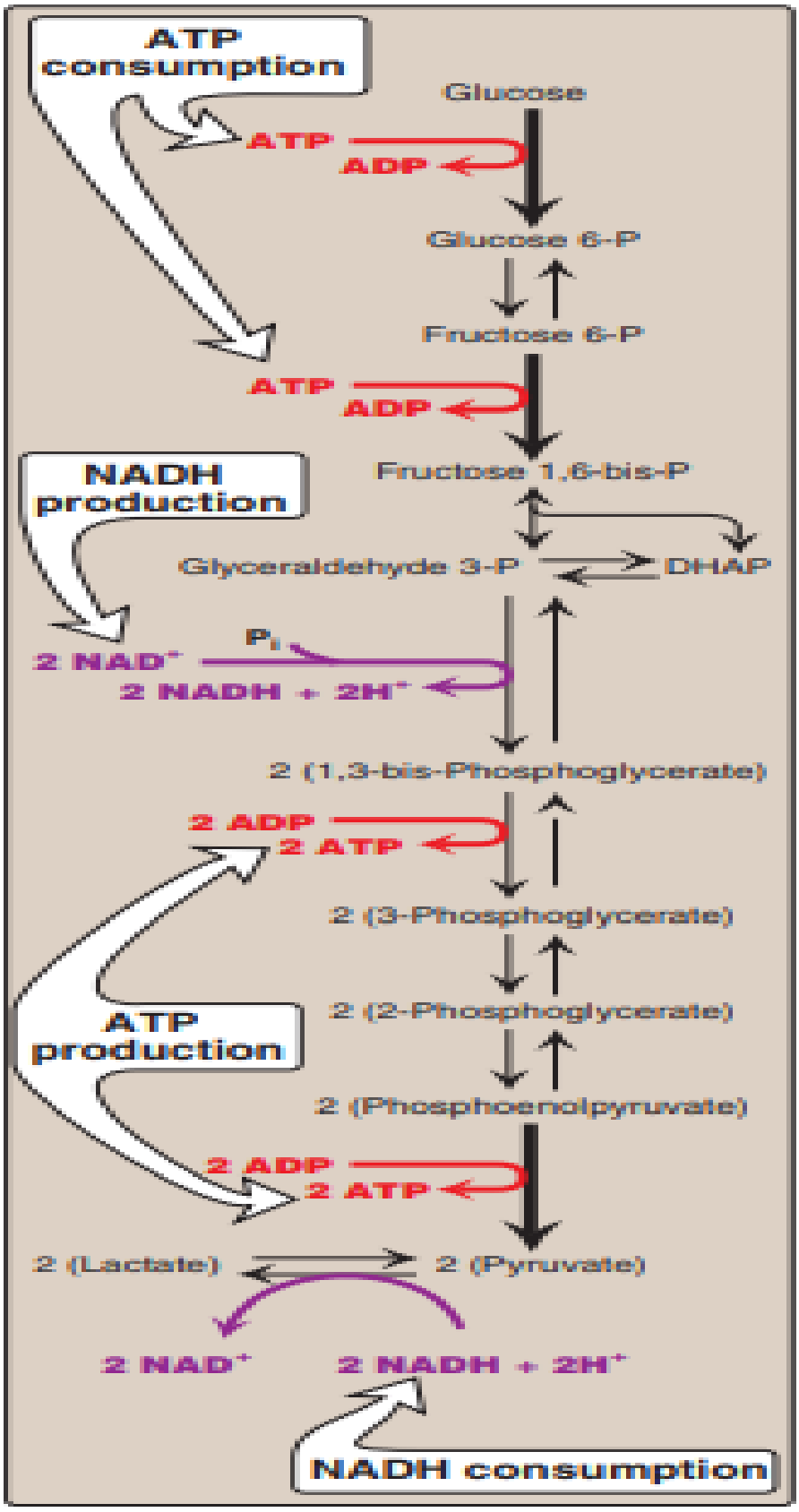
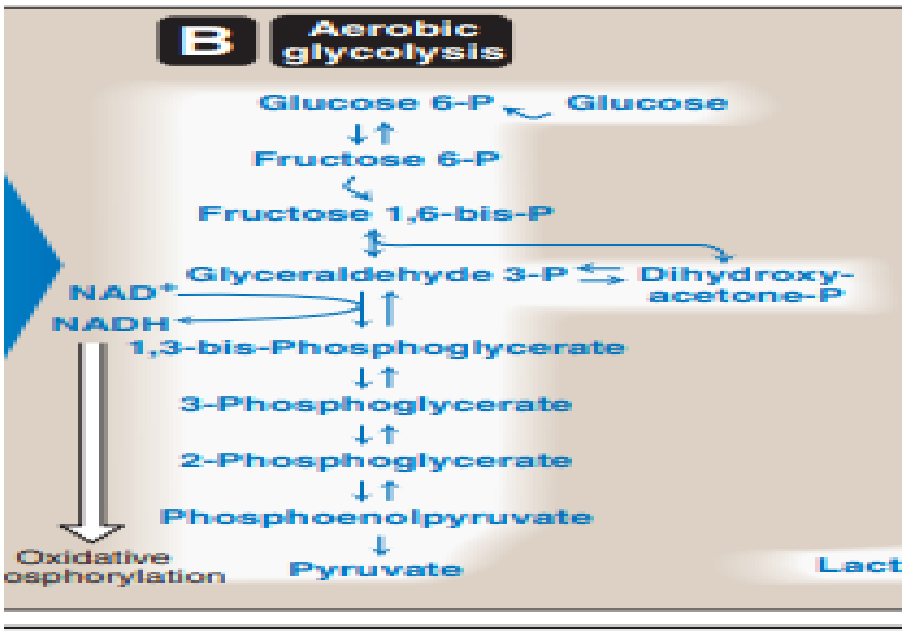
GLYCOLYSIS

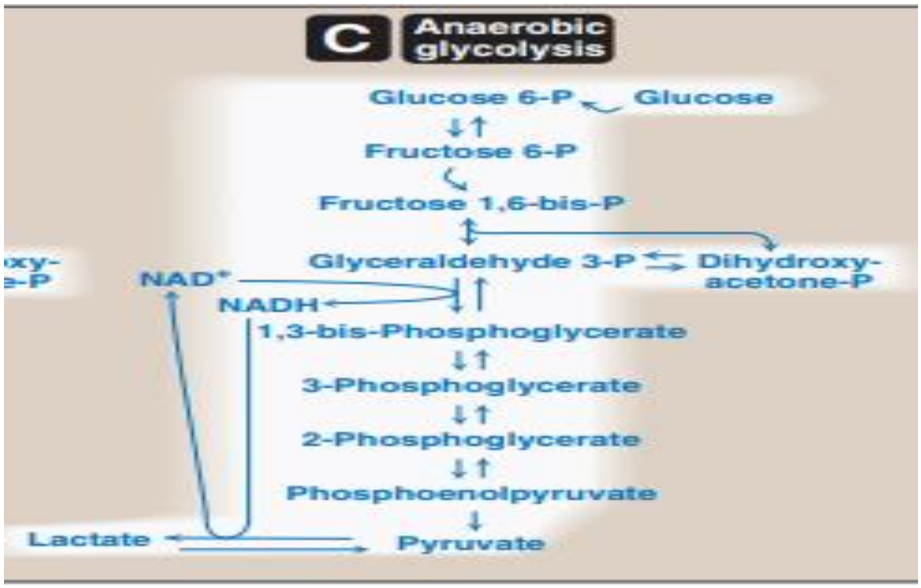
The glycolytic pathway is employed by all tissues for the breakdown of glucose to provide energy (in the form of ATP) and intermediates for other metabolic pathways.

This series of ten reactions is called

1. **aerobic glycolysis:** because oxygen is required to reoxidize the NADH formed during the oxidation of glyceraldehyde 3-phosphate. Aerobic glycolysis sets the stage for the oxidative decarboxylation of pyruvate to acetyl CoA, a major fuel of the TCA (or citric acid) cycle.
2. **anaerobic glycolysis:** pyruvate is reduced to lactate as NADH is oxidized to NAD+. This conversion of glucose to lactate because it can occur without the participation of oxygen. Anaerobic glycolysis allows the production of ATP in tissues that lack mitochondria (for example, red blood cells) or in cells deprived of sufficient oxygen.


ATP consumption
Glucose
ATP
ADP
Glucose 6-P
Fructose 6-P
ATP
ADP
NADH production
Fructose 1,6-bis-P
Glyceraldehyde 3-P
DHAP
P_i
2 NAD^+
2 NADH + $2H^+$
2 (1,3-bis-Phosphoglycerate)
2 ADP
2 ATP
2 (3-Phosphoglycerate)
2 (2-Phosphoglycerate)
ATP production
2 (Phosphoenolpyruvate)
2 ADP
2 ATP
2 (Lactate)
2 (Pyruvate)
2 NAD^+
2 NADH + $2H^+$
NADH consumption



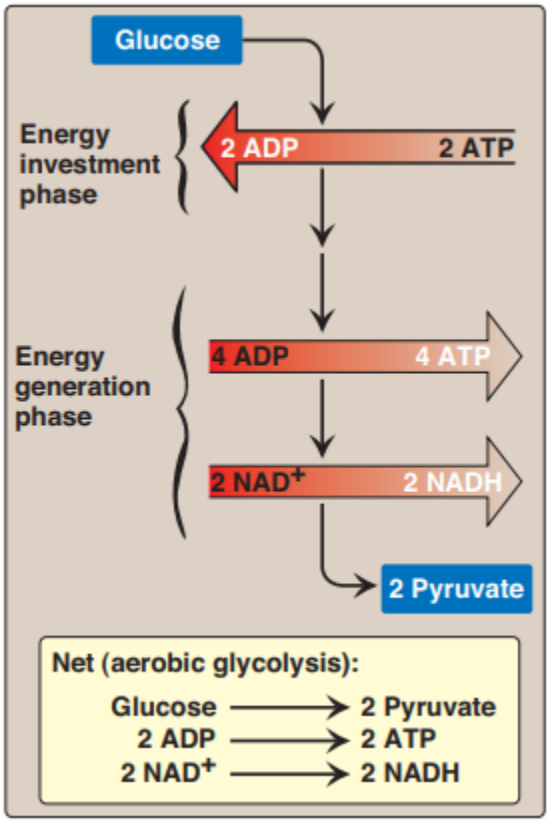


REACTIONS OF GLYCOLYSIS:

The conversion of glucose to pyruvate occurs in two stages.

1. The first five reactions of glycolysis correspond to an energy investment phase in which the phosphorylated forms of intermediates are synthesized at the expense of ATP.

2. The second an energy generation of ATP are formed by substrate-level dephosphorylation per glucose molecule metabolized. phase the subsequent reactions of glycolysis in which a net of two molecules.

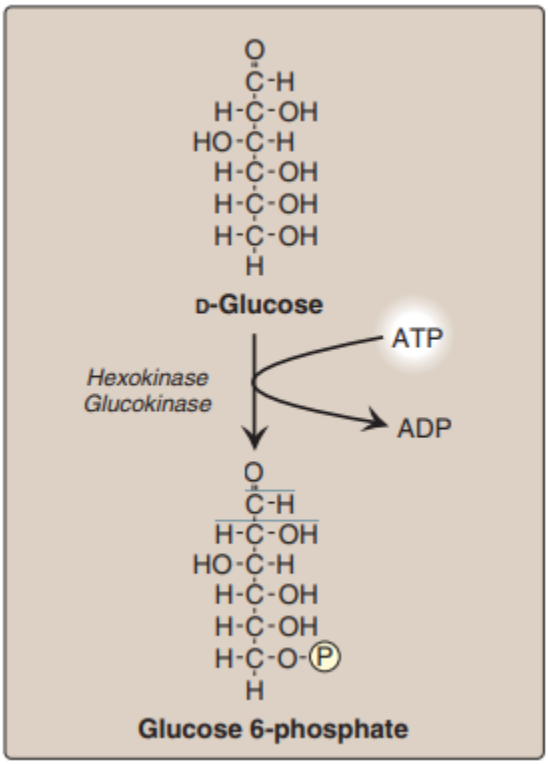


Ten Reactions Of Glycolysis:

A. Phosphorylation of glucose

Phosphorylated sugar molecules do not readily penetrate cell membranes, because there are no specific trans membrane carriers for these compounds, and because they are too polar to diffuse through the lipid core of membranes. The irreversible phosphorylation of glucose therefore, effectively traps the sugar as cytosolic glucose 6-phosphate, thus committing it to further metabolism in the cell. Mammals have several isozymes of the

enzyme hexokinase that catalyze the phosphorylation of glucose to glucose 6-phosphate.



1. **Hexokinase:** In most tissues, the phosphorylation of glucose is catalyzed by hexokinase, one of three regulatory enzymes of glycolysis (phosphofructokinase and pyruvate kinase). Hexokinase has broad substrate specificity and is able to phosphorylate several hexoses in addition to glucose. Hexokinase is inhibited by the reaction product, glucose 6-phosphate, which accumulates when further metabolism of this hexose phosphate is reduced.
2. **Glucokinase:** In liver parenchymal cells and β cells of the pancreas, glucokinase (also called hexokinase D, or type IV) is the predominant enzyme responsible for the phosphorylation of glucose. In β cells, glucokinase functions as the glucose sensor, determining the threshold for insulin secretion In the liver, the enzyme facilitates glucose phosphorylation during hyperglycemia.

[Note: Hexokinase also serves as a glucose sensor in neurons of the hypothalamus, playing a key role in the adrenergic response to hypoglycemia)

Regulation of Glucokinase by fructose 6-phosphate and glucose:

Glucokinase activity is not directly inhibited by glucose 6-phosphate as are the other hexokinases, but rather is indirectly inhibited by fructose 6-phosphate (which is in equilibrium with glucose 6-phosphate, a product of glucokinase), and is indirectly stimulated by glucose (a substrate of glucokinase) via the following mechanism. Glucokinase regulatory protein (GKRP) in the liver regulates the activity of glucokinase through reversible binding. In the presence of fructose 6-phosphate, glucokinase is translocated into the nucleus and binds tightly to the regulatory protein, thus rendering the enzyme inactive .When glucose levels in the blood (and also in the hepatocyte) increase, glucokinase is released from the regulatory protein, and the enzyme re-enters the cytosol where it phosphorylates glucose to glucose 6-phosphate.

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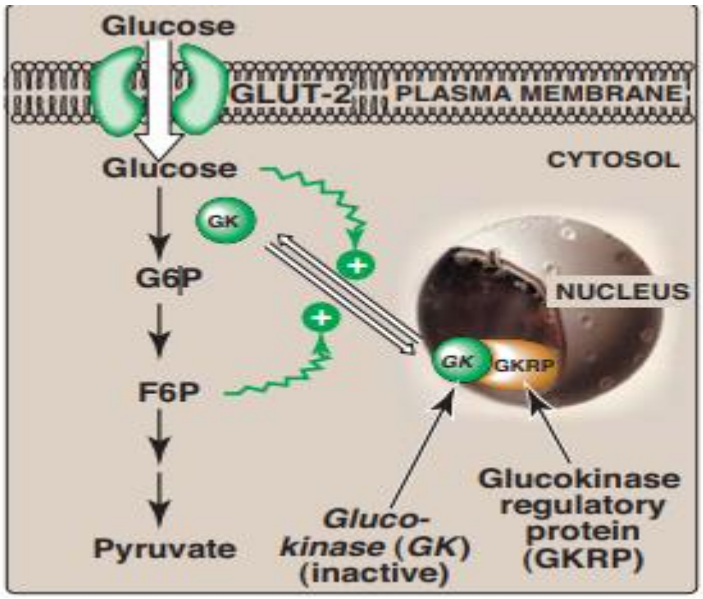
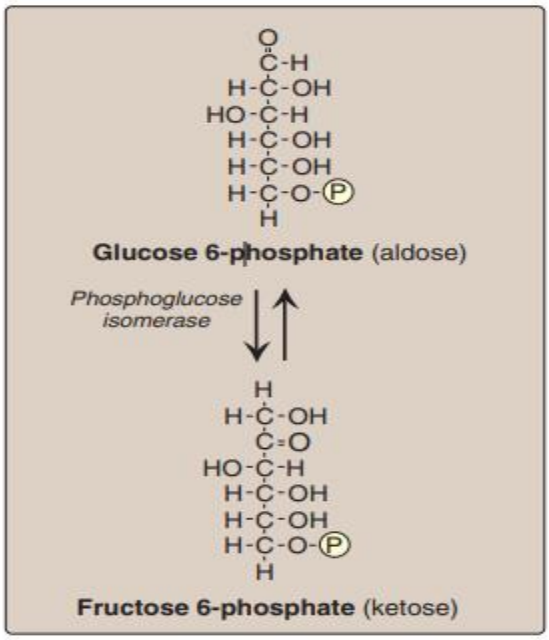


B. Isomerization of glucose 6-phosphate

The isomerization of glucose 6-phosphate to fructose 6-phosphate is catalyzed by phosphoglucose isomerase. The reaction is readily reversible and is not a rate-limiting or regulated step.



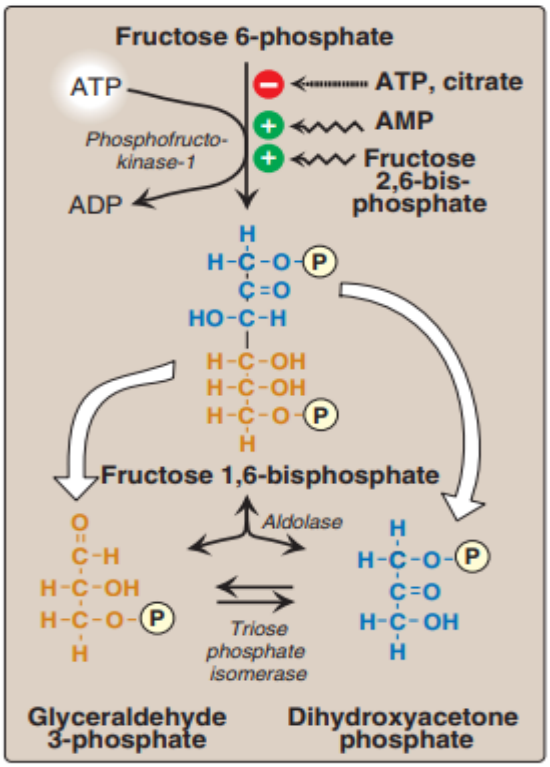
C. Phosphorylation of fructose 6-phosphate :

The irreversible phosphorylation reaction catalyzed by phospho - fructokinase-1 (PFK-1) is the most important control point and the rate-limiting and committed step of glycolysis. PFK-1 is controlled by the available concentrations of the substrates ATP and fructose 6- phosphate, and by regulatory substances.

Regulation of Phosphorylation of fructose 6-phosphate

Regulation by energy levels within the cell: PFK-1 is inhibited allosterically by elevated levels of ATP, which act as an “energyrich” signal indicating an abundance of high-energy compounds. Elevated levels of citrate, an

intermediate in the TCA cycle, also inhibit PFK-1. Conversely, PFK-1 is activated allosterically by high concentrations of AMP, which signal that the cell's energy stores are depleted.



During the well-fed state: Decreased levels of glucagon and elevated levels of insulin, such as occur following a carbohydrate- rich meal, cause an increase in fructose 2,6-bisphosphate and, thus, in the rate of glycolysis in the liver .Fructose 2,6-bisphosphate, therefore, acts as an intracellular signal, indicating that glucose is abundant.

b. During starvation: Elevated levels of glucagon and low levels of insulin, such as occur during fasting, decrease the intracellular concentration

of hepatic fructose 2,6-bisphosphate. This results in a decrease in the overall rate of glycolysis and an increase in gluconeogenesis.

D. Cleavage of fructose 1,6-bisphosphate Aldolase:

cleaves fructose 1,6-bisphosphate to dihydroxyacetone phosphate and glyceraldehyde 3-phosphate. The reaction is reversible and not regulated.

E. Isomerization of dihydroxyacetone phosphate:

Triose phosphateisomerase interconverts dihydroxyacetonephosphate and glyceraldehyde 3-phosphate. Dihydroxyacetonephosphate must be isomerized to glyceraldehyde 3-phosphate for further metabolism by the glycolytic pathway. This isomerization results in the net production of two molecules of glyceraldehyde 3-phosphate from the cleavage products of fructose 1,6-bisphosphate bisphosphate in liver.

F. Oxidation of glyceraldehyde 3-phosphate :

The conversion of glyceraldehyde 3-phosphate to 1,3-bisphosphoglycerate by glyceraldehyde 3-phosphate dehydrogenase is the first oxidation-reduction reaction of glycolysis .

G. Synthesis of 3-phosphoglycerate producing ATP

When 1,3-BPG is converted to 3-phosphoglycerate, the high-energy phosphate group of 1,3-BPG is used to synthesize ATP from ADP.This reaction is catalyzed by phosphoglycerate kinase, which, unlike most other kinases, is physiologically reversible. Because two molecules of 1,3-BPG are formed from each glucose

molecule, this kinase reaction replaces the two ATP molecules consumed by the earlier formation of glucose 6-phosphate and fructose 1,6-bisphosphate.

G. Shift of the phosphate group from carbon 3 to carbon 2 The shift of the phosphate group from carbon 3 to carbon 2 of phosphoglycerate by phosphoglycerate mutase is freely reversible

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H. Dehydration of 2-phosphoglycerate

The dehydration of 2-phosphoglycerate by enolase redistributes the energy within the 2-phosphoglycerate molecule, resulting in the formation of phosphoenolpyruvate (PEP), which contains a highenergy enol phosphate. The reaction is reversible despite the high-energy nature of the product.

I. Formation of pyruvate

producing ATP The conversion of PEP to pyruvate is catalyzed by pyruvate kinase, the third irreversible reaction of glycolysis. The equilibrium of the pyruvate kinase reaction favors the formation of ATP

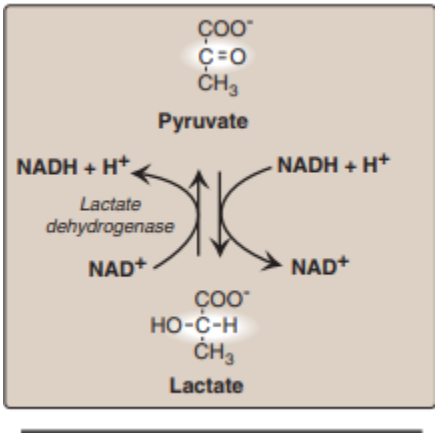
k. Reduction of pyruvate to lactate :

Lactate, formed by the action of lactate dehydrogenase, is the final product of anaerobic glycolysis in eukaryotic cells. The formation of lactate is the major fate for pyruvate in lens and cornea of the eye, kidney medulla, testes, leukocytes and red blood cells, because these are all poorly vascularized and/or lack mitochondria.

1. Lactate formation in muscle: In exercising skeletal muscle, NADH production (by glyceraldehyde 3-phosphate dehydrogenase and by the three NAD+-linked dehydrogenases of the citric acid cycle, exceeds the oxidative capacity of the respiratory chain. This results in an elevated NADH/NAD+ ratio, favoring reduction of pyruvate to lactate. Therefore, during intense exercise, lactate

accumulates in muscle, causing a drop in the intracellular pH, potentially resulting in cramps. Much of this lactate eventually diffuses into the bloodstream, and can be used by the liver to make glucose

2. Lactate consumption: The direction of the lactate dehydrogenase reaction depends on the relative intracellular concentrations of pyruvate and lactate, and on the ratio of NADH/NAD+ in the cell. For example, in liver and heart, the ratio of NADH/NAD+ is lower than in exercising muscle. These tissues oxidize lactate (obtained from the blood) to pyruvate. In the liver, pyruvate is either converted to glucose by gluconeogenesis or oxidized in the TCA cycle. Heart muscle exclusively oxidizes lactate to CO2 and H2O via the citric acid cycle.



3. **Lactic acidosis:** Elevated concentrations of lactate in the plasma, termed lactic acidosis, occur when there is a collapse of the circulatory system, such as in myocardial infarction, pulmonary embolism, and uncontrolled hemorrhage, or when an individual is in shock. The failure to bring adequate amounts of oxygen to the tissues results in impaired oxidative and decreased ATP synthesis. To survive, the cells use anaerobic glycolysis as a backup system for generating ATP, producing lactic acid as the endproduct.

HORMONAL REGULATION OF GLYCOLYSIS

Regular consumption of meals rich in carbohydrate or administration of insulin initiates an increase in the amount of glucokinase, phosphofructokinase, and pyruvate kinase in liver .These changes reflect an increase in gene transcription, resulting in increased enzyme synthesis. High activity of these three enzymes favors the conversion of glucose to pyruvate, a characteristic of the wellfed state . Conversely, gene transcription and synthesis of glucokinase, phosphofructokinase, and pyruvate kinase are decreased when plasma glucagon is high and insulin is low, for example, as seen in fasting or diabetes.