CARBOHYDRATE METABOLISM

INTRODUCTION

Carbohydrates constitute a major part of our diet and our food is the ultimate source of all the sugars that enter our metabolic pathways. About two-thirds of ingested carbohydrate is the plant polysaccharide, starch. Disaccharides like lactose and sucrose and some other polysaccharides like cellulose are also a part of our food, but our intake of *free* mono saccharides like glucose, fructose and galactose is relatively minimal.

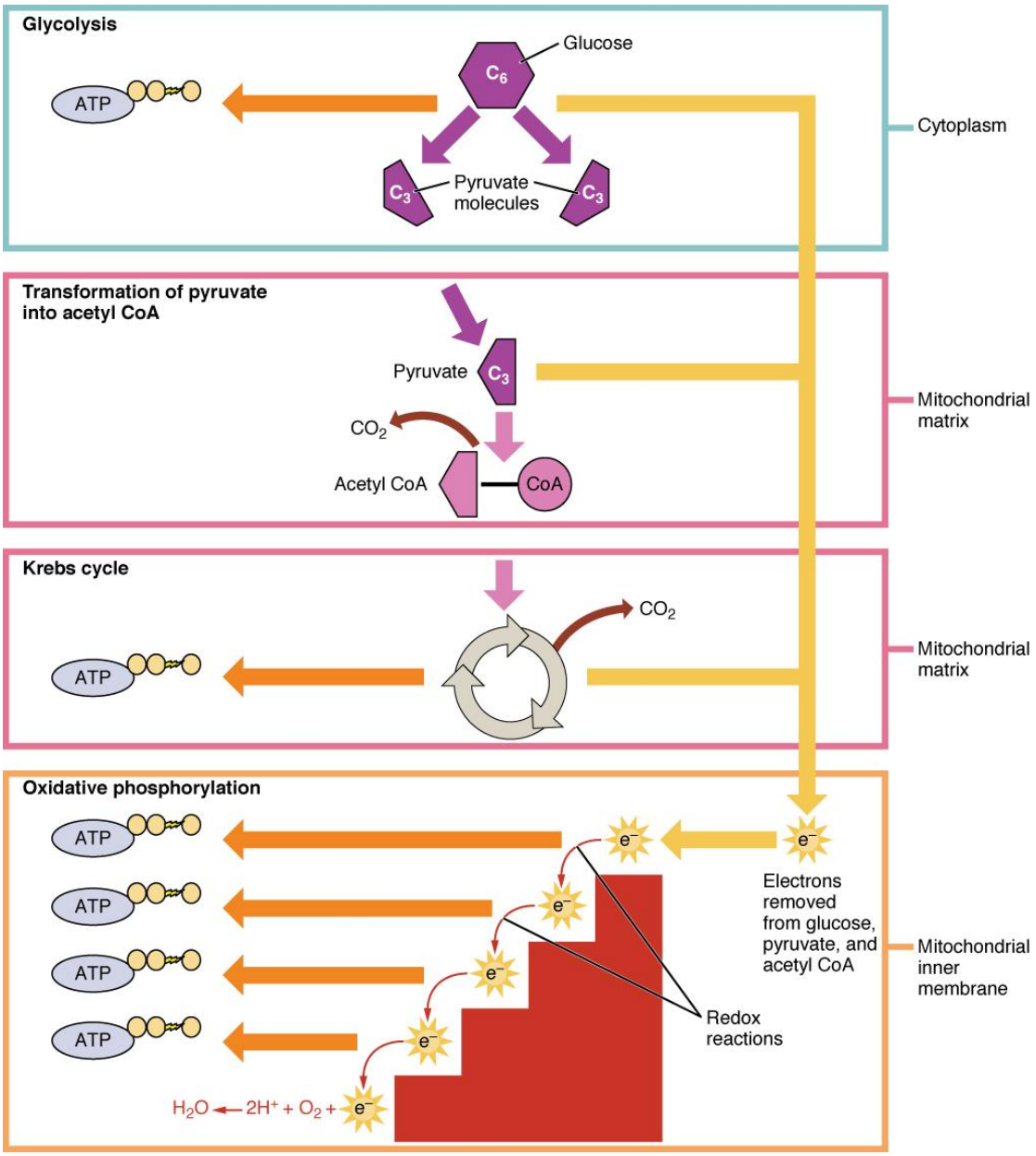
The table below indicates the class of dietary carbohydrate from which we derive the main sugars that enter our blood stream.

TABLE 1.1. COMMON CARBOHYDRATES IN OUR FOOD

Class	Examples	Made of
Polysaccharides	Starch Cellulose Glycogen	Glucose Glucose Glucose
Disaccharides	Sucrose Lactose Maltose	Glucose-fructose Glucose-galactose Glucose-glucose
Monosaccharides	Glucose Fructose Galactose	

During digestion, carbohydrates are broken down into simple, soluble sugars that can be transported across the intestinal wall into the circulatory system to be transported throughout the body. Carbohydrate digestion begins in the mouth with

the action of **salivary amylase** on starches and ends with mono saccharides being absorbed across the epithelium of the small intestine. Once the absorbed mono saccharides are transported to the tissues, the process of **cellular respiration** begins (Figure 1). This section will focus first on glycolysis, a process where the monosaccharide glucose is oxidized, releasing the energy stored in its bonds to produce ATP.



GLYCOLYSIS

The glycolytic pathway is employed by all tissues for the oxidation of glucose to provide energy (in the form of ATP) and intermediates for other metabolic pathways. **Glycolysis** is at the hub of carbohydrate metabolism because virtually all sugars, whether arising from the diet or from catabolic reactions in the body, can ultimately be converted to glucose . Pyruvate is the end product of glycolysis in cells with mitochondria and an adequate supply of oxygen. This series of ten reactions is called **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 cycle. Alternatively, pyruvate is reduced to lactate as NADH is oxidized to NAD^+ . This conversion of glucose to lactate is called **anaerobic glycolysis** 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 and parts of the eye) or in cells deprived of sufficient oxygen.

Glycolysis is defined as the sequence of reactions converting glucose (or glycogen) to pyruvate or lactate, with the production of ATP.

TRANSPORT OF GLUCOSE INTO CELLS

Glucose cannot diffuse directly into cells but enters by one of two transport mechanisms:a Na^+-independent, facilitated diffusion transport system or an ATP-dependent Na^+- monosaccharide cotransport system.

A. Sodium-independent facilitated diffusion transport system

This system is mediated by a family of 14 glucose transporters found in cell membranes. They are designated GLUT-1 to GLUT-14 (glucose transporter isoforms 1–14). These monomeric protein transporters exist in the membrane in two conformational states .Extracellular glucose binds to the transporter, which then alters its conformation, transporting glucose across the cell membrane.

1. Tissue specificity of glucose transporter gene expression: The GLUTs display a tissue-specific pattern of expression. For example, GLUT-3 is the primary glucose transporter in neurons. GLUT-1 is abundant in erythrocytes and the blood–brain barrier but is low in adult muscle, whereas GLUT-4 is abundant in muscle and adipose tissue. [Note: The number of GLUT-4 transporters active in these tissues is increased by insulin. GLUT-2 is abundant in liver, kidney, and β cells of the pancreas. The other GLUT isoforms also have tissue-specific distributions.

2. Specialized functions of glucose transporter isoforms: In facilitated diffusion, transporter-mediated glucose movement is down a concentration gradient (that is, from a high glucose concentration to a lower one and, therefore, does not require energy). For example, GLUT-1, GLUT-3, and GLUT-4 are primarily involved in glucose uptake from the blood. In contrast, GLUT-2, in the liver and kidney, can either transport glucose into these cells when blood glucose levels are high or transport glucose from these cells when blood glucose levels are low (for example, during fasting). GLUT-5 is unusual in that it is the primary transporter for fructose (not glucose) in the small intestine and the testes.

B. Sodium–monosaccharide cotransport system

This is an energy-requiring process that transports glucose "against" a concentration gradient (that is, from low glucose concentrations outside the cell to higher concentrations within the cell). This system is a transporter-mediated process in which the movement of glucose is coupled to the concentration gradient of Na+, which is transported into the cell at the same time. The transporter is a sodium-dependent glucose transporter (SGLT). This type of transport occurs in the epithelial cells of the intestine ,renal tubules, and choroid plexus. [Note: The choroid plexus, part of the blood–brain barrier, also contains GLUT-1.]

Reactions of glycolysis

The conversion of glucose to pyruvate occurs in two stages . 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. The subsequent reactions of glycolysis constitute an energy–generation phase in which a net of two molecules of ATP are formed by substrate-level phosphorylation per glucose molecule metabolized.

1. Phosphorylation of glucose

Glucose is phosphorylated to glucose 6-phosphate by hexokinase or glucokinase (both are isoenzymes). This is an irreversible reaction, dependent on ATP and Mg^{2+} .The enzyme hexokinase is present in almost all the tissues. It catalyses the phosphorylation of various hexoses (fructose, mannose etc.), has low Km for substrates (about 0.1 mM) and is inhibited by glucose 6-phosphate. **Glucokinase**

present in liver, catalyses the phosphorylation of only glucose, has high Km for glucose (10 mM) and is not inhibited by glucose 6-phosphate. Due to high affinity (low Km), glucose is utilized by hexokinase even at low concentration, whereas glucokinase acts only at higher levels of glucose i.e., after a meal when blood glucose concentration is above 100 mg/dl.

2. 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.

3. Phosphorylation of fructose 6-phosphate

The irreversible phosphorylation reaction catalyzed by phosphofructokinase-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 .

4. 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.

5. Isomerization of dihydroxyacetone phosphate

Triose phosphate isomerase interconverts dihydroxyacetone phosphate (DHAP) and glyceraldehyde 3-phosphate . DHAP 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.

6. Oxidation of glyceraldehyde 3-phosphate

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

7. 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.

8. Shift of the phosphate group

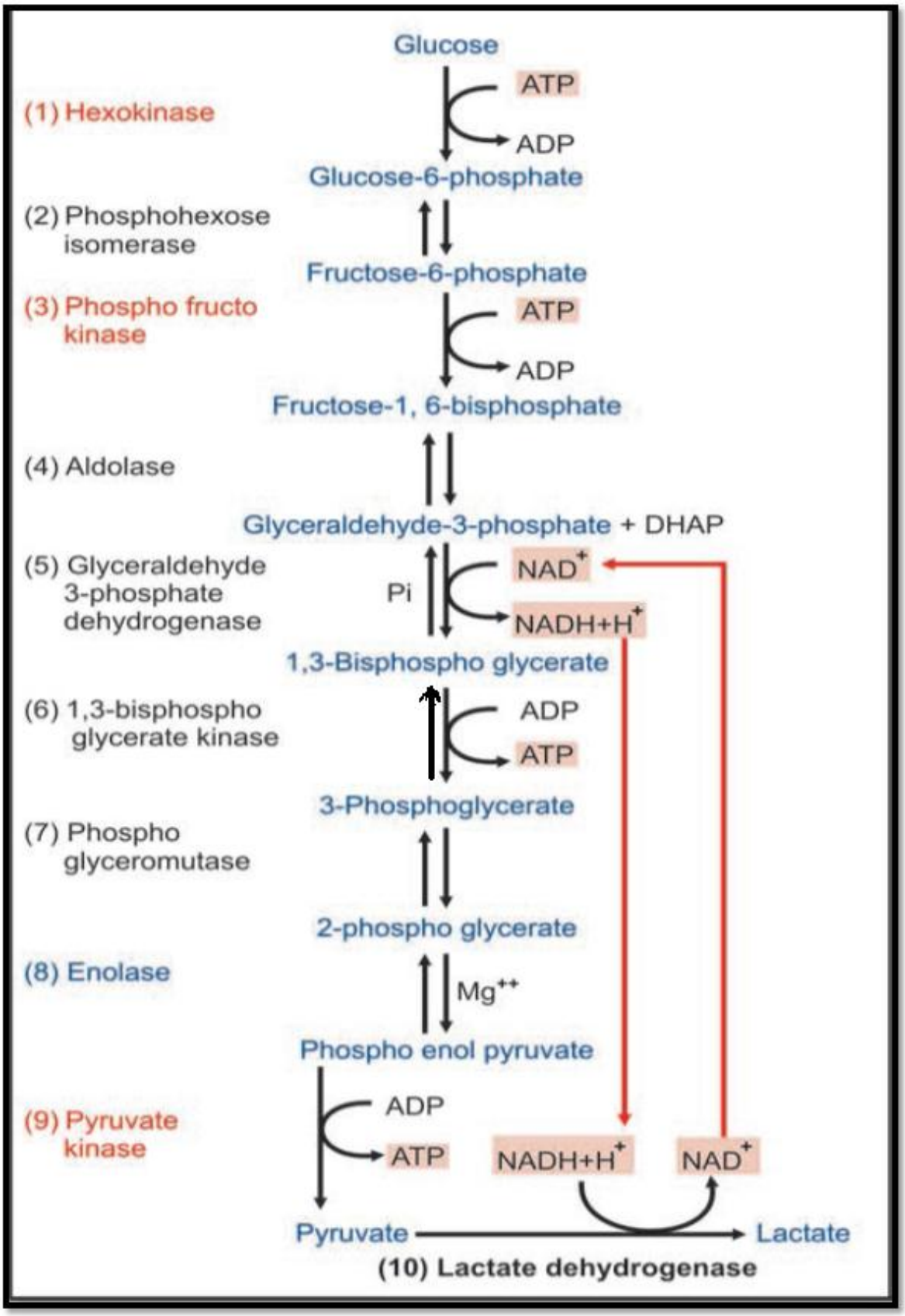
The shift of the phosphate group from carbon 3 to carbon 2 of phosphoglycerate by phosphoglycerate mutase is freely reversible.

9. Dehydration of 2-phosphoglycerate

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

10. Formation of pyruvate, producing ATP

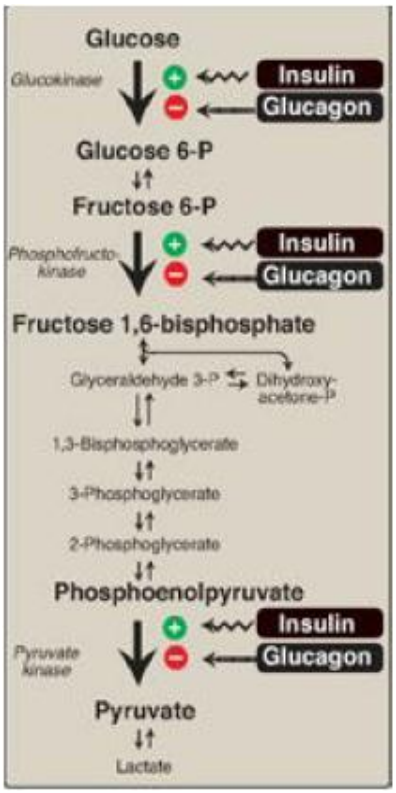
The conversion of PEP to pyruvate is catalyzed by pyruvate kinase (PK), the third irreversible reaction of glycolysis. The high-energy enol phosphate in PEP is used to synthesize ATP from ADP and is another example of substrate-level phosphorylation.


Glucose
ATP
(1) Hexokinase
ADP
Glucose-6-phosphate
(2) Phosphohexose isomerase
Fructose-6-phosphate
(3) Phospho fructo kinase
ATP
ADP
Fructose-1, 6-bisphosphate
(4) Aldolase
Glyceraldehyde-3-phosphate + DHAP
(5) Glyceraldehyde 3-phosphate dehydrogenase
Pi
NAD+
NADH+H+
1,3-Bisphospho glycerate
(6) 1,3-bisphospho glycerate kinase
ADP
ATP
3-Phosphoglycerate
(7) Phospho glyceromutase
2-phospho glycerate
(8) Enolase
Mg++
Phospho enol pyruvate
(9) Pyruvate kinase
ADP
ATP
NADH+H+
NAD+
Pyruvate
Lactate
(10) Lactate dehydrogenase

The overall equation for glycolysis:

Glucose + $2NAD^+$ + 2ADP + 2Pi ⟶ 2 Pyruvate + 2 NADH + $2H^+$ + 2ATP + $2H_2O$

HORMONAL REGULATION OF GLYCOLYSIS



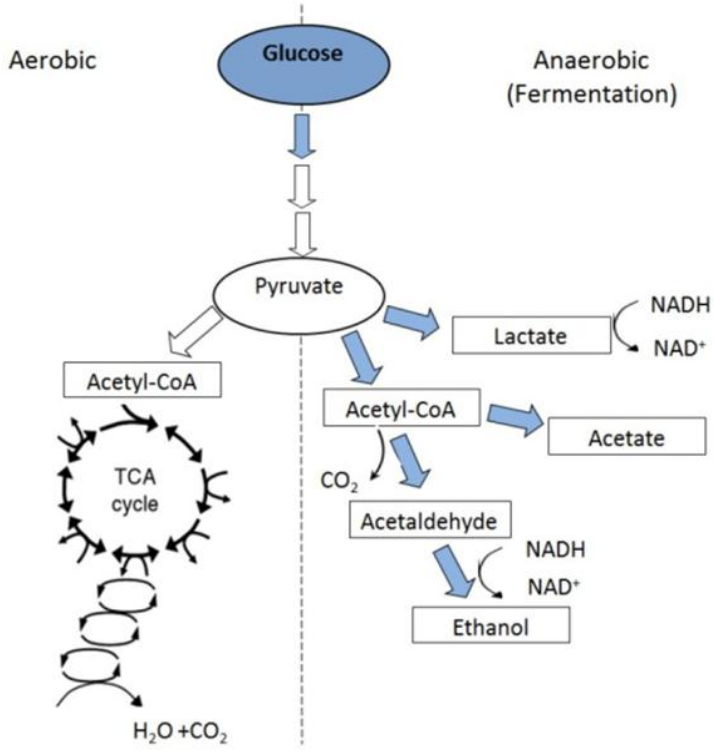
The regulation of glycolysis by allosteric activation or inhibition, or the covalent phosphorylation/dephosphorylation of rate-limiting enzymes, is short-term (that is, they influence glucose consumption over periods of minutes or hours). Superimposed on these moment-to-moment effects are slower, and often more profound, hormonal influences on gene expression, or the amount of enzyme protein synthesized. These effects can result in 10-fold to 20-fold increases in enzyme activity that typically occur over hours to days. Although the current focus is on glycolysis, reciprocal changes occur in the rate-limiting enzymes of gluconeogenesis. Regular consumption of meals rich in carbohydrate or administration of insulin initiates an increase in the amount of glucokinase , phosphofructokinase, and PK in the 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 absorptive state . Conversely, gene transcription and synthesis of glucokinase, phosphofructokinase, and PK are decreased when plasma glucagon is high and insulin is low (for example, as seen in fasting or diabetes).

Energy yield from glycolysis

Despite the production of some ATP during glycolysis, the end product, pyruvate or lactate, still contains most of the energy originally contained in glucose. The TCA cycle is required to release that energy completely .

1. Anaerobic glycolysis: Two molecules of ATP are generated for each molecule of glucose converted to two molecules of lactate . There is no net production or consumption of NADH.

2. Aerobic glycolysis: The direct consumption and formation of ATP is the same as in anaerobic glycolysis (that is, a net gain of two ATP per molecule of glucose). Two molecules of NADH are also produced per molecule of glucose. Ongoing aerobic glycolysis requires the oxidation of most of this NADH by the electron transport chain, producing approximately three ATP for each NADH molecule entering the chain .



Inherited enzyme deficiences of glycolysis

1. Pyruvate kinase deficiency:

Mature RBCs lack mitochondria and are, therefore, completely dependent on glycolysis for ATP production. ATP is required to meet the metabolic needs of RBCs and to fuel the ion pumps necessary for the maintenance of the flexible, biconcave shape that allows them to squeeze through narrow capillaries. The anemia observed in glycolytic enzyme deficiencies is a consequence of the reduced rate of glycolysis, leading to decreased ATP production. The resulting alterations in the RBC membrane lead to changes in cell shape and, ultimately, to phagocytosis by cells of the reticuloendothelial system, particularly macrophages of the spleen. The premature death and lysis of RBCs result in hemolytic anemia.

Among patients exhibiting the rare genetic defects of glycolytic enzymes, the majority has a deficiency in PK. The effects of PK deficiency are restricted to RBCs and include mild-to-severe nonspherocytic hemolytic anemia, with the severe form requiring regular transfusions. [Note: Hepatic PK is encoded by the same gene as the RBC isozyme. Liver cells show no effect, however, because they have mitochondria and can generate ATP by oxidative phosphorylation.] Severity depends both on the degree of enzyme deficiency (generally 5–35% of normal levels) and on the extent to which RBCs compensate by synthesizing increased levels of 2,3-BPG . Almost all individuals with PK deficiency have a mutant enzyme that shows abnormal properties such as altered kinetics. Individuals heterozygous for PK deficiency have resistance to the most severe forms of malaria.

2. Lactic acidosis:

Elevated concentrations of lactate in the plasma, termed lactic acidosis (a type of metabolic 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 phosphorylation and decreased ATP synthesis. To survive, the cells rely on anaerobic glycolysis for generating ATP, producing lactic acid as the end product. The excess oxygen required to recover from a period when the availability of oxygen has been inadequate is termed the "oxygen debt.".