BIOCHEMISTRY

Fourth Class-First Couse

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BIOMEDICAL IMPORTANCE

Most tissues have at least some requirement for glucose. In the brain, the requirement is substantial. Glycolysis, the **major pathway for glucose metabolism, occurs in the cytosol** of all cells. It is unique, in that it can function either aerobically or anaerobically, depending on the availability of oxygen and the electron transport chain.

Erythrocytes, which lack mitochondria, are completely reliant on glucose as their metabolic fuel, and metabolize it by anaerobic glycolysis. However, to oxidize glucose beyond pyruvate (the end product of glycolysis) requires both oxygen and mitochondrial enzyme systems: the pyruvate dehydrogenase complex, the citric acid cycle, and the respiratory chain.

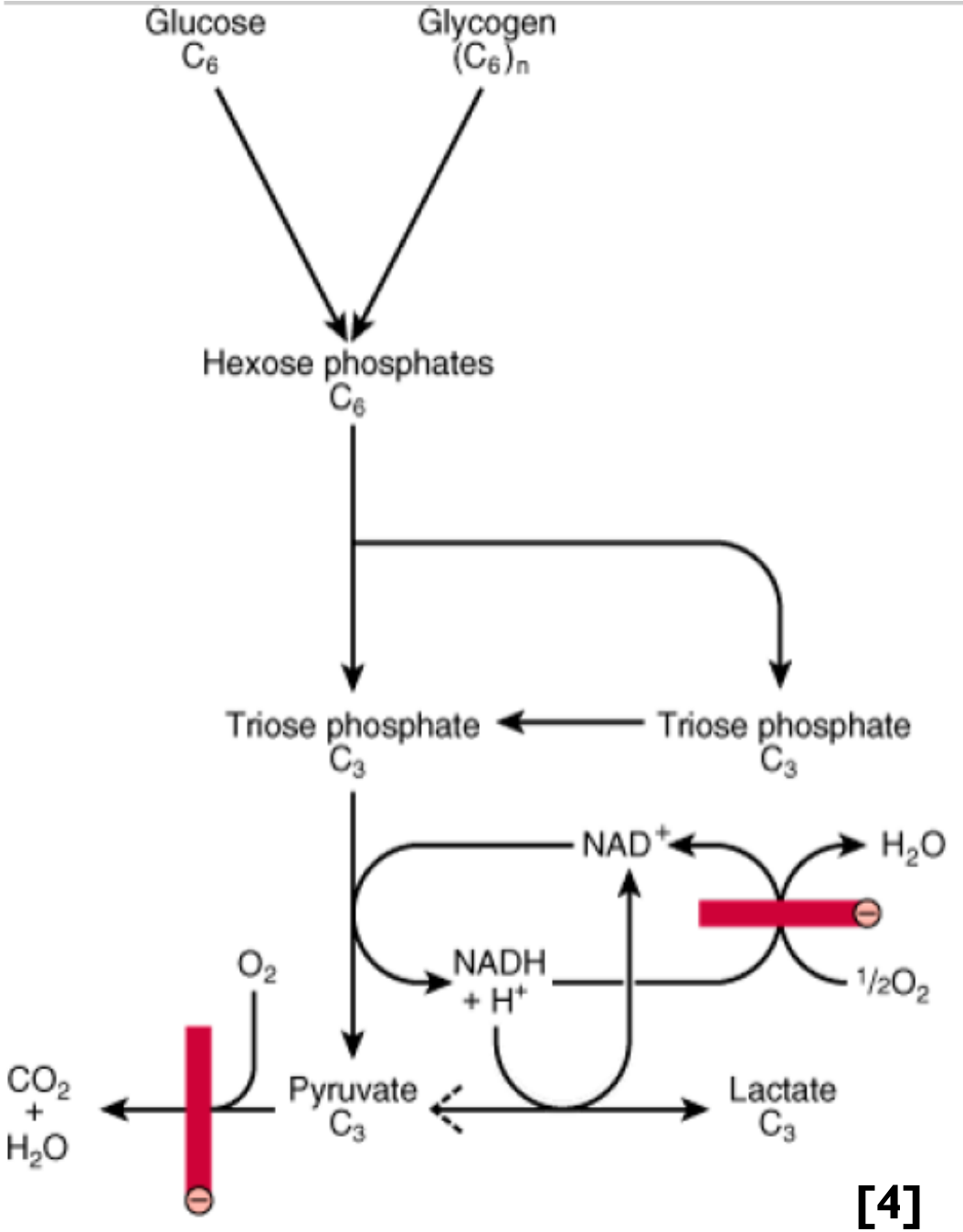
Glycolysis is both the principal route for glucose metabolism and also the main pathway for the metabolism of fructose, galactose, and other carbohydrates derived from the diet. The ability of glycolysis to provide ATP in the absence of oxygen is especially important, because this allows skeletal muscle to perform at very high levels when oxygen supply is insufficient, and it allows tissues to survive anoxic episodes.

GLYCOLYSIS CAN FUNCTION UNDER ANAEROBIC CONDITIONS

Early in the investigations of glycolysis it was realized that fermentation in yeast was similar to the breakdown of glycogen in muscle. It was noted that when a muscle contracts in an anaerobic medium, ie, one from which oxyge is excluded, **glycogen disappears and lactate appears. When oxygen is admitted, aerobic recovery takes place** and lactate is no longer produced. However, if contraction occurs under aerobic conditions, lactate does not accumulate and pyruvate is the major end product of glycolysis. Pyruvate is oxidized further to CO_2 and water (Figure 10). When oxygen is in short supply, mitochondrial reoxidation of NADH formed during glycolysis is impaired, and NADH is reoxidized by reducing pyruvate to lactate, so permitting glycolysis to proceed (Figure 10). While glycolysis can occur under anaerobic conditions, this has a price, for it limits the amount of ATP formed per mole of glucose oxidized, so that much more glucose must be metabolized under anaerobic than aerobic conditions. In yeast and some other microorganisms, pyruvate formed in anaerobic glycolysis is not reduced to lactate, but is decarboxylated and reduced to ethanol.

[3]

Figure 10: Summar glycolysis.



[4]

THE REACTIONS OF GLYCOLYSIS CONSTITUTE THE MAIN PATHWAY OF GLUCOSE UTILIZATION

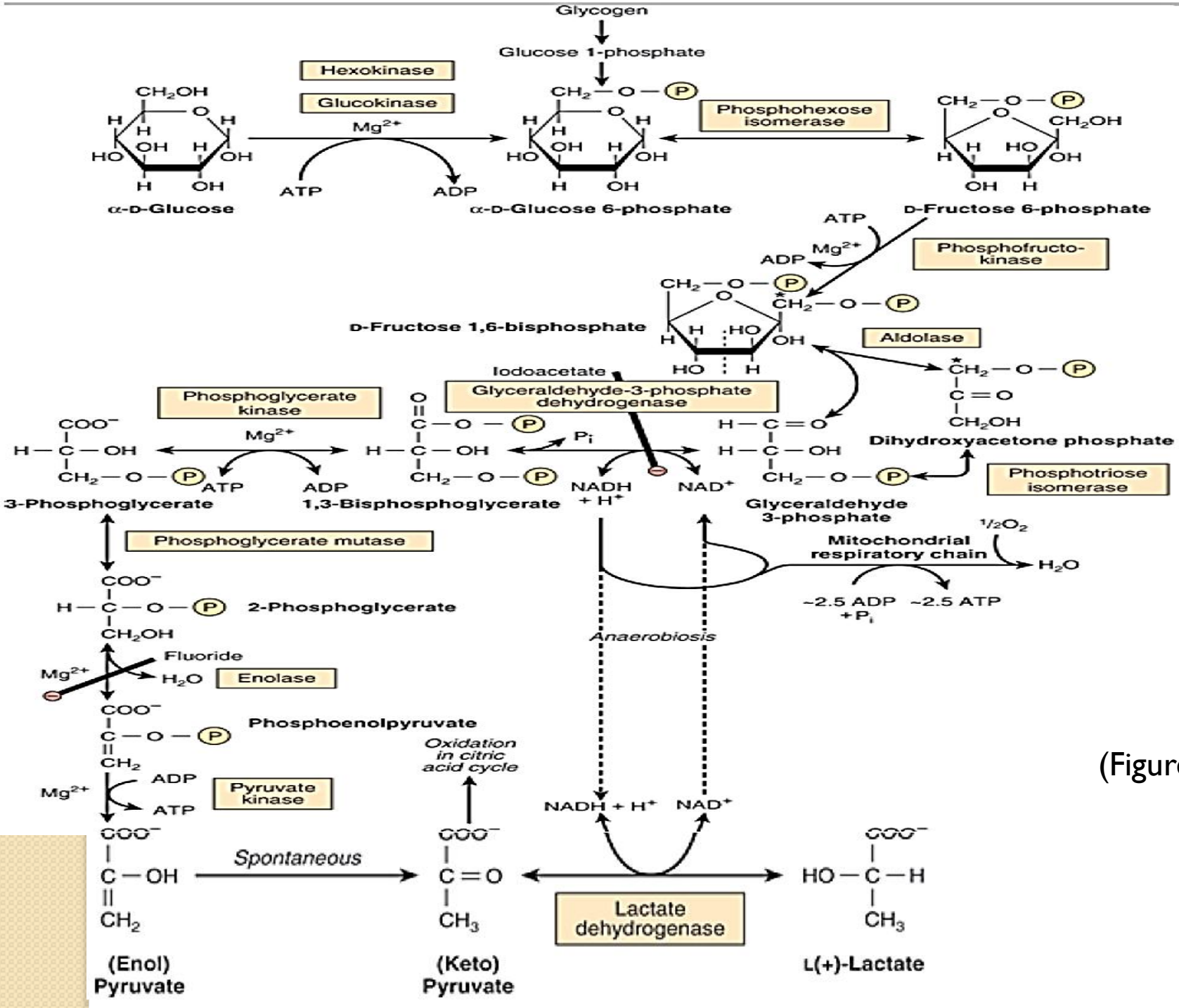
The overall equation for glycolysis from glucose to different compounds as follows:

Glucose + 2NAD$^+$ + 2ADP + 2Pi ⟶ 2Pyruvate + 2NADH + 2H$^+$ + 2ATP

$$\text{Glucose} + 2\,\text{ADP} + 2\,P_i \rightarrow 2\,\text{Lactate} + 2\,\text{ATP} + 2\,H_2O$$

Glucose + 2ADP + 2Pi ⟶ 2Ethanol + 2ATP

All of the enzymes of glycolysis (Figure 11) are found in the cytosol. Glucose enters glycolysis by phosphorylation to glucose 6-phosphate, catalyzed by **hexokinase, using ATP as the phosphate donor. Under** physiologic conditions, the phosphorylation of glucose to glucose 6-phosphate can be regarded as irreversible.


Glycogen
Glucose 1-phosphate
Hexokinase
Glucokinase
Mg2+
ATP
ADP
α-D-Glucose
α-D-Glucose 6-phosphate
Phosphohexose isomerase
D-Fructose 6-phosphate
Phosphofructo-kinase
D-Fructose 1,6-bisphosphate
Aldolase
Iodoacetate
Glyceraldehyde-3-phosphate dehydrogenase
Phosphoglycerate kinase
Pi
NADH + H+
NAD+
3-Phosphoglycerate
1,3-Bisphosphoglycerate
Dihydroxyacetone phosphate
Glyceraldehyde 3-phosphate
Phosphotriose isomerase
Phosphoglycerate mutase
2-Phosphoglycerate
Mitochondrial respiratory chain
1/2O2
H2O
~2.5 ADP +Pi
~2.5 ATP
Anaerobiosis
Fluoride
Enolase
Phosphoenolpyruvate
Oxidation in citric acid cycle
Pyruvate kinase
Spontaneous
Lactate dehydrogenase
(Enol) Pyruvate
(Keto) Pyruvate
L(+)-Lactate

(Figure 11)

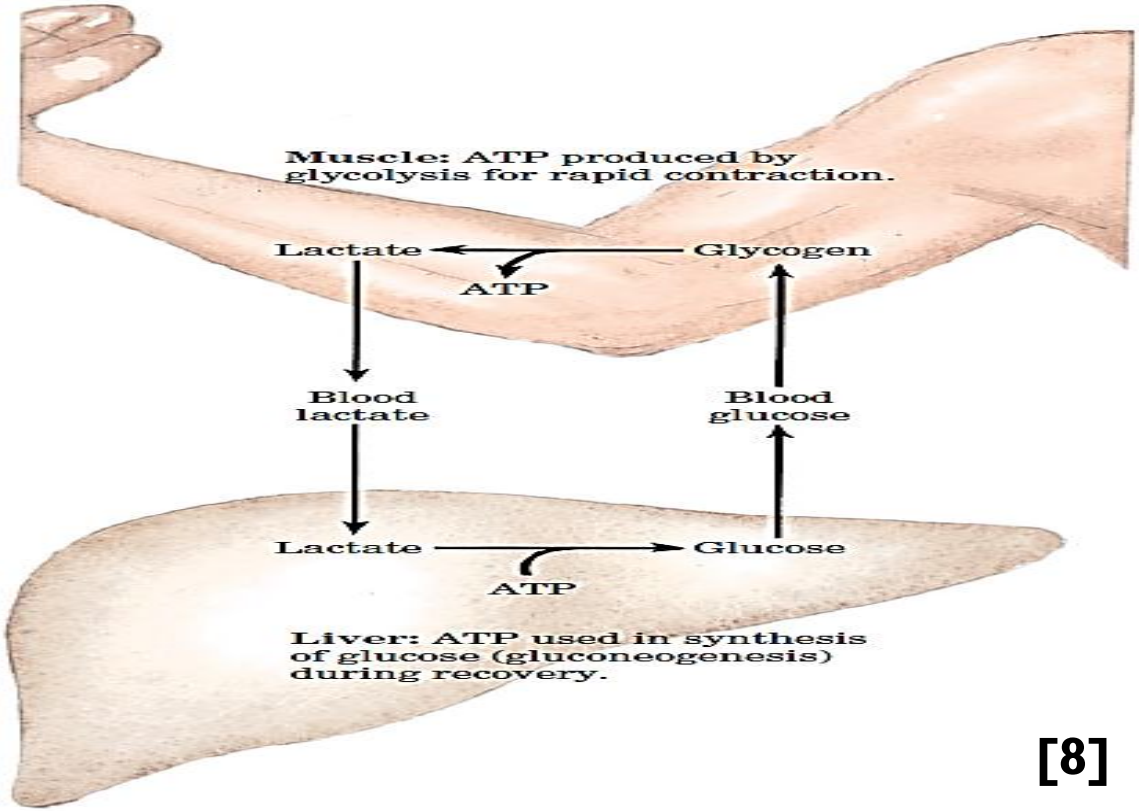
[6]

Tissues that Function under Hypoxic Conditions Produce Lactate

This is true of skeletal muscle, particularly the white fibers, where the rate of work output, and hence the need for ATP formation, may exceed the rate at which oxygen can be taken up and utilized. Glycolysis in erythrocytes always terminates in lactate, because the subsequent reactions of pyruvate oxidation are mitochondrial, and erythrocytes lack mitochondria. The liver, kidneys, and heart usually take up lactate and oxidize it, but produce it under hypoxic conditions When lactate production is high, as in vigorous exercise, septic shock, and cancer cachexia, much is used in the liver for gluconeogenesis (Produce glucose), leading to an increase in metabolic rate to provide the ATP and GTP needed. The resultant increase in oxygen consumption is seen as **oxygen debt after vigorous exercise.** Under some conditions lactate may be formed in the cytosol, but then enter the mitochondrion to be oxidized to pyruvate for onward metabolism. This provides a pathway for the transfer of reducing equivalents from the cytosol into the mitochondrion for the electron transport chain in addition to the glycerophosphate and malate shuttles (مكوكات (نواقل) كليسروفوسفات ومماليت).

Cori cycle

The cycle of reactions that includes glucose conversion to lactate in muscle and lactate conversion to glucose in liver is called the Cori cycle occur when oxygen absence or very few. **Metabolic cooperation between skeletal muscle and the liver: the Cori cycle.** Extremely active muscles use glycogen as energy source, generating lactate via glycolysis. During recovery, some of this lactate is transported to the liver and converted to glucose via gluconeogenesis. This glucose is released to the blood and returned to the muscles to replenish their glycogen stores. The overall pathway (glucose - lactate - glucose) constitutes the Cori cycle **(Figure 12)**.



(Figure 12)

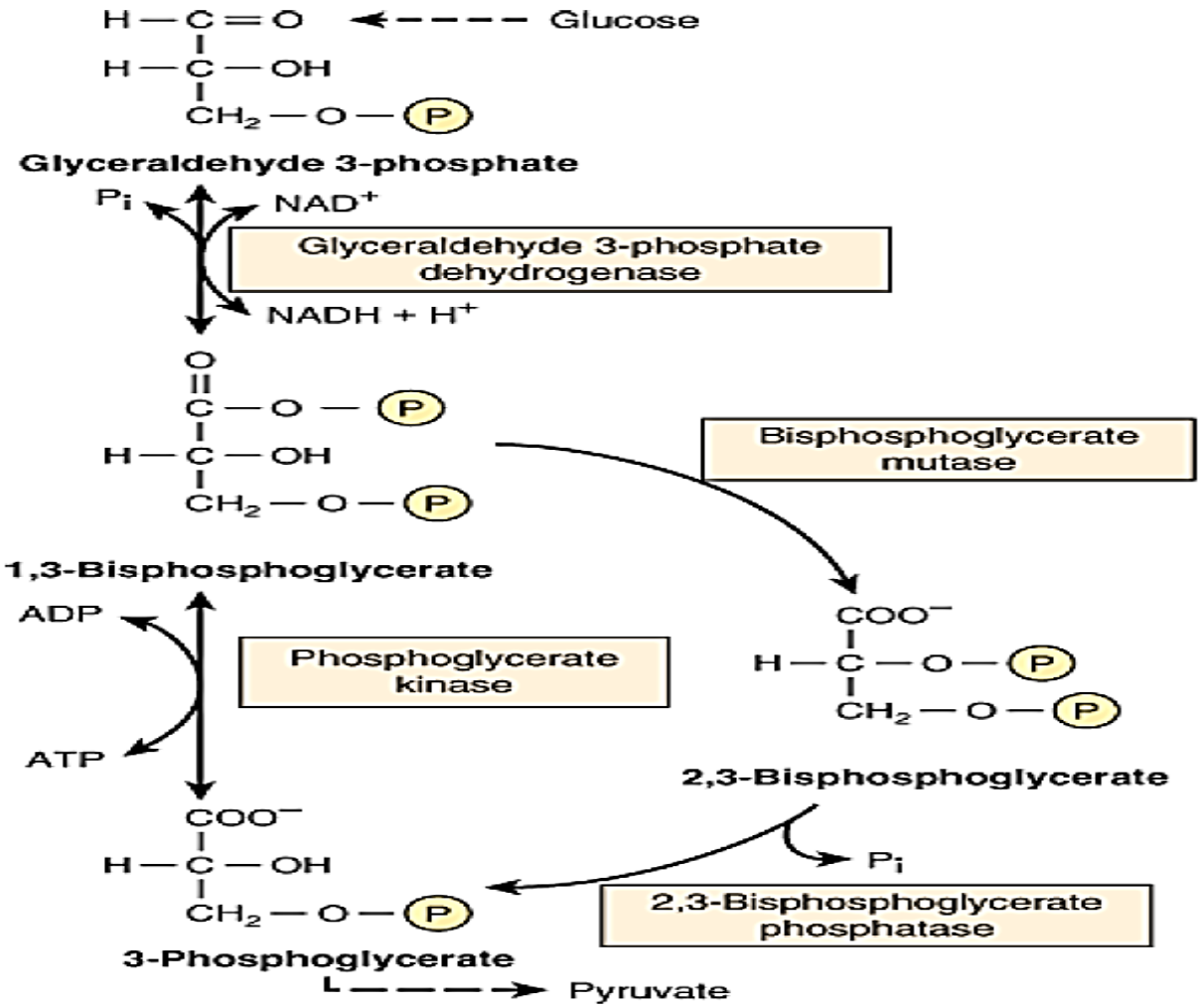
GLYCOLYSIS IS REGULATED AT THREE STEPS INVOLVING NONEQUILIBRIUM REACTIONS

Although most of the reactions of glycolysis are reversible, three are markedly exergonic and must therefore be considered physiologically irreversible. These reactions, catalyzed by **hexokinase (and glucokinase), phosphofructokinase, and pyruvate kinase, are the major sites of regulation of glycolysis. Phosphofructokinase** is significantly inhibited at normal intracellular concentrations of ATP.

Fructose enters glycolysis by phosphorylation to fructose 1-phosphate, and bypasses the main regulatory steps, so resulting in formation of more pyruvate (and acetyl-CoA) than is required for ATP formation. In the liver and adipose tissue, this leads to increased lipogenesis, and a high intake of fructose may be a factor in the development of obesity.

In Erythrocytes, the First Site of ATP Formation in Glycolysis May Be Bypassed

In erythrocytes, the reaction catalyzed by **phosphoglycerate kinase may be bypassed to some extent by the** reaction of **bisphosphoglycerate mutase, which catalyzes the conversion of 1,3-bisphosphoglycerate to 2,3-**bisphosphoglycerate, followed by hydrolysis to 3-phosphoglycerate and Pi , catalyzed by **2,3 bisphosphoglycerate phosphatase (Figure 13). This alternative pathway involves no net yield of ATP from** glycolysis. However, it does serve to provide 2,3-bisphosphoglycerate, which binds to hemoglobin, decreasing its affinity for oxygen, and so making oxygen more readily available to tissues.

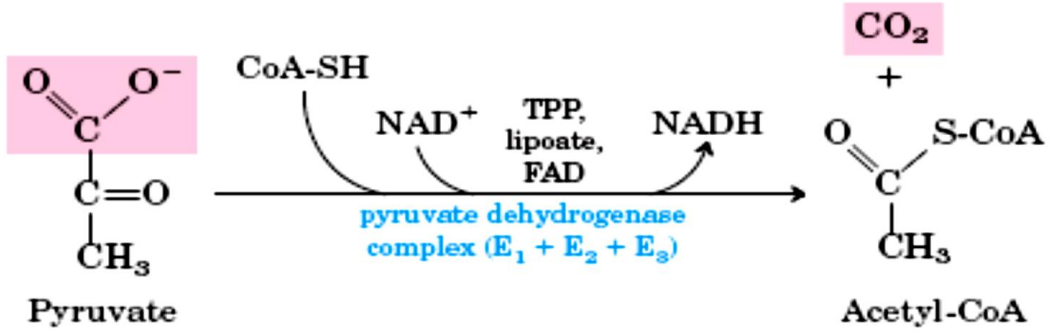

Glucose
Glyceraldehyde 3-phosphate
Pi
NAD+
Glyceraldehyde 3-phosphate dehydrogenase
NADH + H+
Bisphosphoglycerate mutase
1,3-Bisphosphoglycerate
ADP
Phosphoglycerate kinase
ATP
2,3-Bisphosphoglycerate
Pi
2,3-Bisphosphoglycerate phosphatase
3-Phosphoglycerate
Pyruvate

(Figure 13)

THE OXIDATION OF PYRUVATE TO ACETYL-COA IS THE IRREVERSIBLE ROUTE FROM GLYCOLYSIS TO THE CITRIC ACID CYCLE

Pyruvate, formed in the cytosol, is transported into the mitochondrion by a proton symporter Inside the mitochondrion, it is oxidatively decarboxylated to acetyl-CoA by a multienzyme complex that associated with the inner mitochondrial membrane. This **pyruvate dehydrogenase complex is analogous to the** -ketoglutarate dehydrogenase complex of the citric acid cycle (Figure 17–3). **Three enzymes: Pyruvate dehydrogenase Dihydrolipoyl transacetylase and Dihydrolipoyl Dehydrogenas. Beside of, five coenzymes (NAD+, CoA-SH, Thiamin pyrophosphate(TPP), Lipoate and FAD)**

$$\text{Pyruvate} + NAD^+ + CoA \rightarrow \text{Acetyl-CoA} + NADH + H^+ + CO_2$$



Glucose + $4NAD^+$ + 2ADP + 2Pi + 2CoA-SH ⟶

2Acetyl CoA + 4NADH + $4H^+$ + 2ATP + $2CO_2$

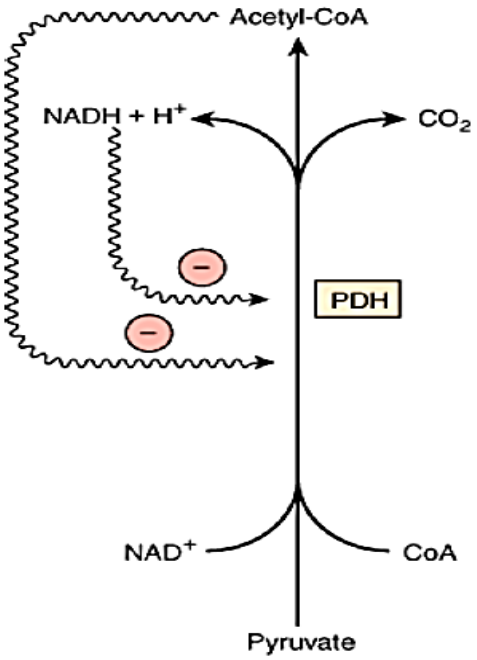
Pyruvate Dehydrogenase Is Regulated by End-Product Inhibition & Covalent Modification

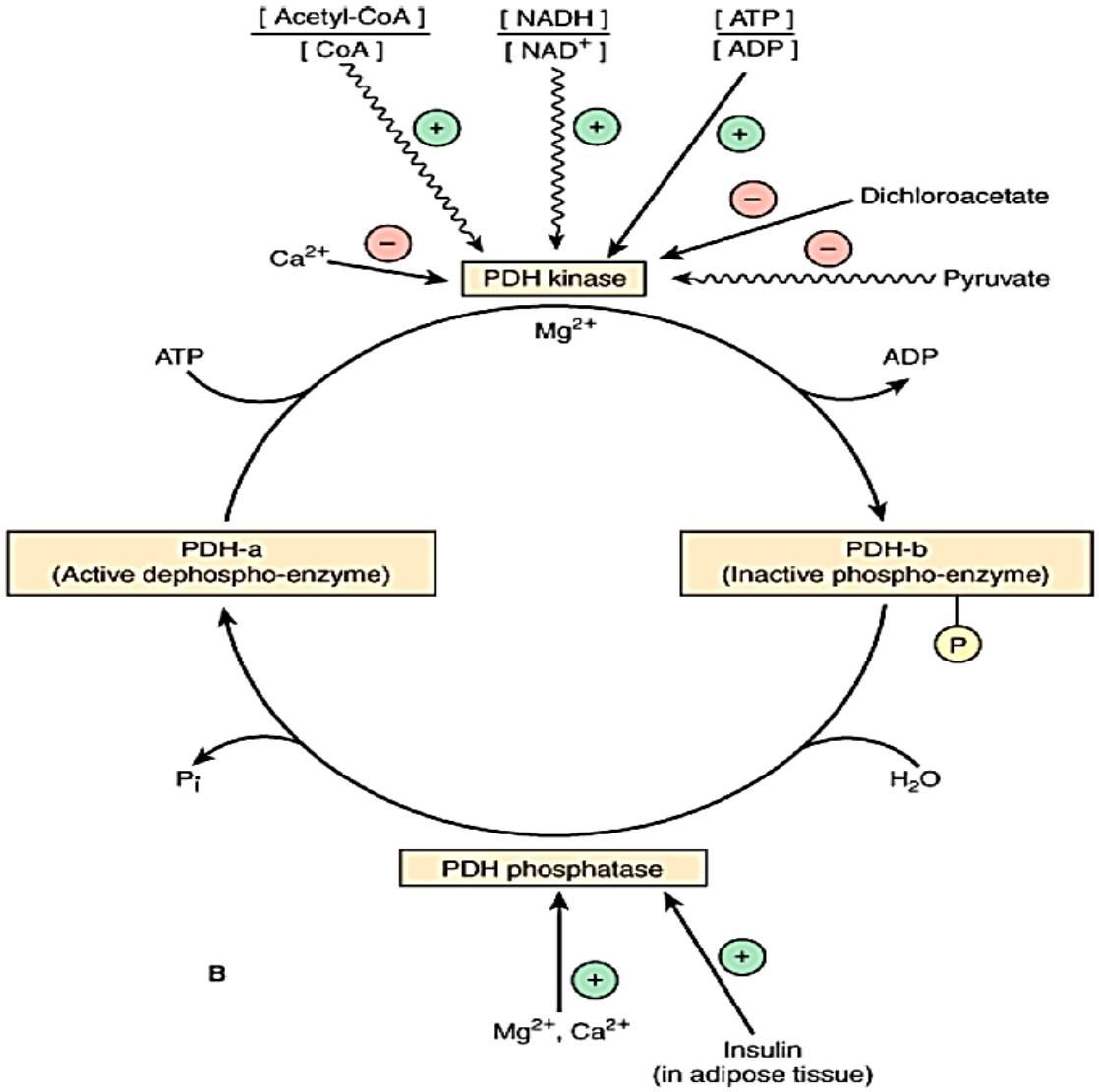
Pyruvate dehydrogenase is inhibited by its products, acetyl-CoA and NADH (Figure 14).

It is also regulated by phosphorylation by a kinase of three serine residues on the pyruvate dehydrogenase component of the multienzyme complex, resulting in decreased activity and by dephosphorylation by a phosphatase that causes an increase in activity.

The kinase is activated by increases in the [ATP]/[ADP], [acetyl-CoA]/[CoA], and [NADH]/[NAD+] ratios. Thus, pyruvate dehydrogenase, and therefore glycolysis, is inhibited both when there is adequate ATP (and reduced coenzymes for ATP formation) available, and also when fatty acids are being oxidized.

In fasting, when free fatty acid concentrations increase, there is a decrease in the proportion of the enzyme in the active form, leading to a sparing of carbohydrate. In adipose tissue, where glucose provides acetyl-CoA for lipogenesis, the enzyme is activated in response to insulin.





(Figure 14)

(A)Regulation by end product inhibition.

(B) Regulation by interconversion of active and inactive forms.

[14]