanistic role
Adenosine triphosphate (ATP)	—	Transfer of phosphoryl or nucleotidyl groups	Cosubstrate
S-Adenosylmethionine	—	Transfer of methyl groups	Cosubstrate
Uridine diphosphate glucose	—	Transfer of glycosyl groups	Cosubstrate
Nicotinamide adenine dinucleotide ($NAD^{\oplus}$) and nicotinamide adenine dinucleotide phosphate ($NADP^{\oplus}$)	Niacin	Oxidation-reduction reactions involving two-electron transfers	Cosubstrate
Flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD)	Riboflavin (B_2)	Oxidation-reduction reactions involving one- and two-electron transfers	Prosthetic group
Coenzyme A (CoA)	Pantothenate (B_3)	Transfer of acyl groups	Cosubstrate
Thiamine pyrophosphate (TPP)	Thiamine (B_1)	Transfer of two-carbon fragments containing a carbonyl group	Prosthetic group
Pyridoxal phosphate (PLP)	Pyridoxine (B_6)	Transfer of groups to and from amino acids	Prosthetic group
Biotin	Biotin	ATP-dependent carboxylation of substrates or carboxyl-group transfer between substrates	Prosthetic group
Tetrahydrofolate	Folate	Transfer of one-carbon substituents, especially formyl and hydroxymethyl groups; provides the methyl group for thymine in DNA	Cosubstrate
Adenosylcobalamin	Cobalamin (B_{12})	Intramolecular rearrangements	Prosthetic group
Methylcobalamin	Cobalamin (B_{12})	Transfer of methyl groups	Prosthetic group
Lipoamide	—	Oxidation of a hydroxyalkyl group from TPP and subsequent transfer as an acyl group	Prosthetic group
Retinal	Vitamin A	Vision	Prosthetic group
Vitamin K	Vitamin K	Carboxylation of some glutamate residues	Prosthetic group
Ubiquinone (Q)	—	Lipid-soluble electron carrier	Cosubstrate

33-3

Coenzymes and Vitamins (Chapter 7.7)

- Pyruvate decarboxylase uses the coenzyme thiamine pyrophosphate (TPP).
  - thiamine pyrophosphate is synthesized from vitamin B_1 (thiamine)

33-4

Coenzymes and Vitamins (Chapter 7.7)

- Pyruvate decarboxylase uses the
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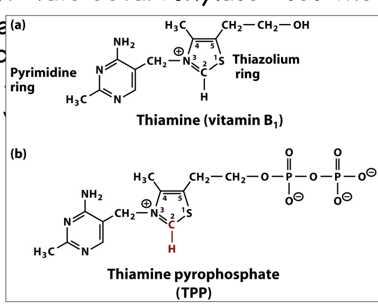

33-5

Coenzymes and Vitamins (Chapter 7.7)

- Pyruvate decarboxylase uses the coenzyme thiamine pyrophosphate (TPP).
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Coenzymes and Vitamins (Chapter 7.7)

- Thiamine pyrophosphate is used in many decarboxylation reactions,
  - Including pyruvate decarboxylase

34-1

Coenzy ... er 7.7)

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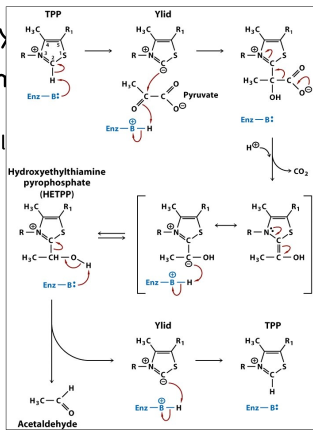


34-2

Coenzymes and Vitamins (Chapter 7.7)

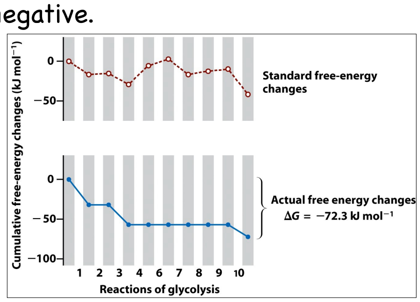
- Thiamine pyrophosphate is used in many decarboxylation reactions,
  - Including pyruvate decarboxylase

Chem 352, Lecture 8, Part I: Glycolysis 34

34-3

Free Energy Changes in Glycolysis

- The overall free energy change is negative.



35-1

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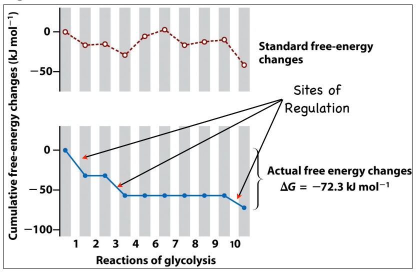

35-2

Regulation of Glycolysis

- The enzymes that catalyze the irreversible reactions are the primary sites of allosteric regulation.

36-1

Regulation of Glycolysis

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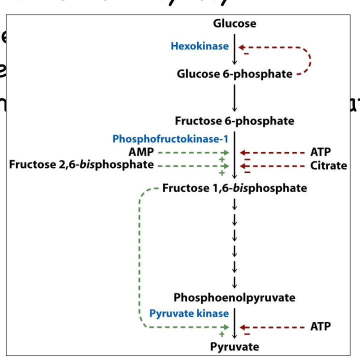

36-2

Regulation of Glycolysis

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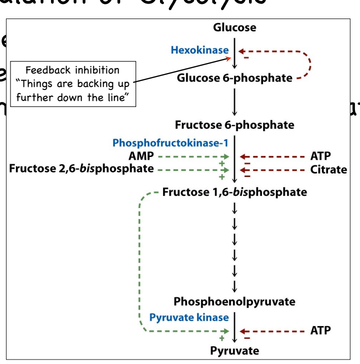

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Regulation of Glycolysis

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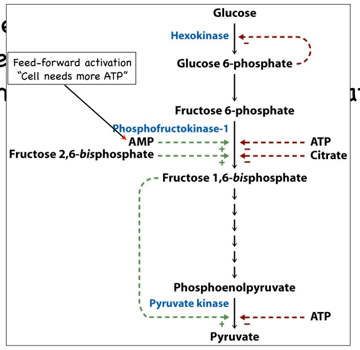

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Regulation of Glycolysis

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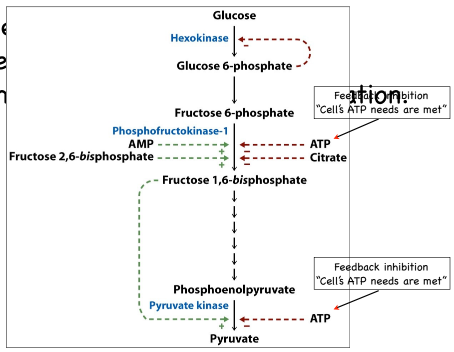

36-5

Regulation of Glycolysis

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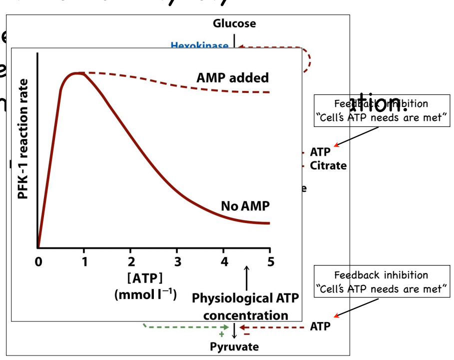

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Regulation of Glycolysis

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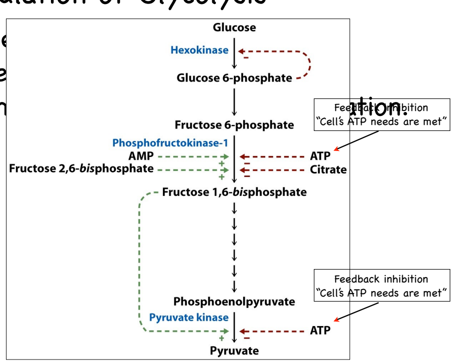

36-7

36-8

Regulation of Glycolysis

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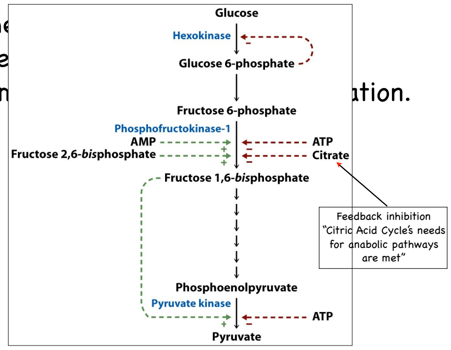

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Regulation of Glycolysis

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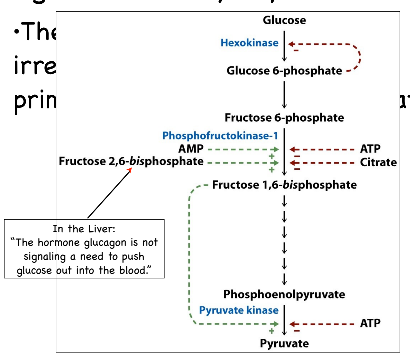

36-10

Regulation of Glycolysis

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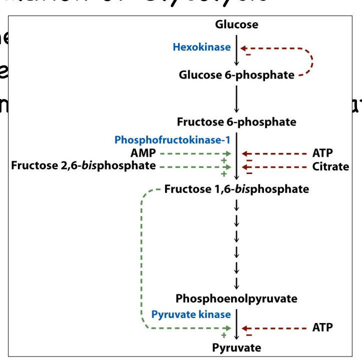

37-1

Regulation of Glycolysis

•In the liver, glucokinase, which is livers form of hexokinase, is also regulated by a regulatory protein that binds to glucokinase when fructose 6-phosphate levels are high.

Regulation of Glycolysis

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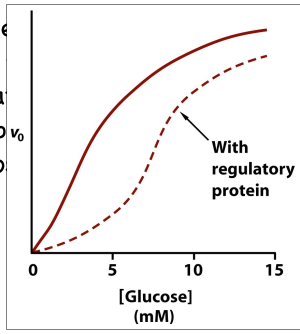

37-2

Regulation of Glycolysis

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37-3

Regulation of Glycolysis

•The liver is the only organ that is able to release glucose back into the blood

- It does so to satisfy the glucose need of other tissues, particularly the brain.

38-1

Regulation of Glycolysis

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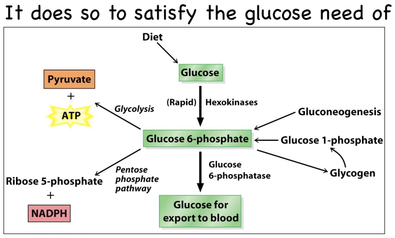


38-2

Regulation of Glycolysis

- The liver is the only organ that is able to release glucose back into the blood
  - It does so to satisfy the glucose need of other tissues, particularly the brain.

38-3

Regulation of Glycolysis

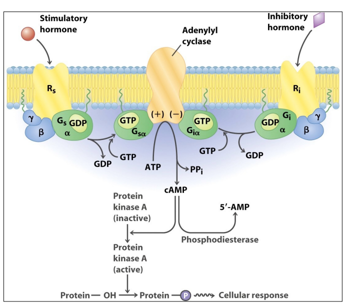
The liver is the only organ that is able to release glucose back into the blood

- Under low blood glucose levels, the hormone glucagon signals the liver to halt glycolysis.
  - It does this using a signal transduction pathway.

39

Transduction of Extracellular Signals

- G-Proteins



40

Regulation of Glycolysis

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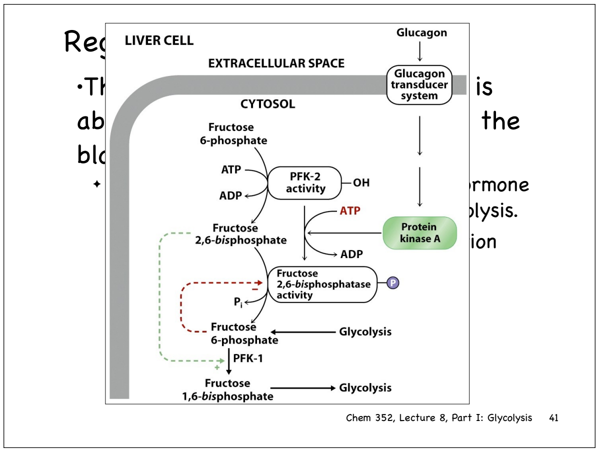
41-1

41-2



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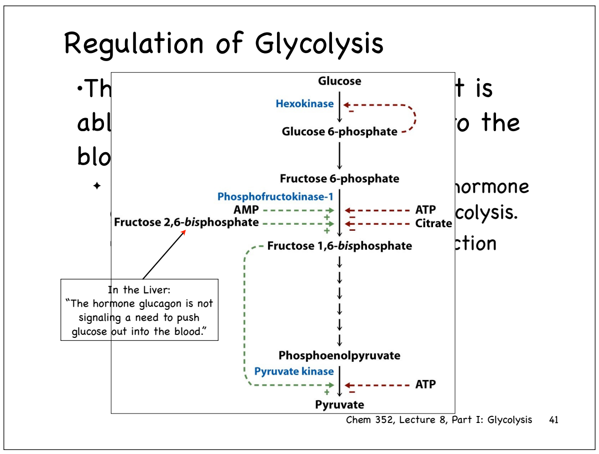
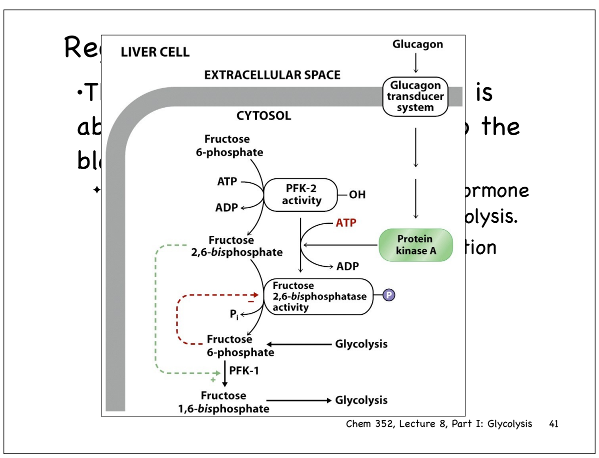


41-4



41-5

Regulation of Glycolysis

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  - Under low blood glucose levels, the hormone glucagon signals the liver to halt glycolysis.
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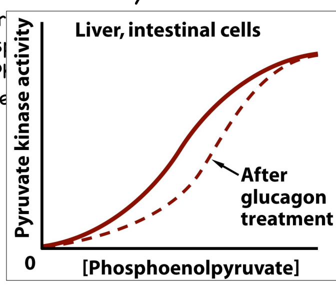
Regulation of Glycolysis

- Regulation of Pyruvate Kinase
  - Pyruvate Kinase is also regulated in response to glucagon.
    - Phosphorylation by Protein Kinase A in response to glucagon, lowers its activity.

42-1

Regulation of Glycolysis

- Regulation of Pyruvate Kinase
  - Pyr
    resp
    - Pl in
      re vity.



42-2

Regulation of Glycolysis

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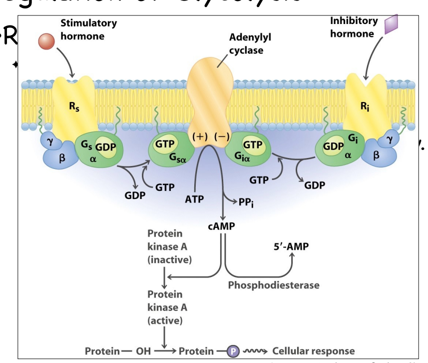

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Regulation of Glycolysis

- Regulation of Pyruvate Kinase
  - Pyr
    resp
    - Pl in
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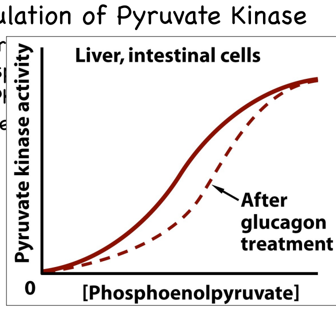

42-4

Regulation of Glycolysis

Regulation of Pyruvate Kinase

- In addition to being allosterically inhibited by ATP, Pyruvate Kinase is also allosterically activated by frucose 6-phosphate.

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Regulation of Glycolysis

Regulation of Pyruvate Kinase

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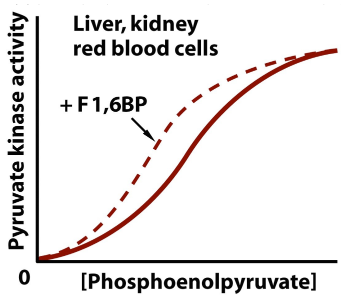

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Regulation of Glycolysis

Regulation of Pyruvate Kinase

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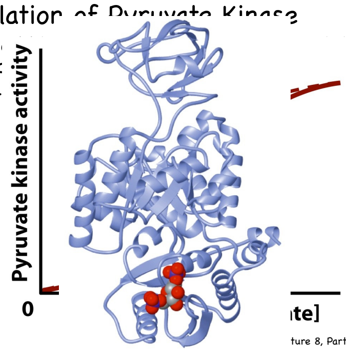

43-3

Regulation of Glycolysis

Regulation of Pyruvate Kinase

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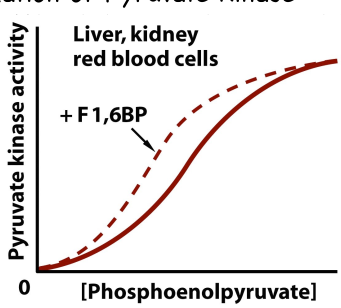

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Other Points

Skip Section 11.6
- Entry of other sugars into glycolysis

Skip Section 11.7
- Entner-Doudoroff Pathway in Bacteria, which lack PFK-1

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Review of Glycolysis

Questions:

What is the metabolic purpose behind the glycolytic pathway?

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Review of Glycolysis

Questions:

What is the metabolic purpose behind the glycolytic pathway?

The "-lysis" part of glycolysis means "to split". Using structural formulas, draw the chemical equation for the reaction in which a 6-carbon molecule is split into two 3-carbon molecules.

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Review of Glycolysis

Questions:

What is the metabolic purpose behind the glycolytic pathway?

The "-lysis" part of glycolysis means "to split". Using structural formulas, draw the chemical equation for the reaction in which a 6-carbon molecule is split into two 3-carbon molecules.

Even though glycolysis is an anaerobic pathway (in the absence of oxygen), there is one reaction in which an oxidation occurs.

A. Using structural formulas, draw the chemical equation for this reaction.

B. What oxidizing reagent is used in this reaction?

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45-4

Review of Glycolysis

Questions:

[illegible] by the [illegible] molecule is split into two 3-carbon molecules.

A. Using structural formulas, show the [illegible] equation for [illegible] reactions that is used to reoxizide this agent when oxygen cannot be utilized.

B. What oxidizing reagent is used in this reaction?

B. What is the name of the pathway you drew?

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Next Up

- Lecture 8 - Carbohydrate Metabolism
  - Part II: Gluconeogenesis, Pentose Phosphate Pathway, and Glycogen Metabolism (Moran et al., Chapter 12)