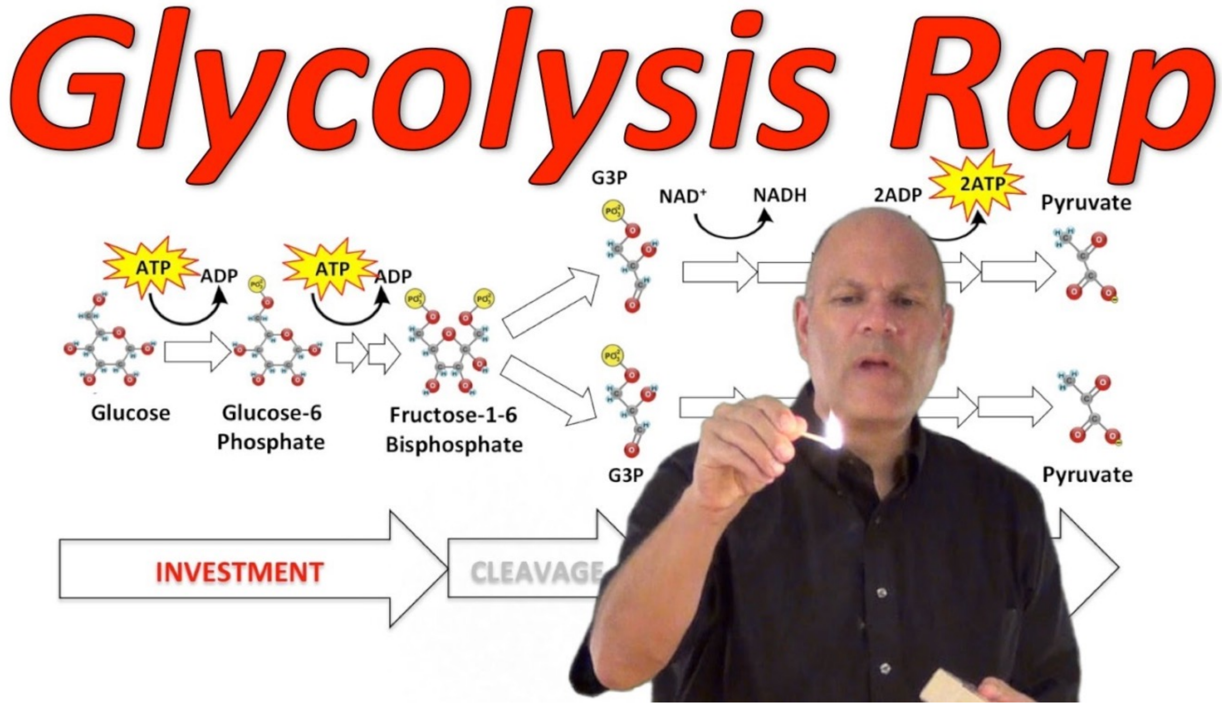
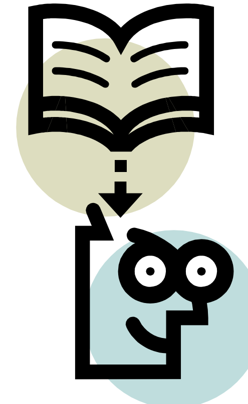


Lecture 9

Glycolysis

https://www.youtube.com/watch?v=EfGlznwfu9U

The Organic Mechanisms of the Coenzymes



Lecture Outline:

- Glycolysis Is an Energy-Conversion Pathway
- NAD^+ and Its Regeneration
- Fructose and Galactose Interconversion
- The Glycolytic Pathway Is Tightly Controlled
- Metabolism in Context: Glycolysis Helps Pancreatic Beta Cells Sense Glucose
- Glucose Can Be Synthesized from Non carbohydrate Precursors
- Gluconeogenesis and Glycolysis Are Reciprocally Regulated
- Precursors Formed by Muscle Are Used by Other Organs

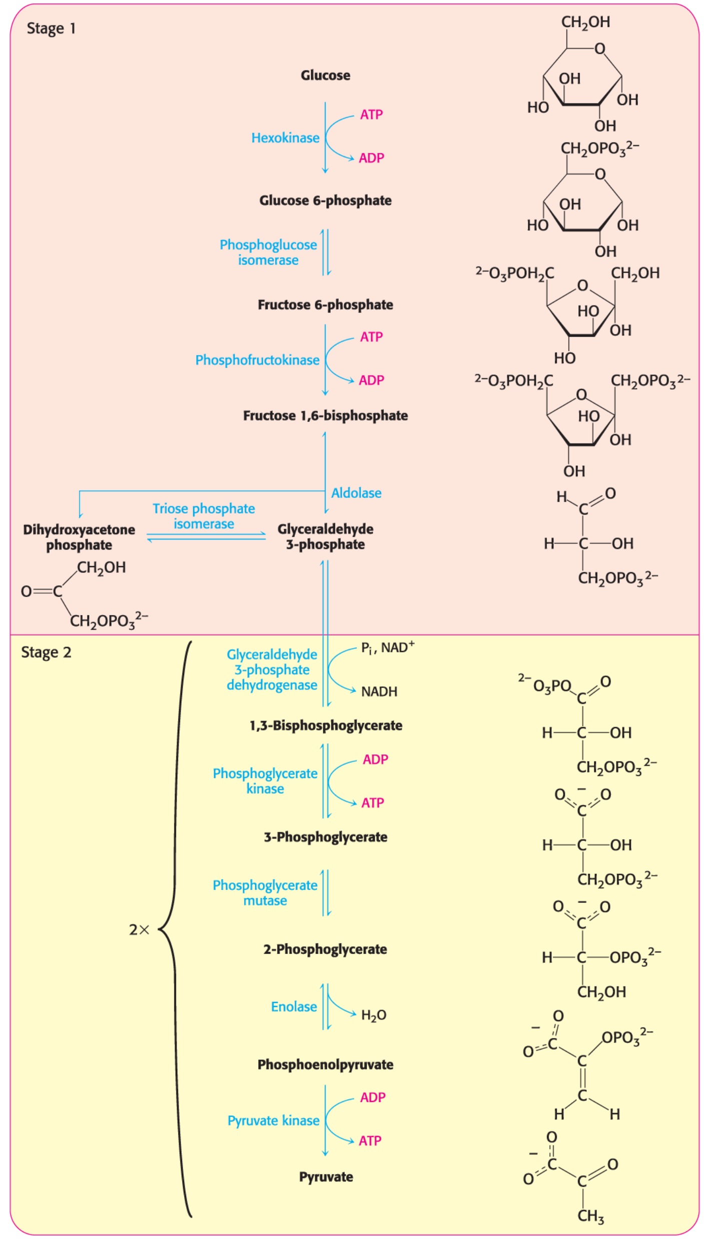
Readings:

Tymochko, Berg, Stryer,
Biochemistry, 2nd Edition,
Ch. 16, 17, pp. 271 – 313
3rd Ed., Ch. 16,17, pp. 281 - 324
4th Ed., Ch. 16,17, pp. 311 - 353

Glycolysis Is an Energy-Conversion Pathway

Glycolysis converts one molecule of glucose to 2 molecules of pyruvate with the generation of **2** molecules of **ATP**.

- anaerobic process (this already exists before substantial amounts of O2 accumulated in the atmosphere
- Common to all cells; pyruvate ➜ lactic acid, ethanol, others…



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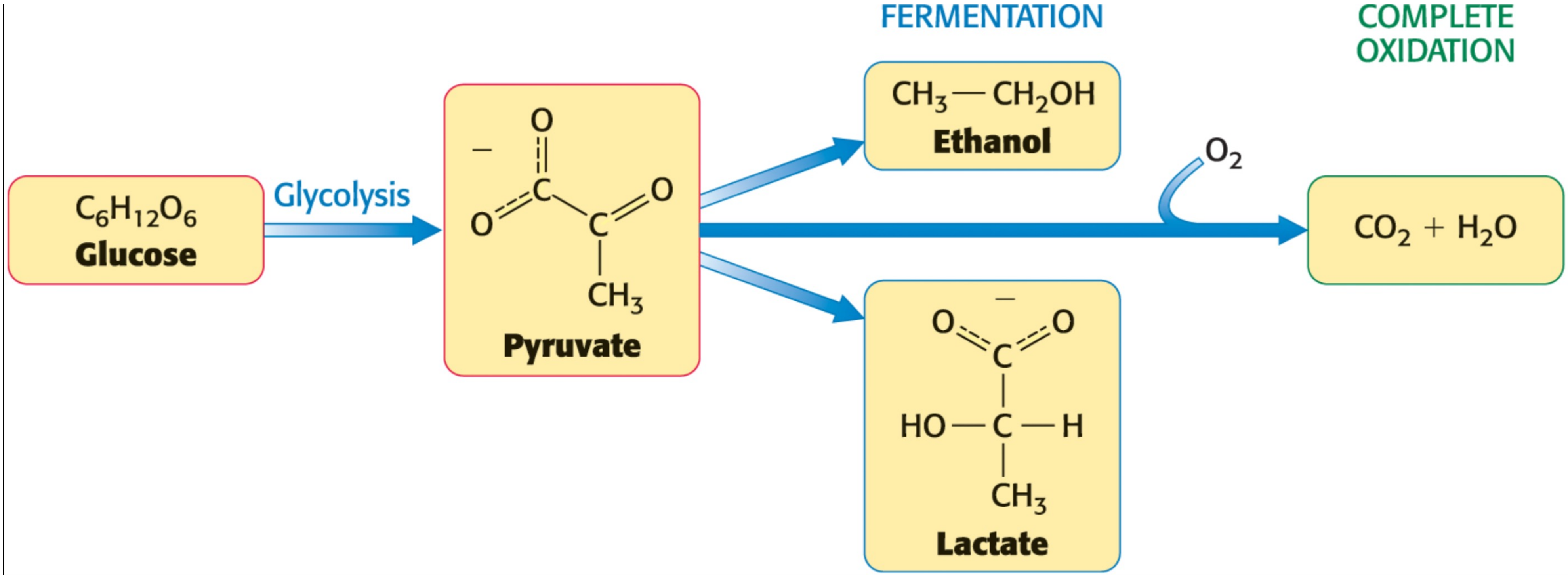
Glycolysis is a 10-enzyme catalyzed reaction

Step	Reaction	Enzyme	Reaction type	$\Delta G^{\circ\prime}$ in kJ mol^{-1} (kcal mol^{-1})	ΔG in kJ mol^{-1} (kcal mol^{-1})
1	Glucose + ATP $\rightarrow$ glucose 6-phosphate + ADP + H^+	Hexokinase	Phosphoryl transfer	–16.7 (–4.0)	–33.5 (–8.0)
2	Glucose 6-phosphate É fructose 6-phosphate	Phosphoglucose isomerase	Isomerization	+1.7 (+0.4)	–2.5 (–0.6)
3	Fructose 6-phosphate + ATP $\rightarrow$ fructose 1, 6-bisphosphate + ADP + H^+	Phosphofructokinase	Phosphoryl transfer	–14.2 (–3.4)	–22.2 (–5.3)
4	Fructose 1, 6-bisphosphate É dihydroxyacetone phosphate + glyceraldehyde 3-phosphate	Aldolase	Aldol cleavage	+23.8 (+5.7)	–1.3 (–0.3)
5	Dihydroxyacetone phosphate É glyceraldehyde 3-phosphate	Triose phosphate isomerase	Isomerization	+7.5 (+1.8)	+2.5 (+0.6)
6	Glyceraldehyde 3-phosphate + P_i + NAD^+ É 1, 3-bisphosphoglycerate + NADH + H^+	Glyceraldehyde 3-phosphate dehydrogenase	Phosphorylation coupled to oxidation	+6.3 (+1.5)	–1.7 (–0.4)
7	1,3-Bisphosphoglycerate + ADP É 3-phosphoglycerate + ATP	Phosphoglycerate kinase	Phosphoryl transfer	–18.8 (–4.5)	+1.3 (+0.3)
8	3-Phosphoglycerate É 2-phosphoglycerate	Phosphoglycerate mutase	Phosphoryl shift	+4.6 (+1.1)	+0.8 (+0.2)
9	2-Phosphoglycerate É phosphoenolpyruvate + H_2O	Enolase	Dehydration	+1.7 (+0.4)	–3.3 (–0.8)
10	Phosphoenolpyruvate + ADP + H^+ $\rightarrow$ pyruvate + ATP	Pyruvate kinase	Phosphoryl transfer	–31.4 (–7.5)	–16.7 (–4.0)

Glucose can be metabolized to different products depending on the organism and presence/absence of O2



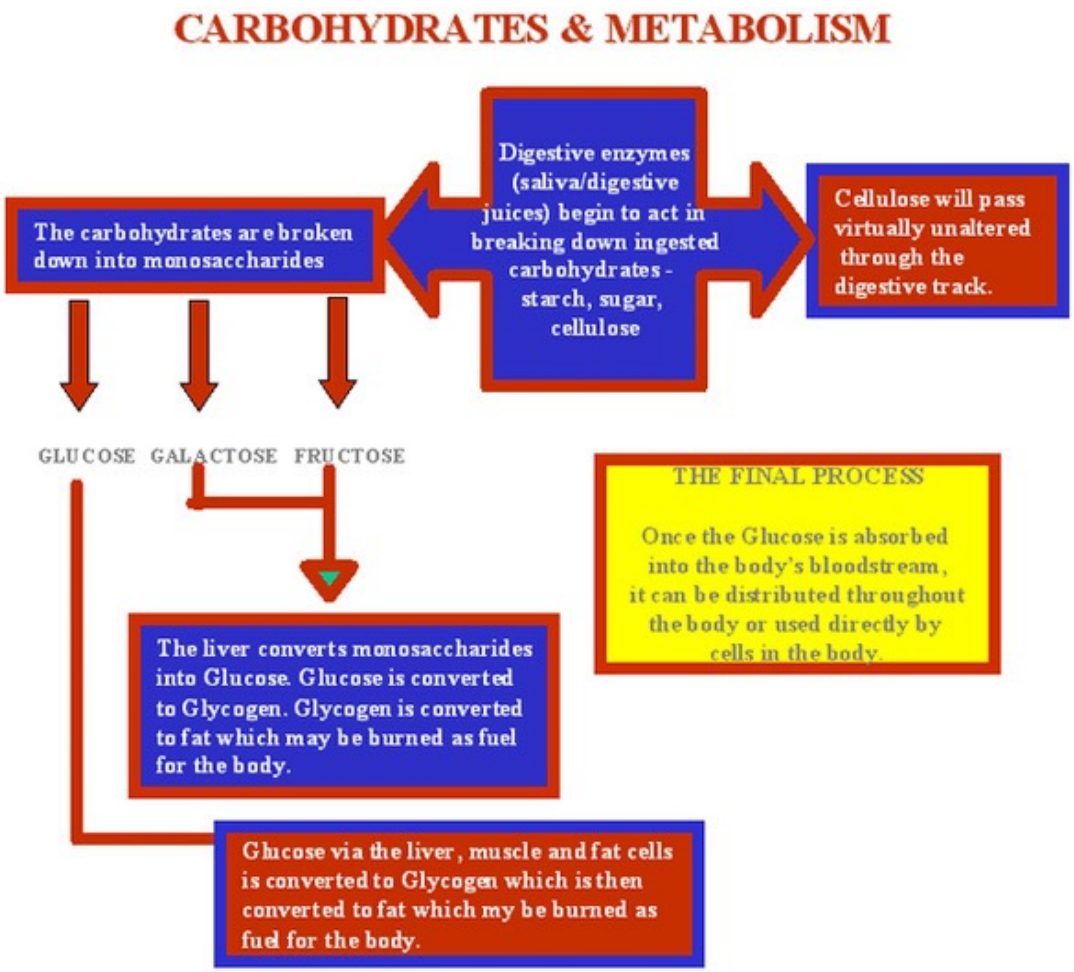
Why Glucose?

Why is glucose such a prominent fuel in all life forms?

1. Glucose may have been available for primitive biochemical systems because it can form under prebiotic conditions.

2. Glucose is the most stable hexose. (-OH in equatorial positions avoiding steric clashes)

3. Glucose has a low tendency to non-enzymatically glycosylate proteins (stability of the rings).



A Family of Transporters Enables Glucose to Enter and Leave Animal Cells

TABLE 16.1 Family of glucose transporters

Name	Tissue location	K_M	Comments
GLUT1	All mammalian tissues	1 mM	Basal glucose uptake
GLUT2	Liver and pancreatic β cells	15–20 mM	In the pancreas, plays a role in the regulation of insulin; in the liver, removes excess glucose from the blood
GLUT3	All mammalian tissues	1 mM	Basal glucose uptake
GLUT4	Muscle and fat cells	5 mM	Amount in muscle plasma membrane increases with endurance training
GLUT5	Small intestine	15 mM	Primarily a fructose transporter

- GLUT transporters (GLUT1 to GLUT5) help move glucose into animal cells.
- Each GLUT has a specific role in glucose uptake.
- GLUT1 and GLUT3 are found in most cells and handle basic glucose transport.

- Like enzymes, transporters have K_m values, which indicate how much glucose is needed for half-maximal transport.
- GLUT1 and GLUT3 have a K_m of ~1 mM, much lower than normal blood glucose levels (4–8 mM).
- Since blood glucose is always higher than their K_m, GLUT1 and GLUT3 work at full speed, ensuring a constant glucose supply.

Glycolysis Is an Energy-Conversion Pathway

Glycolysis can be thought of as occurring in 2 stages:

1. Stage 1 traps glucose in the cell and modifies it so that it can be cleaved into a pair of phosphorylated 3-carbon compounds.

- Dihydroxyacetone phosphate and GAP are readily interconvertible

- No ATP is generated in this phase.

Trapping and Preparation Phase

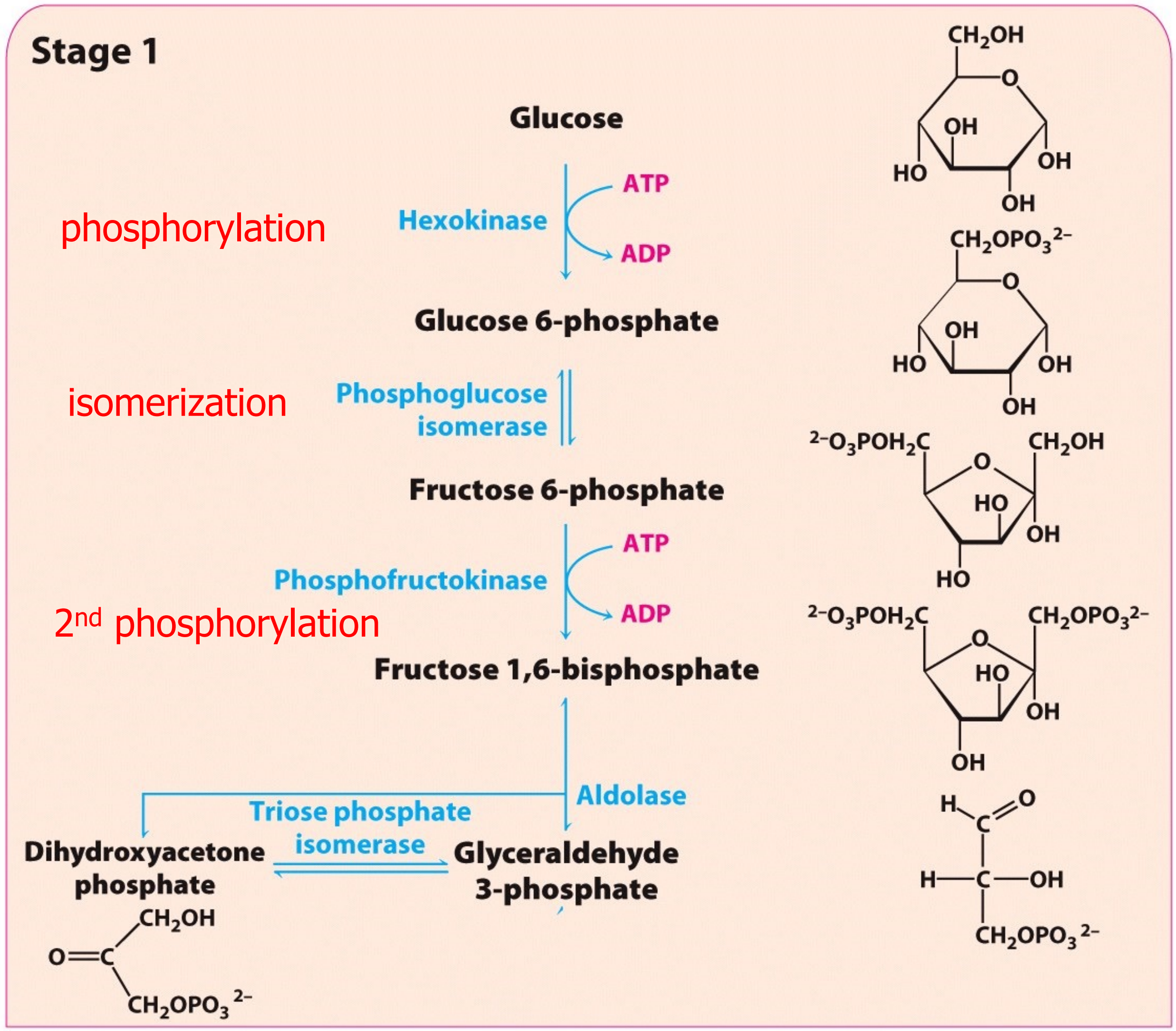
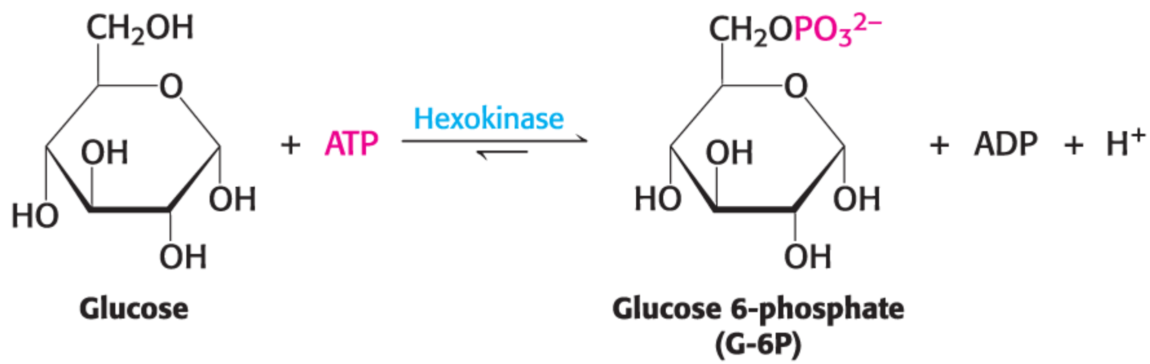


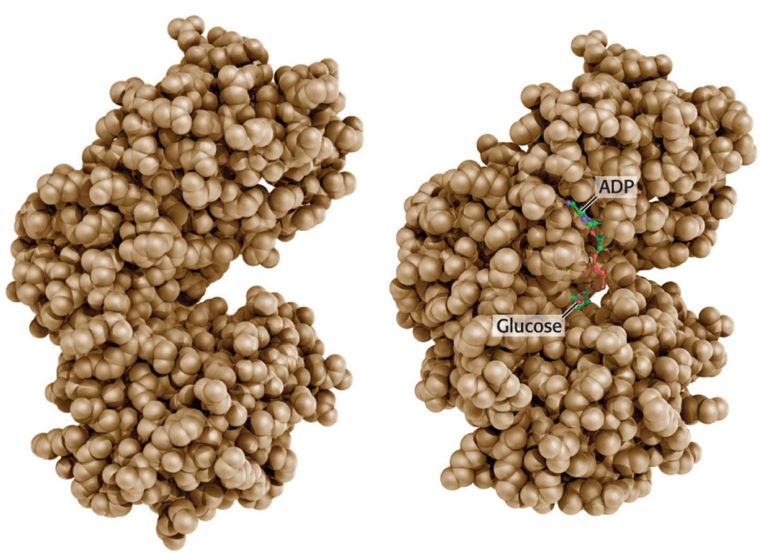
Figure 16.1 part 1
Biochemistry: A Short Course, Second Edition

Hexokinase traps glucose in the cell and begins glycolysis

- Upon entering the cell through a specific transport protein, glucose is phosphorylated at the expense of ATP to form glucose 6-phosphate.
- Hexokinase, which requires Mg^{2+} or Mn^{2+} as a cofactor, catalyzes the reaction.



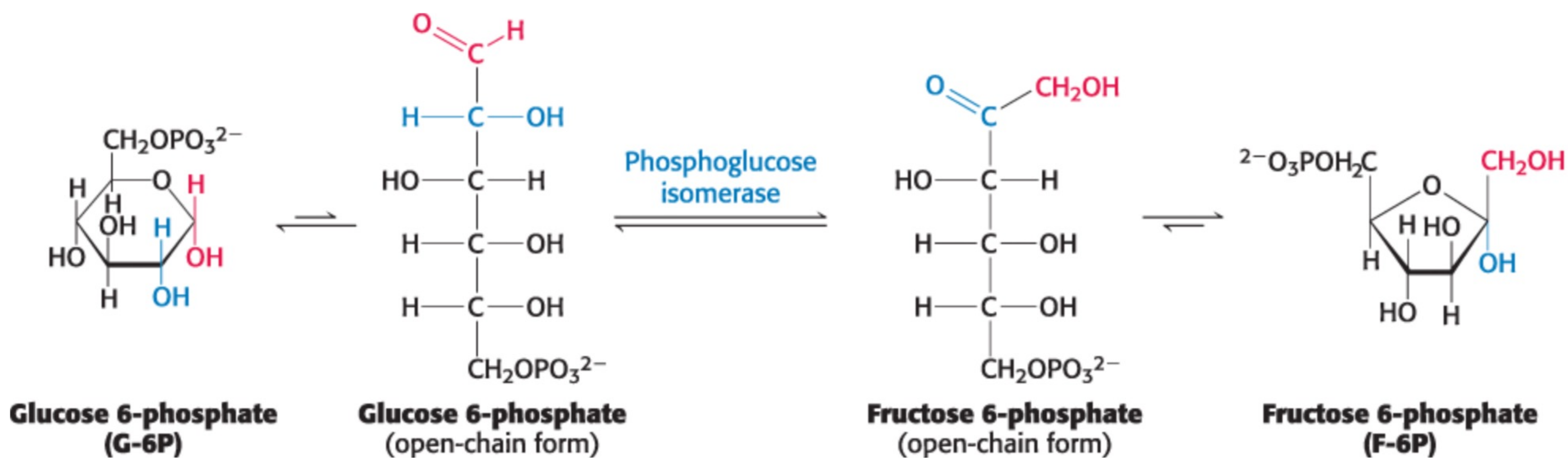
- Glucose 6-phosphate cannot exit the cell because glucose transporters do not recognize it.
- Phosphorylation helps glucose break down into smaller, high-energy molecules (i.e., high phosphoryl transfer potential).



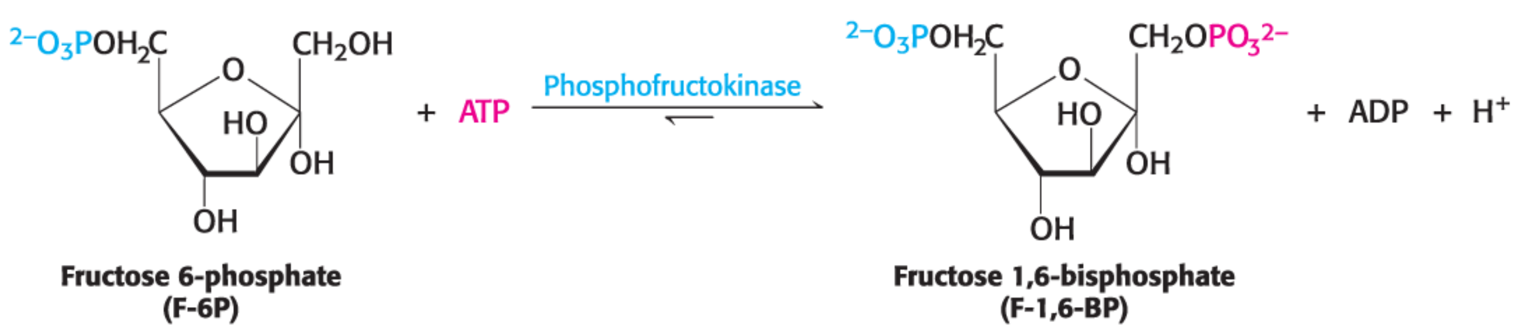
- Hexokinase, like most kinases, employs substrate-binding ***induced fit*** to minimize hydrolysis of ATP.

Glycolysis Is an Energy-Conversion Pathway

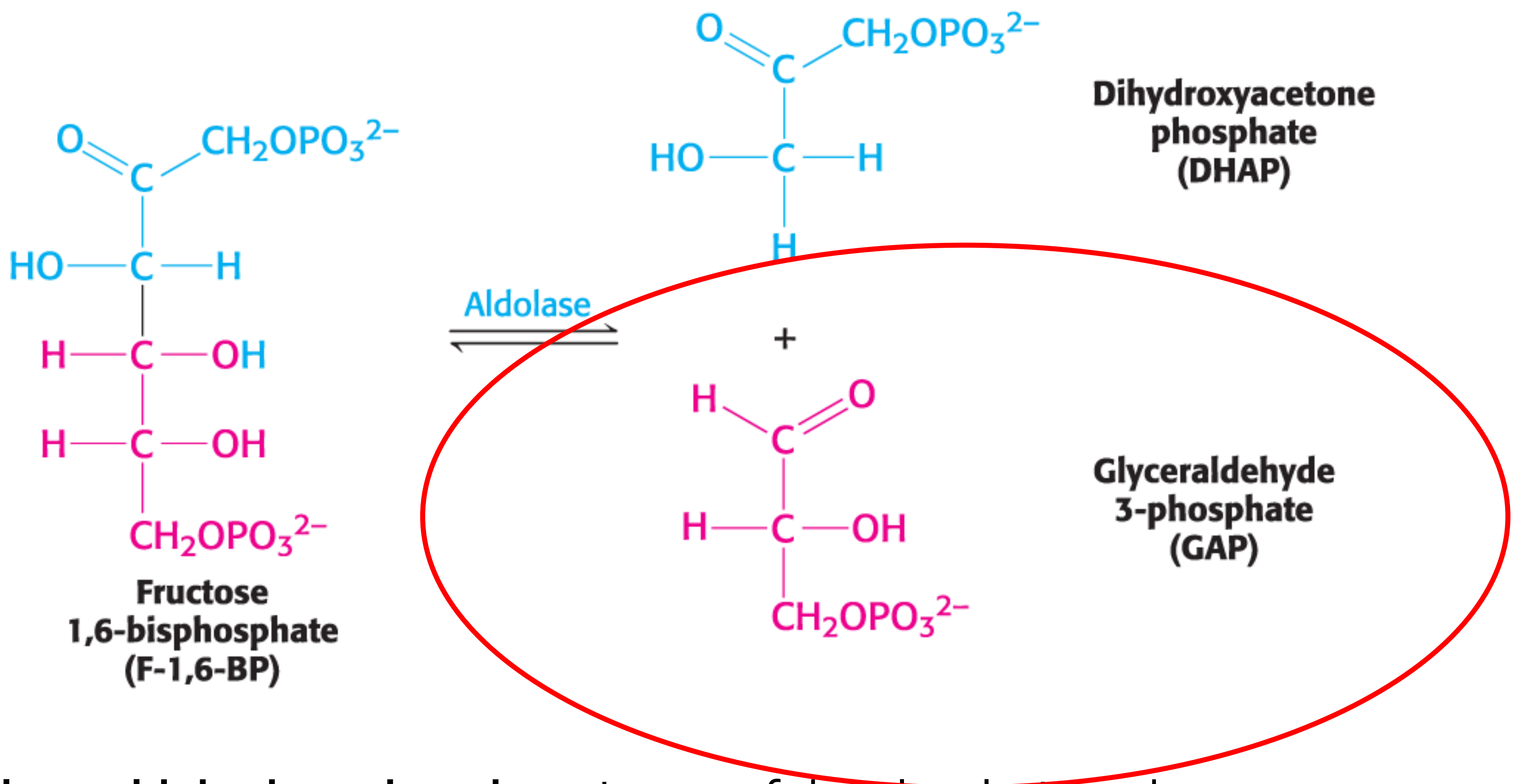
- The conversion of glucose 6-phosphate to fructose 6-phosphate is catalyzed by ***phosphoglucose isomerase***. The reaction is readily reversible.



- The carbohydrate is trapped in the fructose form by the addition of a second phosphate to form fructose 1,6-bisphosphate. This irreversible reaction is catalyzed by the allosteric enzyme ***phosphofructokinase (PFK).***



The Six-C sugar is cleaved into two 3-C fragments



- **Glyceraldehyde 3-phosphate** is part of the glycolysis pathway, but **dihydroxyacetone phosphate** is not.
- These two molecules are **isomers** and can switch forms to prevent waste.
- The enzyme **triose phosphate isomerase (TPI/TIM)** catalyzes this conversion.

Glycolysis Is an Energy-Conversion Pathway

Stage 2 oxidizes the 3-carbon compounds to pyruvate while generating **2** molecules of **ATP**.

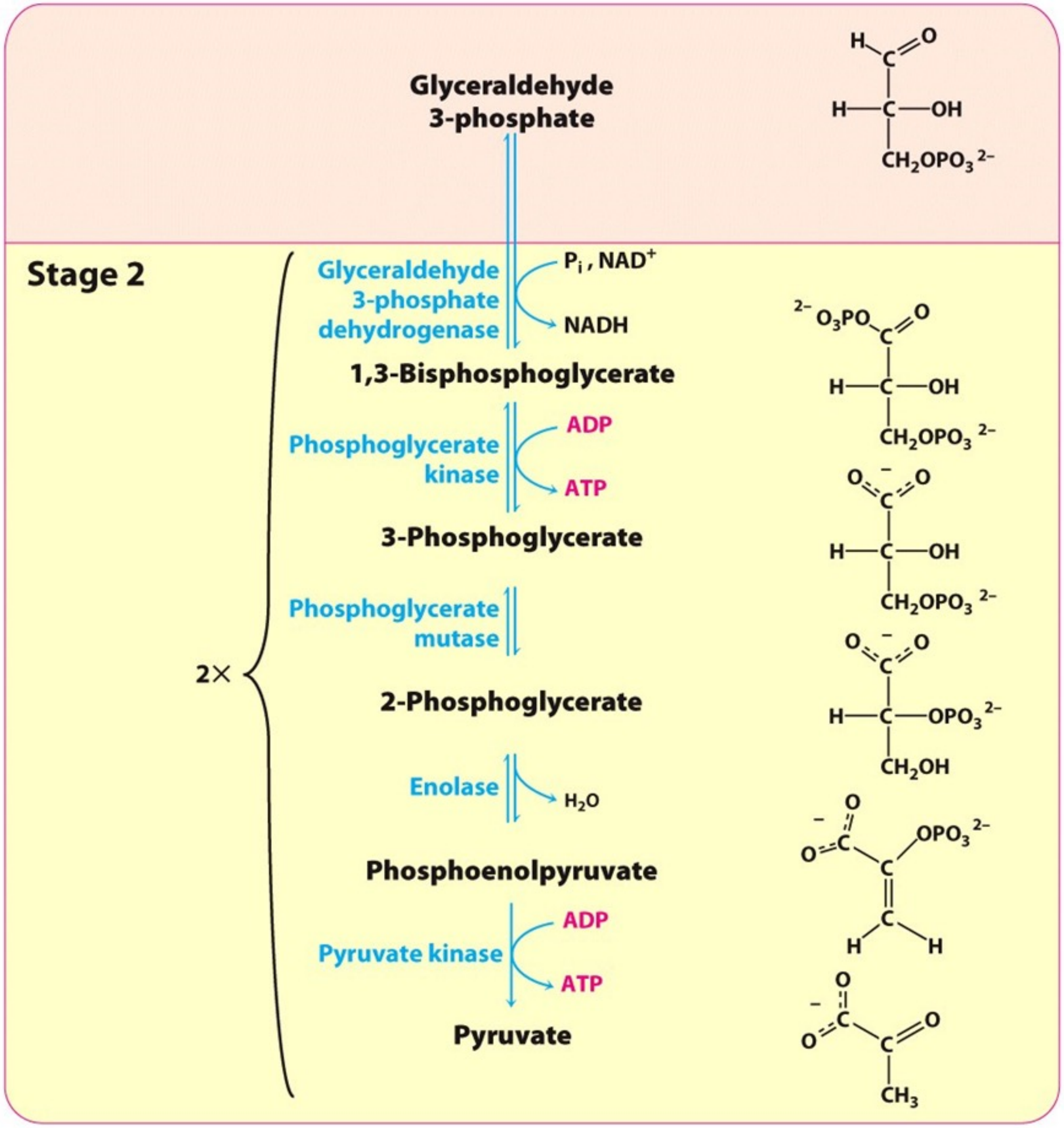


Figure 16.1 part 2

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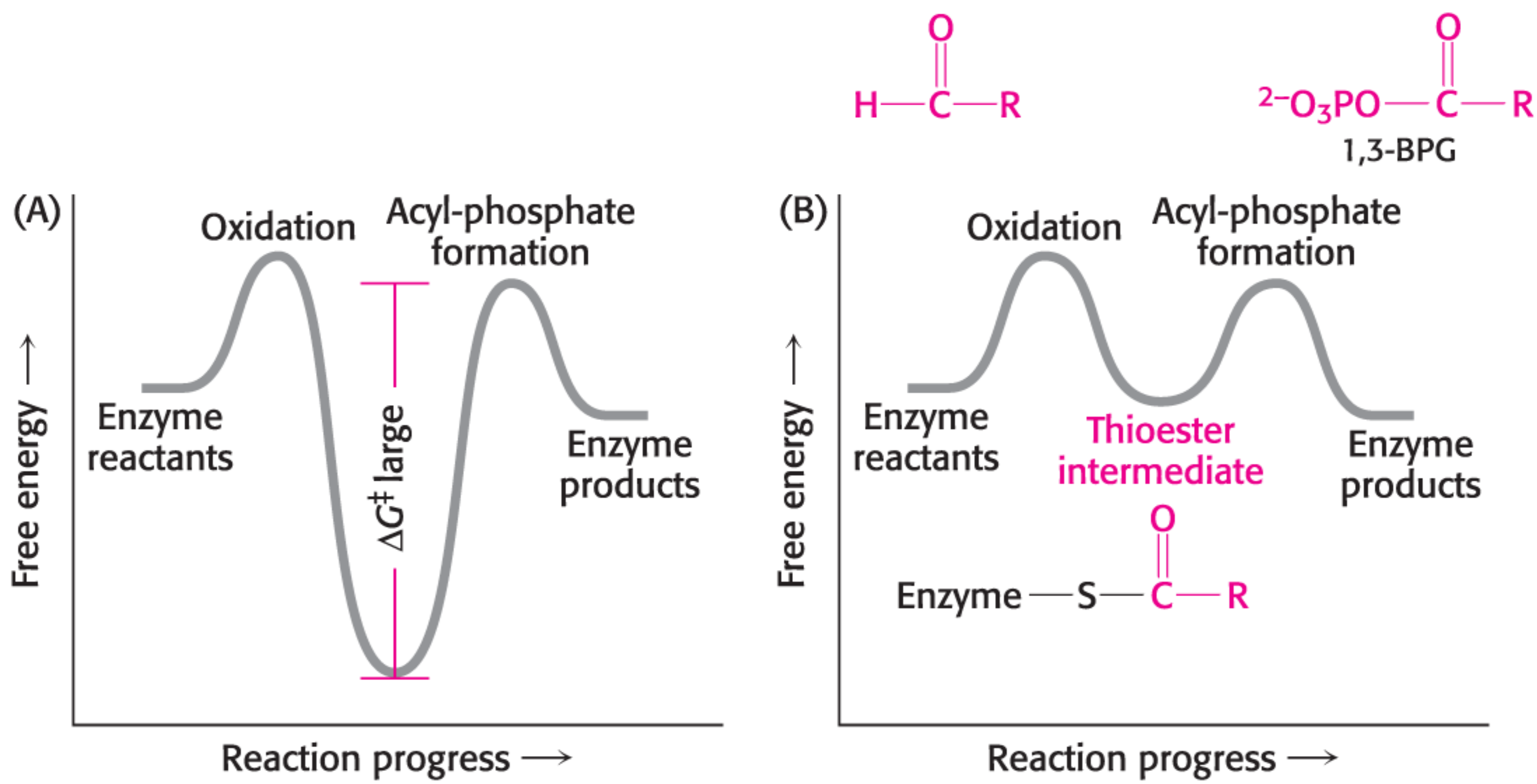
The Oxidation of an Aldehyde Powers the Formation of a Compound Having High Phosphoryl-Transfer Potential

The oxidation of an aldehyde powers the formation of a compound having high phosphoryl-transfer potential.

- In the next reaction of glycolysis, a compound with high phosphoryl transfer potential, 1,3-bisphosphoglycerate, is generated by the oxidation of GAP in a reaction catalyzed by glyceraldehyde 3-phosphate dehydrogenase.



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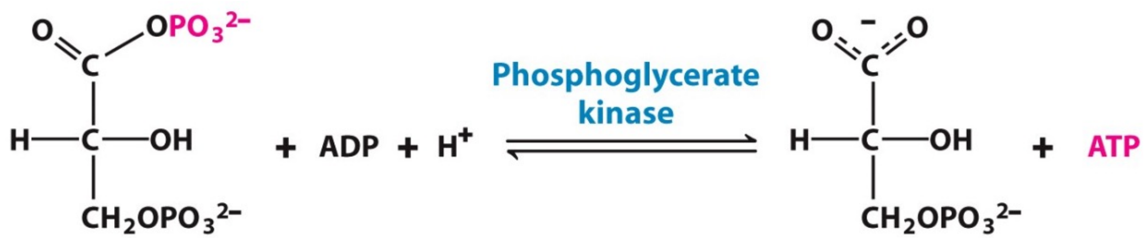
Glycolysis Is an Energy-Conversion Pathway

ATP is formed by phosphoryl transfer from 1,3-bisphosphoglycerate.

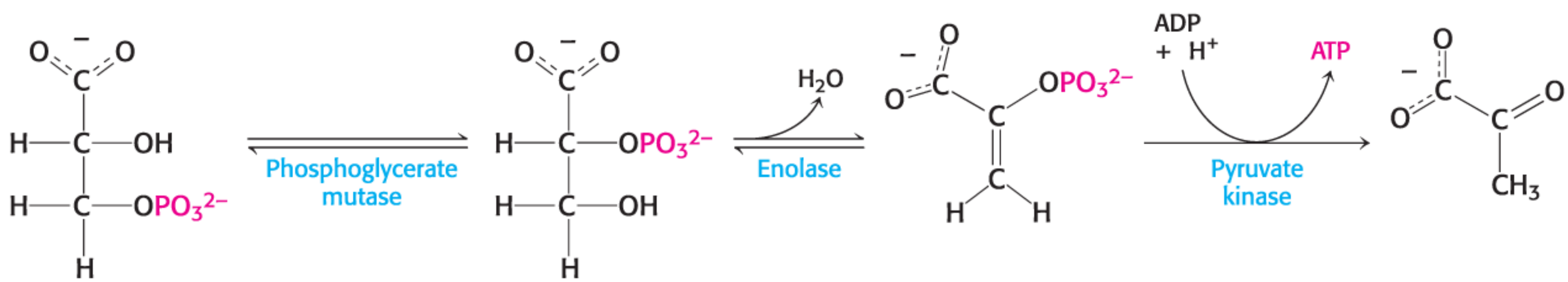
- The energy of oxidation of the carbon atom, initially trapped as 1,3-bisphosphoglucerate, is used to form ATP.
- Glyceraldehyde 1,3-bisphosphoglycerate has a greater phosphoryl transfer potential than ATP, and thus can be used to power the synthesis of ATP from ADP and P_i in a reaction-catalyzed phosphoglycerate kinase.



1,3-Bisphosphoglycerate **3-Phosphoglycerate**

Unnumbered 16 p277
Biochemistry: A Short Course, Second Edition

- Additional ATP is generated with the formation of pyruvate:



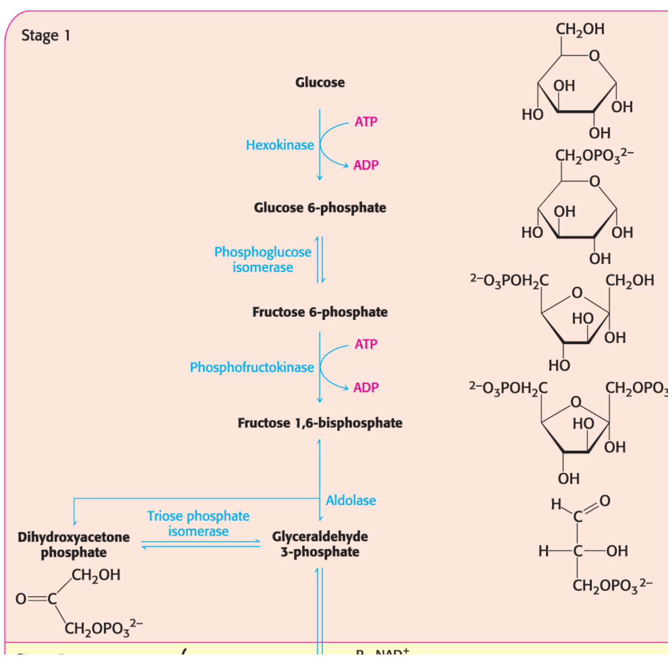
3-Phosphoglycerate **2-Phosphoglycerate** **Phosphoenolpyruvate** **Pyruvate**

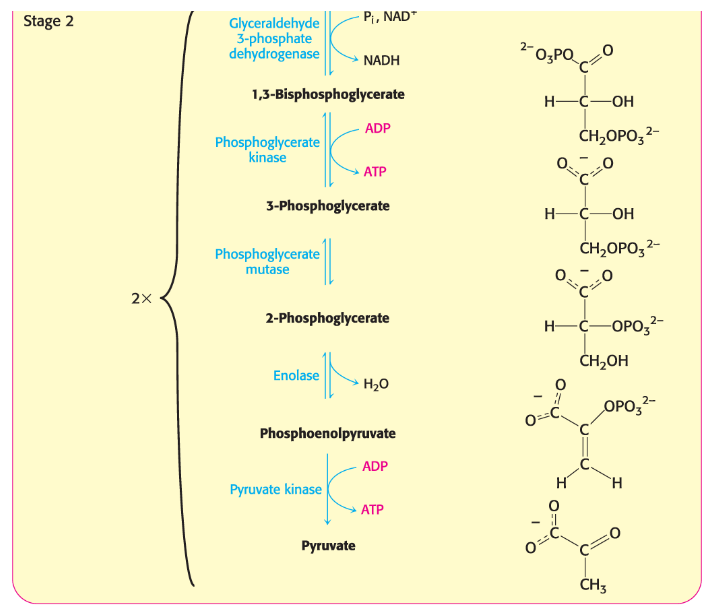
Glycolysis Is an Energy-Conversion Pathway

Two ATP molecules are formed in the convention of glucose into pyruvate.

- The net reaction for glycolysis is:

$$\text{Glucose} + 2P_i + 2\ \text{ADP} + 2\ \text{NAD}^+ \longrightarrow \quad 2\ \text{pyruvate} + 2\ \text{ATP} + 2\ \text{NADH} + 2\ \text{H}^+ + 2\ \text{H}_2\text{O}$$





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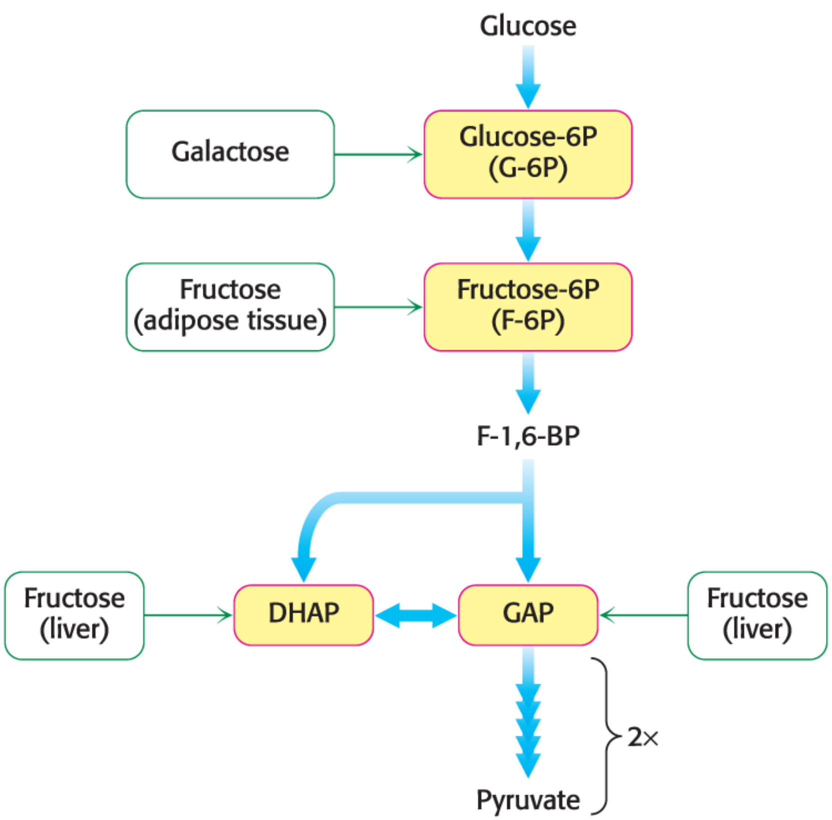
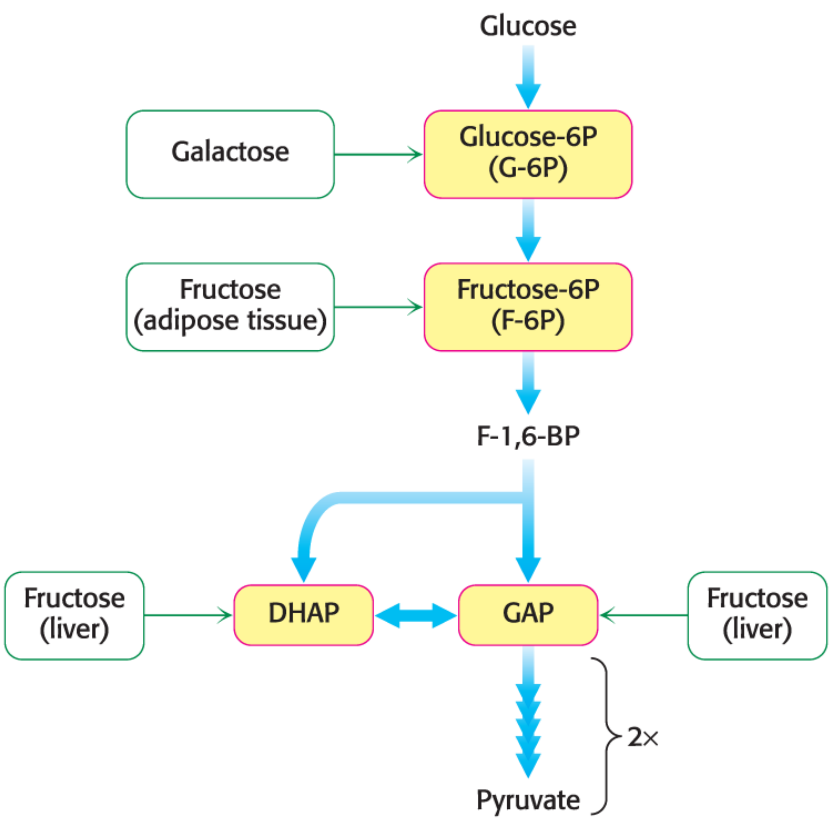
Fructose and Galactose are converted into glycolytic intermediates



- Fructose enters glycolysis through two pathways.
- In the liver, fructose follows the fructose 1-phosphate pathway:
  - Fructokinase converts fructose into fructose 1-phosphate.
  - Fructose 1-phosphate aldolase splits it into glyceraldehyde and dihydroxyacetone phosphate (DHAP).
  - DHAP enters glycolysis directly, while glyceraldehyde is phosphorylated to glyceraldehyde 3-phosphate by triose kinase.
- In adipose tissue, hexokinase phosphorylates fructose into fructose 6-phosphate, which enters glycolysis.

Fructose and Galactose are converted into glycolytic intermediates



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  - DHAP enters glycolysis directly, while glyceraldehyde is phosphorylated to glyceraldehyde 3-phosphate by triose kinase.
- In adipose tissue, hexokinase phosphorylates fructose into fructose 6-phosphate, which enters glycolysis.

- Galactose is converted into glucose 6-phosphate in four steps

Fermentations Are a Means of Oxidizing NADH

- Fermentations are ATP-generated processes in which organic compounds act as both donors and acceptors of electrons.

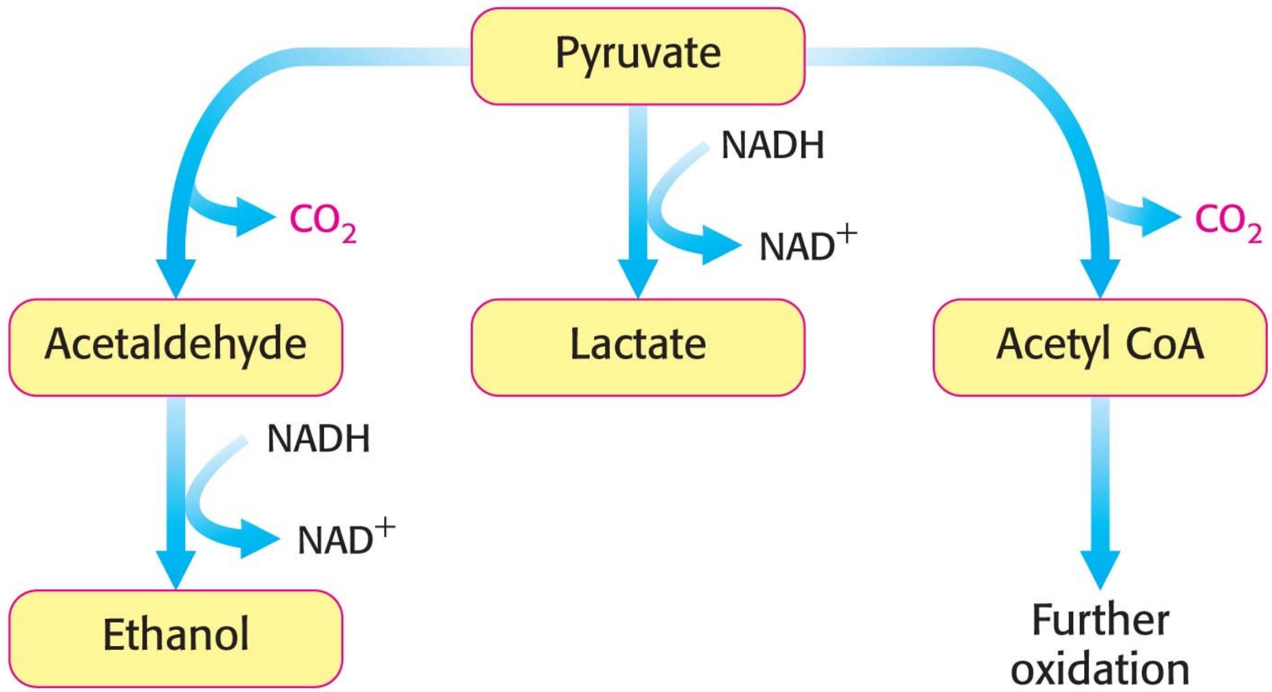

Figure 16.04
Biochemistry, Third Edition
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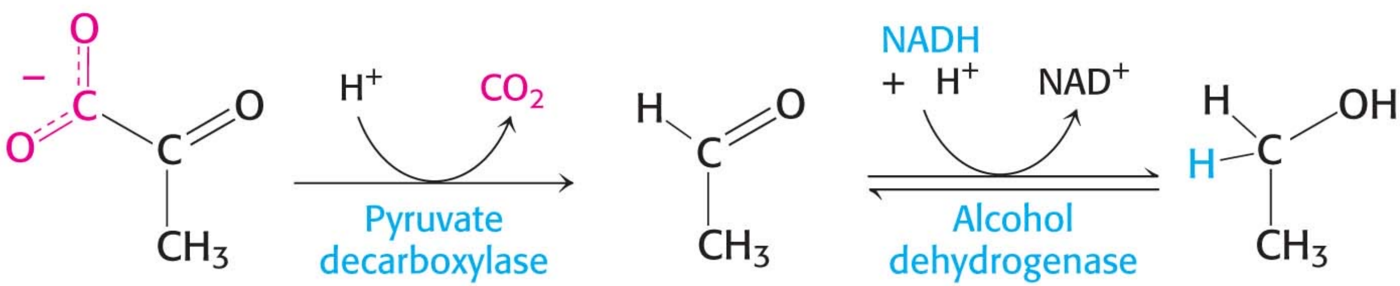
Fermentations Are a Means of Oxidizing NADH

- Fermentations are ATP-generating pathways in which electrons are removed from one organic compound and passed to another organic compound.
- The formation of ethanol from pyruvate regenerates NAD^+.
- Pyruvate carboxylase requires the vitamin thiamine (B_1).

NUTRITION FACTS

Thiamine Also called vitamin B_1, thiamine is a component of the coenzyme thiamine pyrophosphate (TPP), which is used in decarboxylation reactions. Pork and legumes are good sources of thiamine. A deficiency of thiamine results in beriberi, the symptoms of which include muscle weakness, anorexia, and an enlarged heart. [Ruslan/age fotostock]

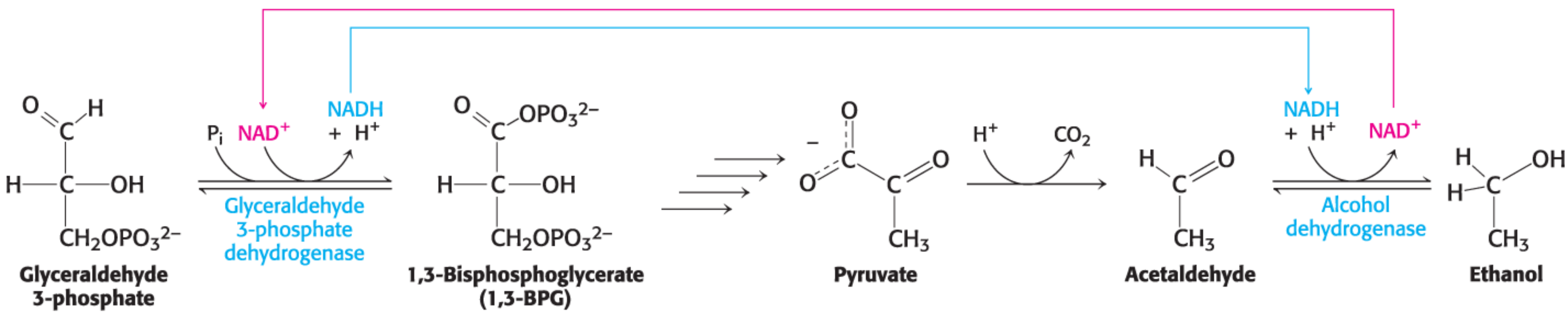


Pyruvate **Acetaldehyde** **Ethanol**

Figure 16.04UN
Biochemistry, Third Edition

$$\text{Glucose} + 2\,P_i + 2\,\text{ADP} + 2\,H^+ \longrightarrow 2\,\text{ethanol} + 2\,CO_2 + 2\,\text{ATP} + 2\,H_2O$$

NAD+ needs to be generated for glycolysis to proceed



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- NADH (Nicotinamide Adenine Dinucleotide, reduced form) is an electron carrier that transfers high-energy electrons in metabolism.

- It plays a crucial role in cellular respiration by helping produce ATP, the energy currency of the cell.

Metabolism in Context: Glycolysis Helps Pancreatic Beta Cells Sense Glucose

- Insulin is secreted by β cells of the pancreas in response to high blood levels of glucose. This secretion is stimulated by the metabolism of glucose by the β cells.
- Glucose enters β cells through GLUT2 and is metabolized to pyruvate, and the pyruvate is subsequently oxidized to CO_2 and H_2O.
- The increase in ATP closes a K^+ channel, which alters the charge across the cell membrane. This alteration in turn opens Ca^{2+} channels. The influx of Ca^{2+} ions stimulates the release of insulin.

- Insulin release is controlled by blood glucose levels.
- Glucose metabolism(glycolysis) increases ATP production. Higher ATP closes an ATP-sensitive potassium channel.
- This changes the membrane charge, opening a calcium channel.
- Calcium influx triggers insulin granules to fuse with the membrane.
- Insulin is released into the blood.

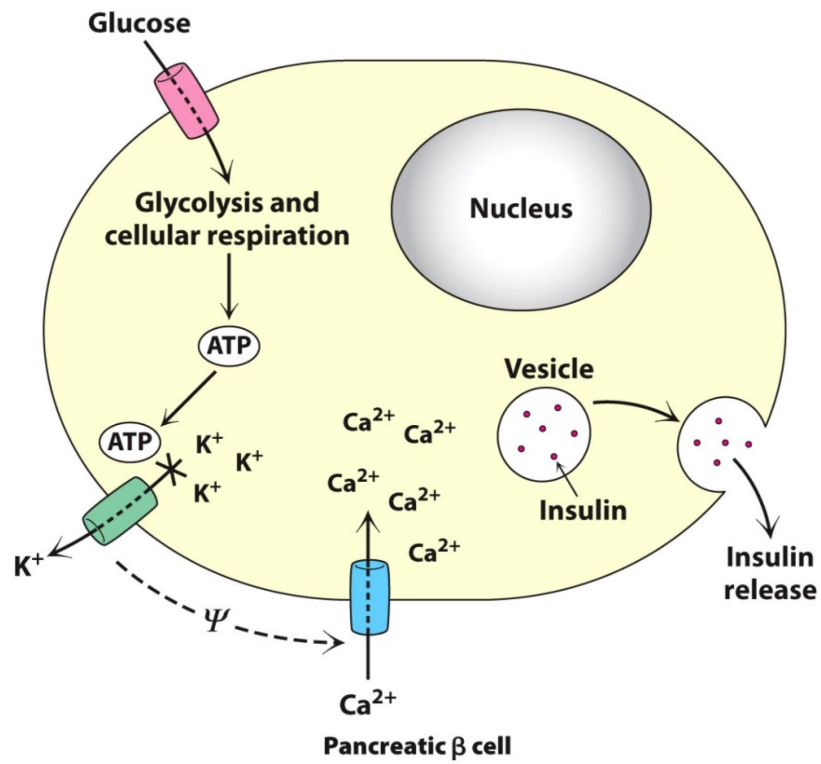

Figure 16.19
Biochemistry: A Short Course, Second Edition

Quick Quiz 2

Fructose can enter the glycolytic pathway at several locations. Which of the following is not an entry point?

A. fructose 6-phosphate

B. glucose 6-phosphate

C. dihydroxyacetone phosphate

D. glyceraldehyde 3-phosphate

E. B & C