

Biomedical  
Science

Molecular  
Genetics



BMS 23110c | Fall 2026-2027

## Protein Activity & Regulation

### Glycolysis



Free Session

*A+ is more than just a platform*



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## OVERVIEW

## PART 1 · OVERVIEW



## Carbohydrates



**Ideal nutrients**



Meet **energy needs**



Feed the **brain and nervous system**



Keep the **digestive system fit**



Keep your **body lean**



**Digestible vs indigestible**

Carbohydrates may be digestible or indigestible.



**Simple vs complex**

**Simple** carbohydrates contain **one or two molecules**; **complex** carbohydrates contain **hundreds to thousands** of molecules.



## Simple Carbohydrates: Monosaccharides & Disaccharides

- Simple carbohydrates are commonly referred to as **sugars**. **Mono** means one and **saccharide** means sugar; **di** means two.

### FOUR MONOSACCHARIDES — A SINGLE SUGAR MOLECULE

**Glucose**

MONOSACCHARIDE

**Fructose**

MONOSACCHARIDE

**Galactose**

MONOSACCHARIDE

**Ribose**

MONOSACCHARIDE

### THREE DISACCHARIDES — TWO SUGAR MOLECULES JOINED TOGETHER

**Lactose**

DISACCHARIDE

**Maltose**

DISACCHARIDE

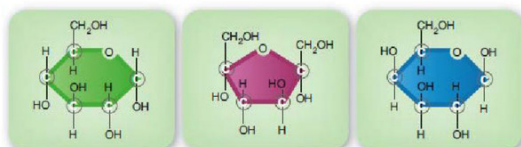
**Sucrose**

DISACCHARIDE

## OVERVIEW

## PART 1 · OVERVIEW

# How Monosaccharides Join to Form Disaccharides

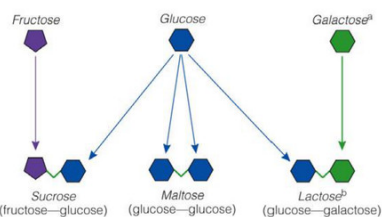


**Glucose**  
Most abundant sugar molecule in our diet; good energy source

**Fructose**  
Sweetest natural sugar; found in fruit, high-fructose corn syrup

**Galactose**  
Does not occur alone in foods; binds with glucose to form lactose

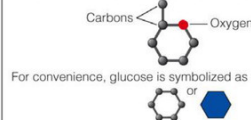
Three types of monosaccharides ...



<sup>a</sup>Galactose does not occur in foods singly but only as part of lactose.

<sup>b</sup>The chemical bond that joins the monosaccharides of lactose differs from those of other sugars and makes lactose hard for some people to digest—lactose intolerance (see later section).

**A note on the glucose symbol:**  
The glucose molecule is really a ring of 5 carbons and 1 oxygen plus a carbon "flag."

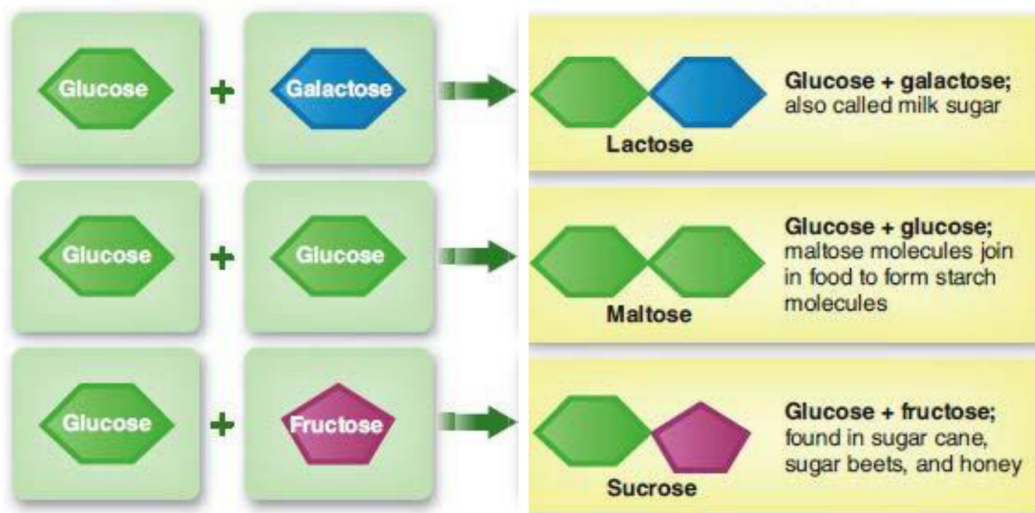


- Very slight differences in the **arrangement of atoms** in these three monosaccharides cause **major differences in their levels of sweetness.**
- Human breast milk has **more lactose** than cow's milk, making human breast milk **taste sweeter.**

## Simple Carbs

### Monosaccharides

### Disaccharides



## OVERVIEW

## PART 1 · OVERVIEW



## Catabolism

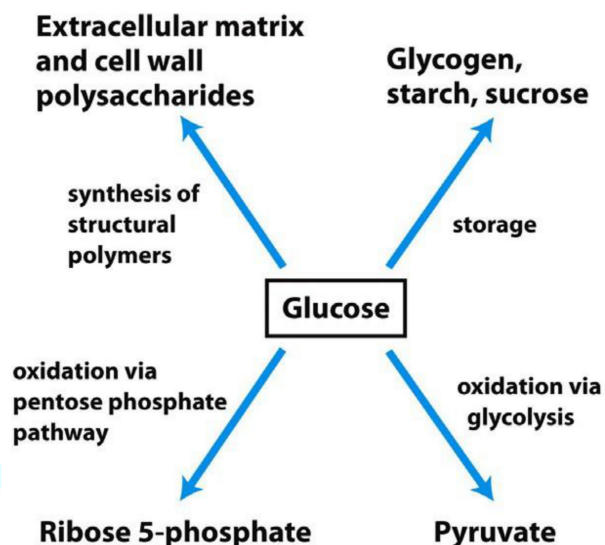
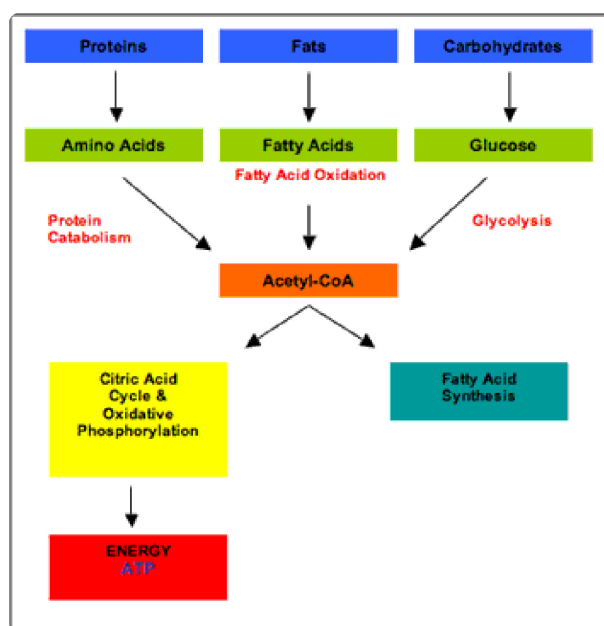


Figure 14-1  
Lehninger Principles of Biochemistry, Fifth Edition  
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Figure 14-1 · Lehninger Principles of Biochemistry



## Carbohydrate Metabolism Overview

☆ DR. ASMAA ADDITION



Glucose

>



Pyruvate  
glycolysis

>



Acetyl-CoA

>



Citric acid cycle  
oxidized to CO<sub>2</sub> and water

REVERSE

Gluconeogenesis runs in the **reverse** direction.

- Gluconeogenesis, glycolysis, and the citric acid cycle are key to carbohydrate metabolism and energy production.
- Gluconeogenesis **synthesizes glucose** from three-carbon precursors, while glycolysis **breaks down glucose into pyruvate**, releasing energy.
- Pyruvate can be further converted into **acetyl CoA**, which enters the citric acid cycle where it is **oxidized to CO<sub>2</sub> and water**.
- These pathways also **intersect** with the metabolism of non-carbohydrate molecules like **amino acids and lipids**.

## OVERVIEW

## PART 1 · OVERVIEW



## The Enzymatic Reactions of Glycolysis

### GLYCOLYSIS

A sequence of **ten enzyme-catalyzed reactions** by which **glucose is converted to pyruvate**.



#### Universal

The enzymes of this pathway are found in **most living species**.



#### Location

The enzymes are located in the **cytosol**.



#### Sole ATP source

In some mammalian cells — **retina and some brain cells** — it is the **only ATP-producing pathway**.



## Net Reaction of Glycolysis



### 2 ATP

molecules of ATP are produced

### 2 NADH

molecules of  $\text{NAD}^+$  are reduced to NADH



## Glycolysis: Hexose & Triose Stages

It can be divided into two stages — the **hexose stage** and the **triose stage**:

### -2 ATP

**Hexose stage** — 2 ATP consumed per glucose

### +4 ATP

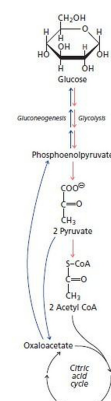
**Triose stage** — 4 ATP produced per glucose

### +2 ATP

**Net** — 2 ATP produced per glucose

▲ Figure 11.1

**Gluconeogenesis, glycolysis, and the citric acid cycle.** Glucose is synthesized from pyruvate via oxaloacetate and phosphoenolpyruvate. In glycolysis, glucose is degraded to pyruvate. Many (but not all) of the steps in glycolysis are the reverse of the gluconeogenesis reactions. The acetyl group of pyruvate is transferred to coenzyme A (CoA) and oxidized to carbon dioxide by the citric acid cycle. Energy in the form of ATP equivalents is required for the synthesis of glucose. Some of this energy is recovered in glycolysis but much more is recovered as a result of the citric acid cycle.



## THE TEN STEPS

## PART 2 · THE TEN STEPS



## The Ten Steps of Glycolysis



Each chemical reaction **prepares a substrate** for the next step in the process



**Interconversion of the trioses** allows both to be further metabolized via glycolytic enzymes



A **hexose is cleaved** to two trioses



ATP is **both consumed** and **produced** in glycolysis

Table 11.1 The reactions and enzymes of glycolysis

|                                                                                                                                        |                                          |
|----------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| 1. Glucose + ATP $\longrightarrow$ Glucose 6-phosphate + ADP + H <sup>+</sup>                                                          | 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 <sup>+</sup>                                       | 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 <sup>+</sup> + P <sub>i</sub> $\rightleftharpoons$ 1,3-Bisphosphoglycerate + NADH + H <sup>+</sup> | 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 <sub>2</sub> O                                                      | Enolase                                  |
| 10. Phosphoenolpyruvate + ADP + H <sup>+</sup> $\longrightarrow$ Pyruvate + ATP                                                        | Pyruvate kinase                          |

Table 11.1 · The reactions and enzymes of glycolysis



## Two Phases of Glycolysis

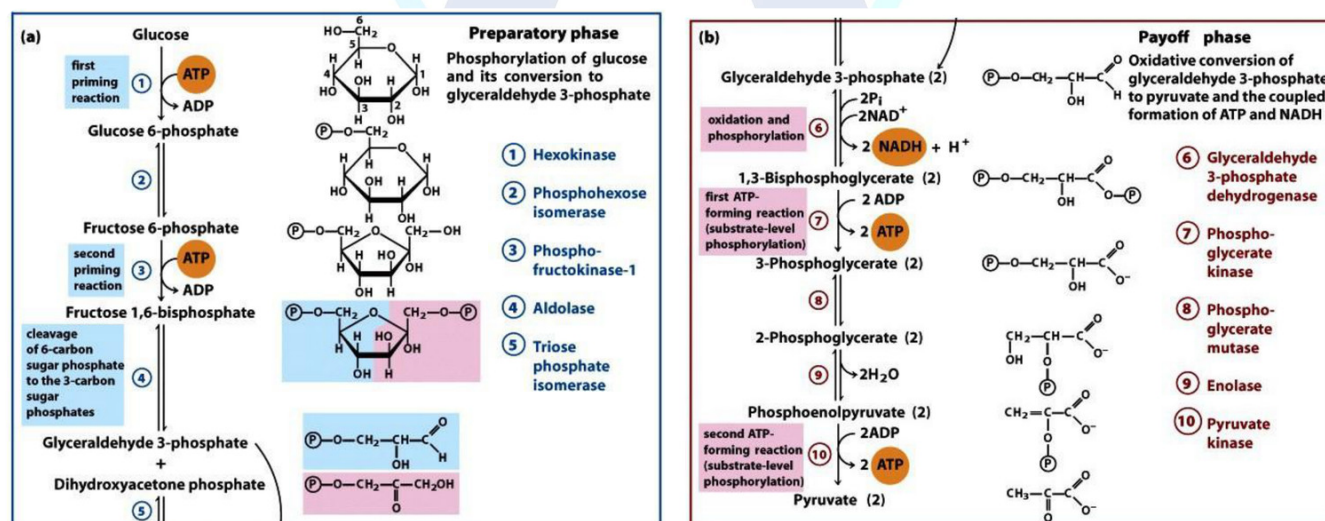


Figure 14-2  
 Lehninger Principles of Biochemistry, Fifth Edition  
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Figure 14-2 · (a) preparatory phase · (b) payoff phase · Lehninger Principles of Biochemistry

## THE TEN STEPS

## PART 2 · THE TEN STEPS



# Pathway Map — All Ten Steps at a Glance

Key:

ATP consumed

ATP produced

NADH formed

Metabolically irreversible

One of the four kinases



## HEXOSE STAGE

## PART 2 · THE TEN STEPS

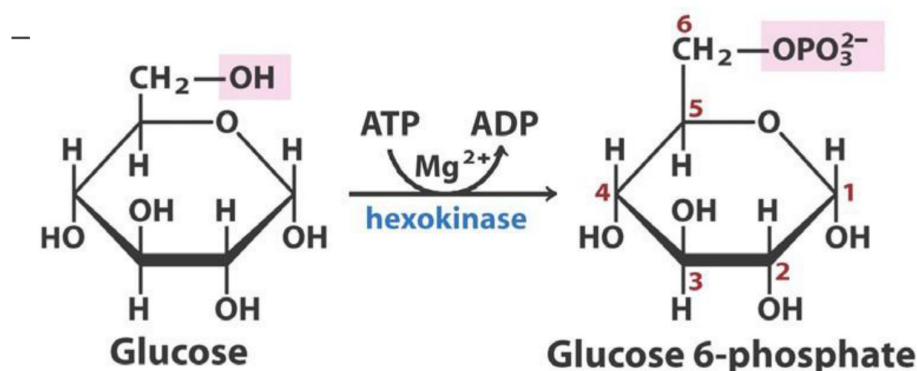
1

## Phosphorylation by Hexokinase

STEP 1 · ENERGY INVESTMENT

ATP → ADP

Irreversible



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

- > Transfers the **γ-phosphoryl of ATP** to the glucose **C-6 oxygen** to generate glucose 6-phosphate (G6P)
- > **Mechanism:** attack of the C-6 hydroxyl oxygen of glucose on the **γ-phosphorus of ATP<sup>2-</sup>**

## FOUR KINASES IN GLYCOLYSIS

1

Hexokinase

3

PFK-1

7

PGK

10

Pyruvate kinase

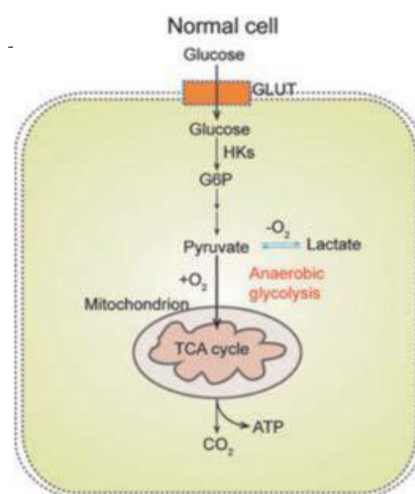
- All four kinases **require Mg<sup>2+</sup>** and have a **similar mechanism**.



## Why Phosphorylate Glucose?

## TRAPPING GLUCOSE IN THE CELL

When glucose enters the cells via glucose transporters, there is a chance for it to **leave the cell**. That is why glucose is phosphorylated by ATP to become **glucose 6-phosphate, which now bears a charge** — this **disqualifies it from leaving** through glucose transporters.



## HEXOSE STAGE

## PART 2 · THE TEN STEPS



## Properties of Hexokinases



### Broad substrate specificity

Hexokinases can phosphorylate **Glucose**

**Mannose**

**Fructose**



### Isozymes

**Multiple forms** of hexokinase occur in **mammalian tissues and yeast**.

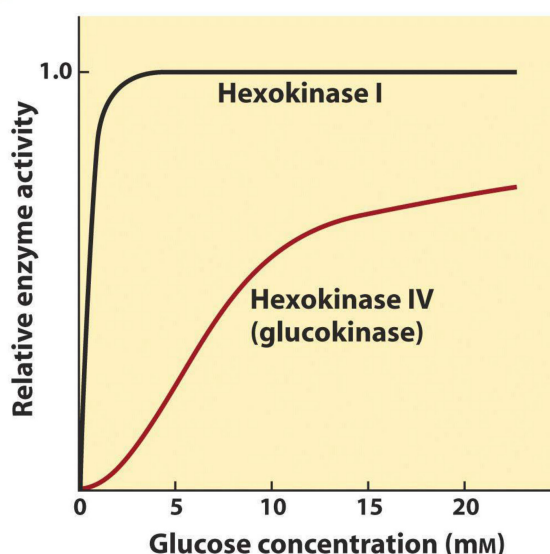


## Hexokinase vs. Glucokinase

| FEATURE          | HEXOKINASES I, II, III                                   | HEXOKINASE IV (GLUCOKINASE)                                            |
|------------------|----------------------------------------------------------|------------------------------------------------------------------------|
| $K_m$            | $\sim 10^{-6}$ to $10^{-4}$ M                            | $\sim 10^{-2}$ M                                                       |
| Active at        | Normal glucose concentrations                            | <b>Higher glucose levels</b>                                           |
| Inhibited by G6P | Yes — allosterically                                     | <b>No</b>                                                              |
| Found in         | Multiple forms (isozymes) in mammalian tissues and yeast | The <b>liver</b> — lets it respond to large increases in blood glucose |

### TISSUE-SPECIFIC ISOZYMES

With high glucose levels, glucokinase is active. Because glucokinase is **never saturated with glucose**, the liver can respond to large increases in blood glucose by phosphorylating it for entry into **glycolysis** or the **glycogen synthesis pathway**.



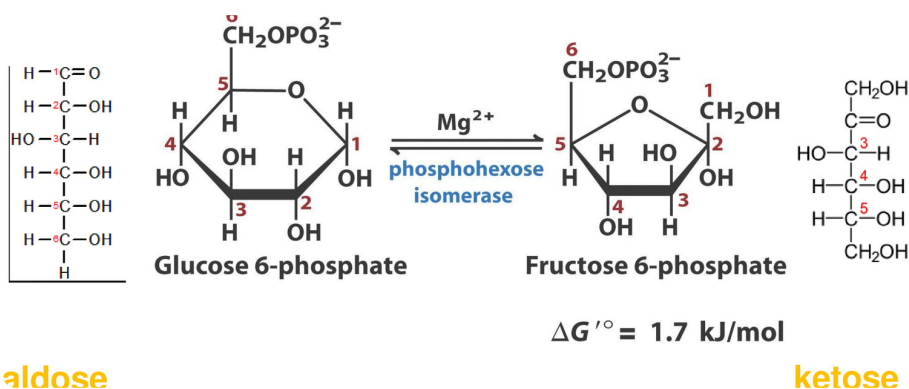
## HEXOSE STAGE

## PART 2 · THE TEN STEPS

2

## Conversion of G6P to F6P — Isomerization

STEP 2 · GLUCOSE 6-PHOSPHATE ISOMERASE



The enzyme is also known as **phosphoglucose isomerase (PGI)**.

- ◆ Converts G6P, an **aldose**, to F6P, a **ketose**
- ◆ Preferentially binds the  **$\alpha$ -anomer of G6P** (converts it to the open-chain form in the active site)
- ◆ Highly **stereospecific** for G6P and F6P
- ◆ The isomerase reaction is **near-equilibrium** in cells

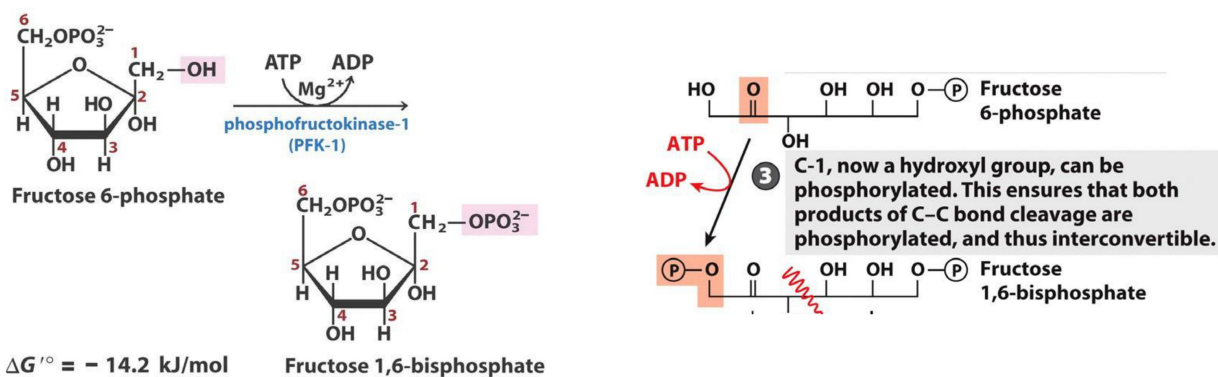
3

## Phosphorylation by Phosphofructokinase-1 (PFK-1)

STEP 3 · THE FIRST COMMITTED STEP

ATP → ADP

Irreversible



- > Transfers a phosphoryl group from ATP to the **C-1 hydroxyl group** of F6P to form **fructose 1,6-bisphosphate (F1,6BP)**
- > PFK-1 is **metabolically irreversible** and a **critical regulatory point** for glycolysis in most cells — the **first committed step**

☆ DR. ASMAA ADDITION

A second phosphofructokinase, **PFK-2**, synthesizes **fructose 2,6-bisphosphate (F2,6BP)**.

## HEXOSE STAGE

## PART 2 · THE TEN STEPS

## 4

## Cleavage by Aldolase

STEP 4 · A HEXOSE BECOMES TWO TRIOSES

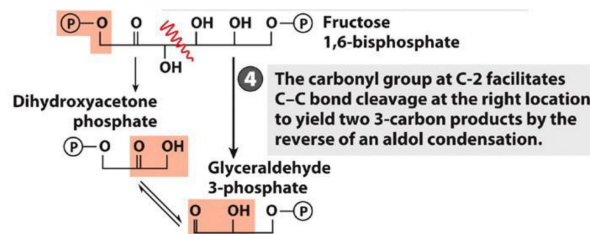
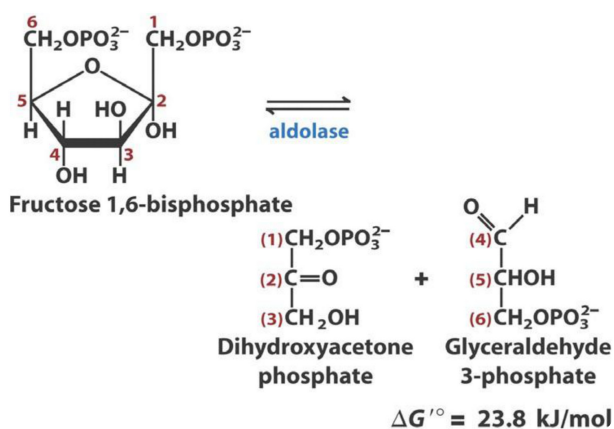


Figure 14-3 part 1  
Lehninger Principles of Biochemistry, Sixth Edition  
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- > Aldolase cleaves the hexose F1,6BP into **two triose phosphates**: GAP and DHAP
- > DHAP comes from **C-1 to C-3** of F1,6BP; GAP comes from **C-4 to C-6**
- > The reaction is **near-equilibrium** — not a control point

## TWO DISTINCT CLASSES OF ALDOLASES

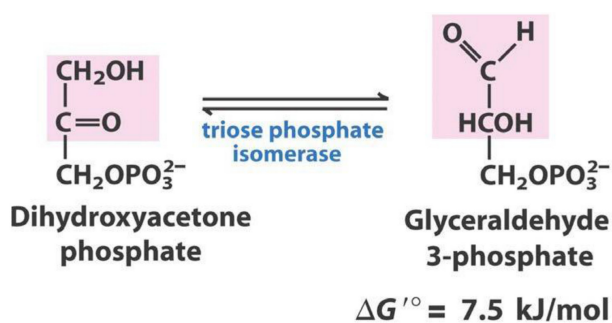
Class I — found in **plants and animals**Class II — more common in **bacteria, fungi, and protists**

Many species have both types of enzyme.

## 5

## Isomerization by Triose Phosphate Isomerase (TPI)

STEP 5 · ONLY GAP MOVES ON



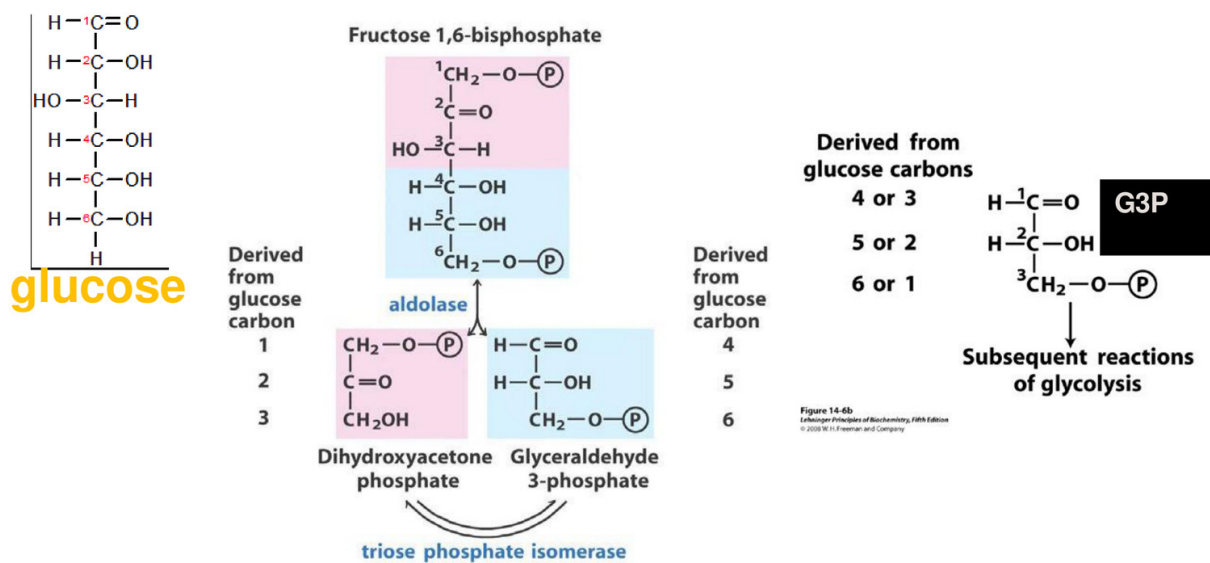
- > Of the two molecules produced by splitting F1,6BP, **only GAP is a substrate** for the next reaction
- > TPI converts **DHAP into GAP**
- > The reaction is **very fast (diffusion controlled)**, and only the **D-isomer** of GAP is formed

## HEXOSE STAGE

## PART 2 · THE TEN STEPS



## Keeping Track of Carbons



Radioisotopic tracer studies show where each carbon of glucose ends up:

**Glucose / F1,6BP**

**C1**

**C2**

**C3**

**C4**

**C5**

**C6**

↓ Aldolase

**DHAP**

**C1**

**C2**

**C3**

from C-1 to C-3

**GAP**

**C4**

**C5**

**C6**

from C-4 to C-6

↓ Triose phosphate isomerase (DHAP → GAP)

**ONE GAP MOLECULE**

GAP C1, C2, C3 come from glucose

**C4**

**C5**

**C6**

**SECOND GAP MOLECULE**

GAP C1, C2, C3 come from glucose

**C3**

**C2**

**C1**

## TRIOSE STAGE

## PART 2 · THE TEN STEPS



## The Second Phase of Glycolysis

## PAYOFF PHASE

The **second phase of glycolysis**, where **ATP and NADH are formed**.

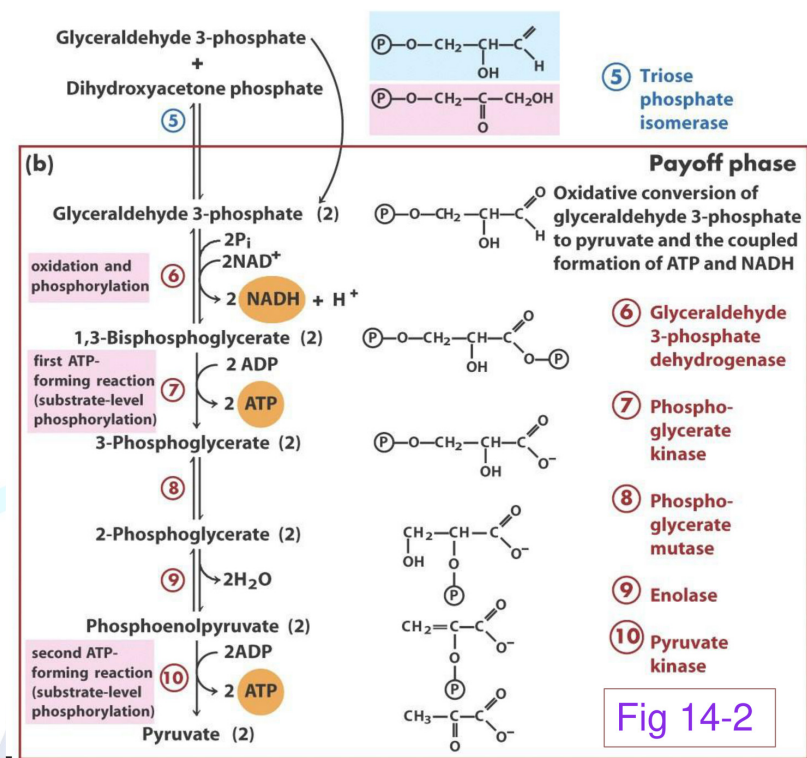
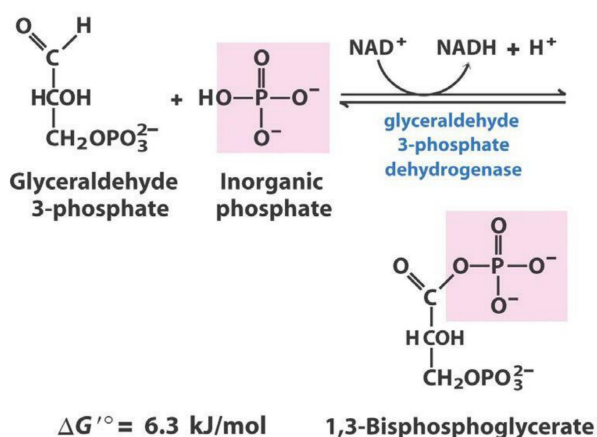


Figure 14-2 (b) · payoff phase

6

## Oxidation by Glyceraldehyde 3-Phosphate Dehydrogenase (GAPDH)

STEP 6 · NADH IS FORMED

NAD<sup>+</sup> → NADH

- > Converts GAP to **1,3-bisphosphoglycerate (1,3BPG)**
- > A molecule of **NAD<sup>+</sup> is reduced to NADH**
- > Oxidation of the aldehyde group of GAP proceeds with a **large negative free-energy change**

## REDOX

An oxidation–reduction reaction: the **oxidation of GAP is coupled to the reduction of NAD to NADH**.

## TRIOSE STAGE

## PART 2 · THE TEN STEPS

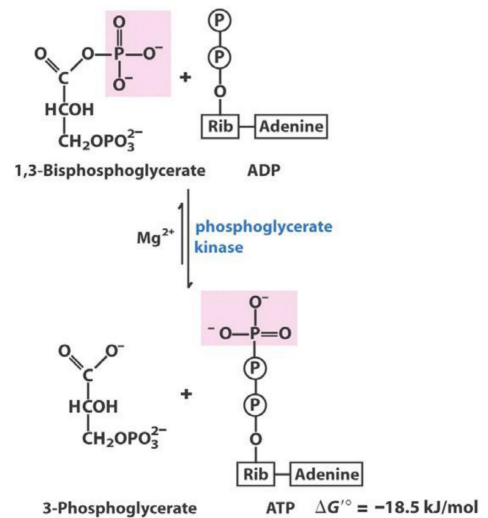
7

## Phosphorylation by Phosphoglycerate Kinase (PGK)

STEP 7 · THE FIRST ATP-GENERATING STEP

ADP → ATP

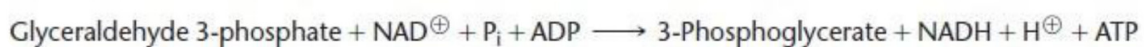
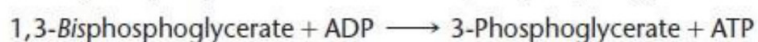
- The **C-1 phosphoryl group** of 1,3BPG is transferred to ADP to form ATP; the remaining energy is conserved as **reducing equivalents (NADH)**
- The NADH formed by GAPDH is reoxidized — for example by the **membrane-associated electron transport chain**



100

## Steps 6 and 7 Are Coupled

- ◆ Transfer of a phosphoryl group from the **energy-rich mixed anhydride 1,3BPG** to ADP yields **ATP and 3-phosphoglycerate (3PG)**
- ◆ **Substrate-level phosphorylation** — steps 6 and 7 couple **oxidation of an aldehyde to a carboxylic acid** with the phosphorylation of ADP to ATP



## KEY POINT

This reaction is the **first ATP-generating step** of glycolysis.

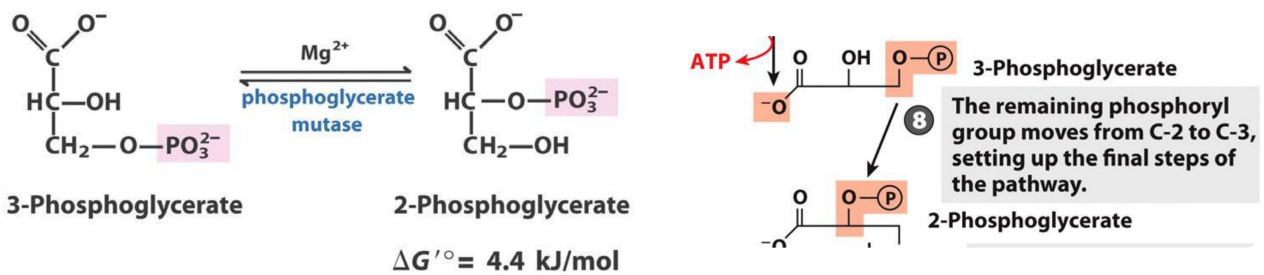
## TRIOSE STAGE

## PART 2 · THE TEN STEPS

8

## Shift of the Phosphoryl Group by Phosphoglycerate Mutase

STEP 8 · 3PG → 2PG

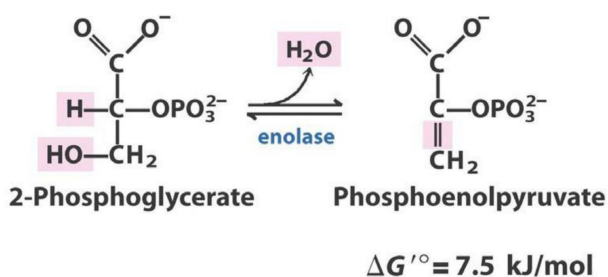


- ◆ Transfers a phosphoryl group from **one part of a substrate molecule to another**
- ◆ Occurs **without input of ATP energy**
- ◆ The mechanism requires **2 phosphoryl-group transfer steps**

9

## Dehydration by Enolase

STEP 9 · 2PG → PEP



- > **2-Phosphoglycerate (2PG)** is dehydrated to **phosphoenolpyruvate (PEP)**
- > Elimination of water from **C-2 and C-3** yields the enol-phosphate PEP
- > PEP has a **very high phosphoryl group transfer potential** because it exists in its unstable enol form

## ENOLASE REQUIRES MG — TWO MAGNESIUM IONS PARTICIPATE

- A **"conformational"** ion binds to the carboxylate group of the substrate
- A **"catalytic"** ion participates in the dehydration reaction

## TRIOSE STAGE

## PART 2 · THE TEN STEPS

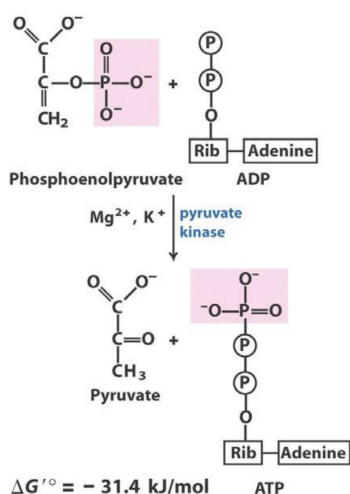
10

## Substrate-Level Phosphorylation by Pyruvate Kinase (PK)

STEP 10 · PEP → PYRUVATE

ADP → ATP

Irreversible

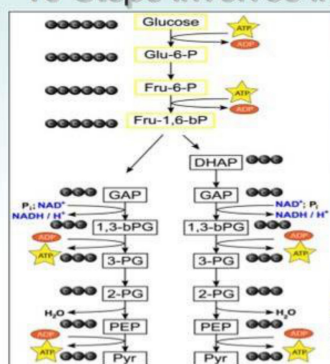


- > Catalyzes a **substrate-level phosphorylation**
- > A **metabolically irreversible** reaction
- > The pyruvate kinase gene can be regulated by **various hormones and nutrients**
- > Because PK is regulated, **PEP is maintained at a high enough level** to drive ATP formation during glycolysis



## Summary — Energy Investment, Cleavage &amp; Energy Harvest

## 10 Steps involves in Glycolysis



10 steps involved in glycolysis

Energy investment

Cleavage

Energy harvest

## ENERGY LEDGER PER MOLECULE OF GLUCOSE

| STEP            | ENZYME          | ATP    | NADH    |
|-----------------|-----------------|--------|---------|
| 1               | Hexokinase      | -1     | —       |
| 3               | PFK-1           | -1     | —       |
| 6 (×2)          | GAPDH           | —      | +2      |
| 7 (×2)          | PGK             | +2     | —       |
| 10 (×2)         | Pyruvate kinase | +2     | —       |
| Net per glucose |                 | +2 ATP | +2 NADH |

-2

ATP consumed — hexose stage

+4

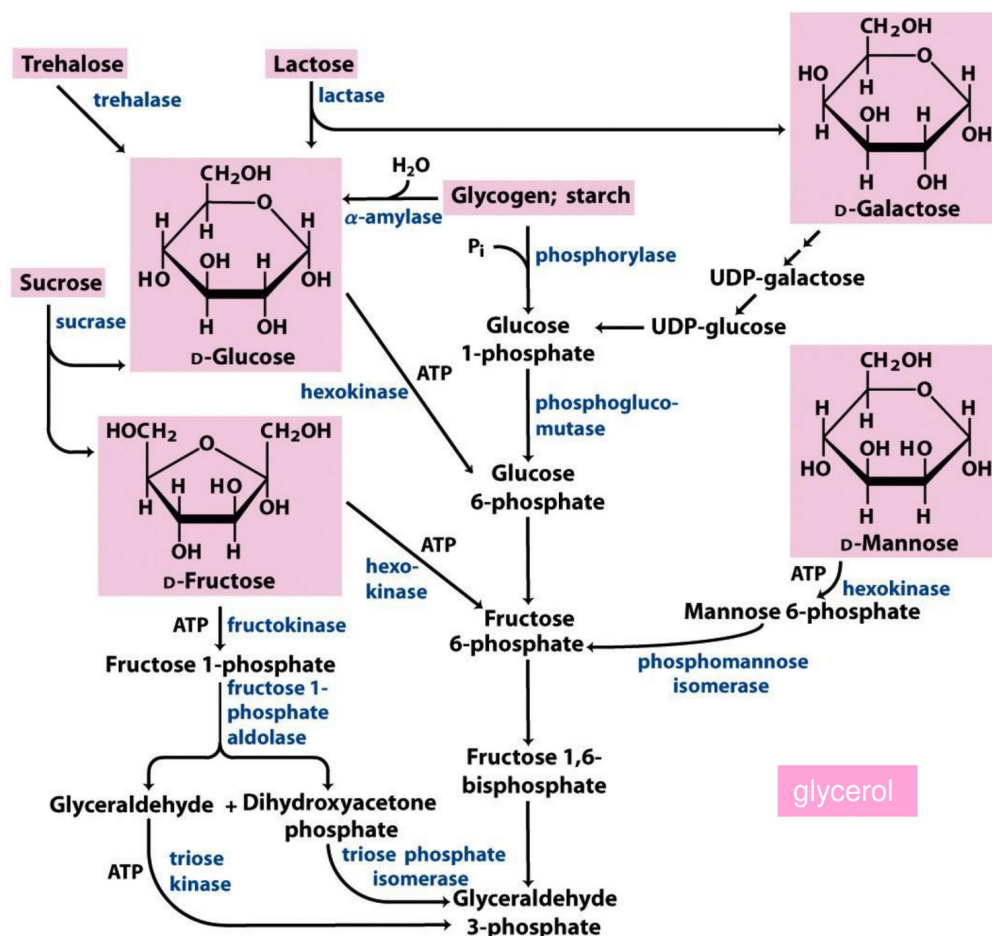
ATP produced — triose stage

+2

net ATP per glucose



## Feeder Pathways



**Figure 14-10**  
 Lehninger Principles of Biochemistry, Fifth Edition  
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Figure 14-10 · Lehninger Principles of Biochemistry



### All carbohydrates

All carbohydrates enter glycolysis.



### In muscle

Entry is often **via hexokinase**.



### Glycerol

Highlighted on the figure as a feeder into glycolysis.

## THE FATE OF PYRUVATE

## PART 3 · FEEDERS &amp; PYRUVATE



# The Fate of Pyruvate



## Aerobic conditions

MOLECULAR OXYGEN AVAILABLE

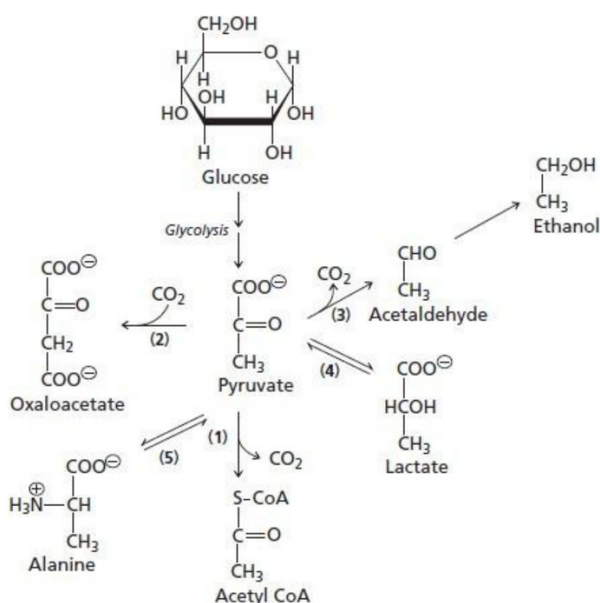
NADH can be oxidized by the **membrane-associated electron transport system**, which requires **molecular oxygen**.



## Anaerobic conditions

NO OXYGEN

The synthesis of **ethanol or lactate** consumes NADH and **regenerates the NAD<sup>+</sup>** essential for continued glycolysis.



◀ Figure 11.9

**Five major fates of pyruvate:** (1) Under aerobic conditions, pyruvate is oxidized to the acetyl group of acetyl CoA, which can enter the citric acid cycle for further oxidation. (2) Pyruvate can be converted to oxaloacetate, which can be a precursor in gluconeogenesis. (3) Under anaerobic conditions, certain microorganisms ferment glucose to ethanol via pyruvate. (4) Glucose undergoes anaerobic glycolysis to lactate in vigorously exercising muscles, red blood cells, and certain other cells. (5) Pyruvate is converted to alanine.



# Metabolism of Pyruvate to Ethanol

In **yeast** — the anaerobic production of **beer and wine**. Two reactions are required:



Pyruvate

&gt;



Acetaldehyde

(1) pyruvate carboxylase

&gt;



Ethanol

(2) alcohol dehydrogenase

## THE FATE OF PYRUVATE

## PART 3 · FEEDERS &amp; PYRUVATE



## Fermentation

### FERMENTATION

Electrons from glycolysis — in the form of **NADH** — are passed to an **organic molecule such as ethanol**, instead of to the membrane-associated electron transport chain and ultimately **oxygen** (respiration).

The sum of the glycolytic reactions and the conversion of pyruvate to ethanol is:



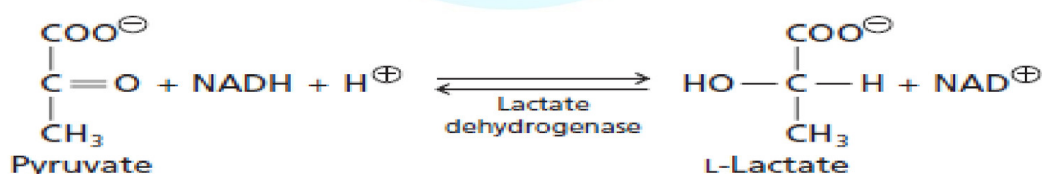
### KEY CONCEPT

In the absence of oxygen, eukaryotes have to **give up the net gain of 2 NADH** molecules in order to make lactate or ethanol.



## Reduction of Pyruvate to Lactate

- > Muscles lack **pyruvate dehydrogenase** and **cannot produce ethanol** from pyruvate
- > Common in **anaerobic bacteria** and also in **mammals**
- > Muscle **lactate dehydrogenase** converts pyruvate to lactate in a **reversible reaction**
- > **Regenerates NAD<sup>+</sup>** for use by GAPDH in glycolysis



## Recycling of Lactate



### Skeletal muscle

lactate formed during exercise



### Transport

to the liver



### Liver

lactate dehydrogenase reconverts lactate to pyruvate

### CLINICAL

**Lactic acidosis** can result from insufficient oxygen — an increase in lactic acid and a decrease in blood pH.

## ENERGY &amp; REGULATION

## PART 4 · REGULATION



## Overall Reactions: Glucose Degradation to Lactate



### 2 ATP

per molecule of glucose consumed

### No O<sub>2</sub>

oxygen is not required

### Either end

same yield whether ethanol or lactate

- Regardless of the final product — ethanol or lactate — glycolysis generates **two ATP per glucose** without oxygen. This is essential for **anaerobic organisms** and for **some specialized cells** in multicellular organisms.



## Free-Energy Changes in Glycolysis

Actual free-energy changes ( $\Delta G$ ) are **large only for three steps**:

1

LARGE  $\Delta G$ 

2

 $\approx 0$ 

3

LARGE  $\Delta G$ 

4

 $\approx 0$ 

5

 $\approx 0$ 

6

 $\approx 0$ 

7

 $\approx 0$ 

8

 $\approx 0$ 

9

 $\approx 0$ 

10

LARGE  $\Delta G$ 

### Hexokinase · step 1

Large  $\Delta G$  — metabolically irreversible and regulated.



### Phosphofructokinase · step 3

Large  $\Delta G$  — metabolically irreversible and regulated.



### Pyruvate kinase · step 10

Large  $\Delta G$  — metabolically irreversible and regulated.

ALL OTHER STEPS

$\Delta G$  is **close to zero** — they are near-equilibrium in cells.

## ENERGY &amp; REGULATION

## PART 4 · REGULATION



## Regulation of Glycolysis



**When ATP is needed**  
GLYCOLYSIS IS ACTIVATED

AMP and fructose 2,6-bisphosphate (F2,6BP) relieve the inhibition of PFK-1 by ATP.



**When ATP levels are sufficient**  
GLYCOLYSIS ACTIVITY DECREASES

- > PFK-1 is inhibited by **ATP and citrate**
- > Hexokinase is inhibited by **excess glucose 6-phosphate**



## Regulation of Hexose Transporters

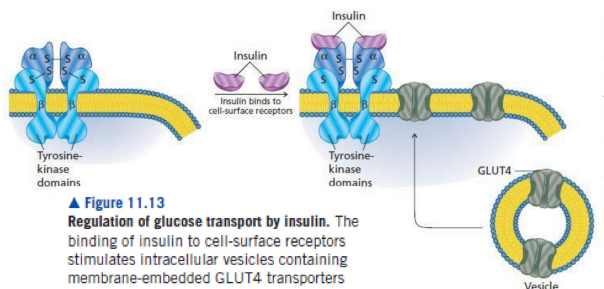
- The **first potential step** for regulating glycolysis is the **transport of glucose into the cell**. Glucose enters mammalian cells by **passive transport** down a concentration gradient from blood to cells.

| TRANSPORTER   | WHERE                                 | ROLE                                                                                                     |
|---------------|---------------------------------------|----------------------------------------------------------------------------------------------------------|
| SGLT1         | Intestinal and kidney cells           | Na <sup>+</sup> -dependent cotransport — absorbs <b>dietary</b> and <b>urinary</b> glucose, respectively |
| GLUT1 & GLUT3 | Most tissues                          | Basal level of glucose transport in the <b>absence of insulin</b>                                        |
| GLUT2         | Liver                                 | Transports glucose <b>into and out of</b> the liver                                                      |
| GLUT4         | Skeletal and heart muscle, adipocytes | <b>Insulin</b> stimulates high rates of glucose uptake                                                   |
| GLUT5         | Small intestine                       | Transports <b>fructose</b>                                                                               |

- Other mammalian cells contain transporters from the **GLUT family** of passive hexose transporters — each of its six members has **unique properties** suited to its tissue.



## Regulation of Glucose Transport by Insulin



- Because GLUT4 is found at high levels only in **striated muscle and adipose tissue**, insulin-regulated glucose uptake **occurs only in these tissues**.

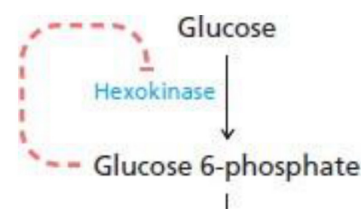
## ENERGY &amp; REGULATION

## PART 4 · REGULATION



## Regulation of Hexokinase

- The hexokinase reaction is **metabolically irreversible**
- At physiological concentrations, the product **G6P allosterically inhibits** hexokinase isozymes **I, II, and III** — **but not glucokinase**
- G6P levels increase when glycolysis is **inhibited further along** the pathway



## COORDINATION

Inhibition of hexokinases I, II and III by G6P **coordinates hexokinase activity** with the subsequent enzymes of glycolysis.



### Glucokinase

Forms G6P in the **liver** (for glycogen synthesis) when glucose is abundant; activity is modulated by **fructose phosphates and a regulatory protein**.



## Box 11.5 — Glucose 6-Phosphate Has a Pivotal Metabolic Role in the Liver

### BOX 11.5 GLUCOSE 6-PHOSPHATE HAS A PIVOTAL METABOLIC ROLE IN THE LIVER

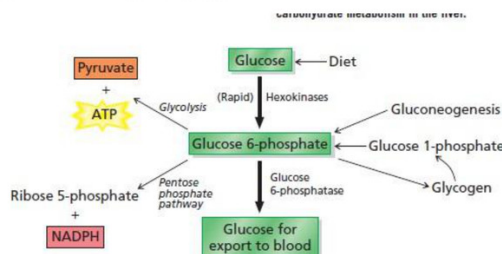
Glucose 6-phosphate is an initial substrate for several metabolic pathways (figure below). We have already seen that it is the initial intermediate in glycolysis. Glucose 6-phosphate is formed rapidly in liver cells from dietary glucose or newly synthesized glucose (from gluconeogenesis in liver cells; Section 12.1).

The principal use of liver glucose 6-phosphate is to maintain a constant concentration of blood glucose. Glucose 6-phosphatase is the enzyme responsible for catalyzing hydrolysis of glucose 6-phosphate to glucose. (This reaction is also the last step in gluconeogenesis.)

Glucose 6-phosphate that is not required for blood glucose is stored as liver glycogen (Section 12.6). Glycogen is

subsequently degraded when a supply of glucose is needed. Hormones regulate both the synthesis and degradation of glycogen.

In addition to using it for balancing the blood glucose concentration, the liver metabolizes glucose 6-phosphate by the pentose phosphate pathway (Section 12.5) to produce ribose 5-phosphate (for nucleotides) and NADPH (for synthesis of fatty acids). We have seen in this chapter that glucose 6-phosphate can also enter the glycolytic pathway, where it is converted initially to pyruvate, which leads to another major metabolite—acetyl CoA.



## ENERGY &amp; REGULATION

## PART 4 · REGULATION

## Regulation of Phosphofructokinase-1 (PFK-1)



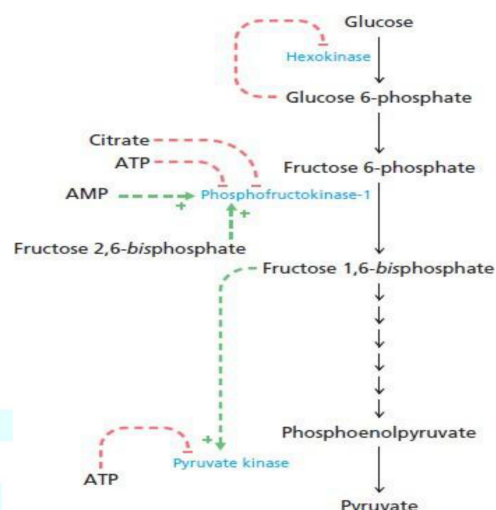
### Inhibitors

- > **ATP** — both a substrate and an allosteric inhibitor of PFK-1
- > **Citrate** — a citric acid cycle intermediate; elevated citrate means the cycle is blocked, so **further pyruvate production would be pointless**



### Activators

- > **AMP** in mammals — acts by **relieving the inhibition caused by ATP**
- > **ADP** activates the bacterial enzyme

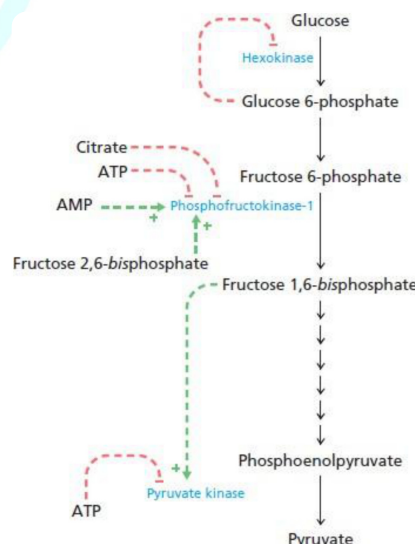


## Regulation of Pyruvate Kinase

- ◆ **Four PK isozymes** exist in mammalian tissues
- ◆ PK is **allosterically activated by F1,6BP** and **inhibited by ATP**
- ◆ Liver PK activity **decreases on starvation** and **increases** on a diet high in carbohydrate
- ◆ **Glucagon** stimulates protein kinase A, which phosphorylates PK into a **less active form** (liver and intestinal cells)

### FEED-FORWARD

Activation of PK by F1,6BP is an example of **feed-forward activation**.





## Review Questions

☆ DR. ASMAA ADDITION

**1. Which molecule acts as an allosteric inhibitor of phosphofructokinase-1 (PFK-1), reducing the rate of glycolysis when energy is abundant?**

- a) AMP
- b) ADP
- c) ATP
- d) Fructose-2,6-bisphosphate

**2. Feedback inhibition typically occurs when a metabolic pathway is regulated by:**

- a) The initial substrate
- b) The intermediate products
- c) The end product of the pathway
- d) A coenzyme involved in the process

## GLYCOLYSIS

## SUMMARY



## To Summarise...

## PATHWAY 10 steps

## Glycolysis

- Glucose → 2 pyruvate in the cytosol
- Hexose stage -2 ATP; triose stage +4 ATP
- Net: 2 ATP + 2 NADH per glucose

## KINASES 1 · 3 · 7 · 10

## Kinases &amp; control points

- All four kinases need  $Mg^{2+}$
- Steps 1, 3, 10: large  $\Delta G$ , irreversible
- PFK-1 is the first committed step

## SPLIT DHAP + GAP

## Cleavage

- Aldolase: F1,6BP → DHAP + GAP
- TPI converts DHAP to GAP
- Every triose step runs twice per glucose

## HARVEST ATP + NADH

## Energy harvest

- GAPDH:  $NAD^+ \rightarrow NADH$
- PGK & PK: substrate-level phosphorylation
- PEP has very high transfer potential

PYRUVATE O<sub>2</sub> ?

## Fate of pyruvate

- Aerobic: NADH via the electron transport system
- Anaerobic: ethanol (yeast) or lactate (muscle)
- Both regenerate  $NAD^+$ ; lactate recycled in liver

## CONTROL PFK-1

## Regulation

- HK I-III inhibited by G6P, not glucokinase
- PFK-1: - ATP, citrate; + AMP, F2,6BP
- PK: + F1,6BP (feed-forward); - ATP, glucagon

## GLYCOLYSIS IN ONE MINUTE

## Invest

2 ATP phosphorylate  
glucose & F6P

## Split

F1,6BP → two trioses  
(GAP)

## Harvest

4 ATP + 2 NADH from 2  
GAP

## Pyruvate

aerobic: acetyl CoA ·  
anaerobic: ethanol or  
lactate