GLYCOLYSIS

In glycolysis (from the Greek glykys, meaning "sweet," and lysis, meaning "splitting"), a molecule of glucose is degraded in a series of enzyme-catalyzed reactions to yield two molecules of the three-carbon compound pyruvate. During the sequential reactions of glycolysis, some of the free energy released from glucose is conserved in the form of ATP and NADH.

Glycolysis was the first metabolic pathway to be elucidated and is probably the best understood. From Eduard Buchner's discovery in 1897 of fermentation in broken extracts of yeast cells until the elucidation of the whole pathway in yeast.

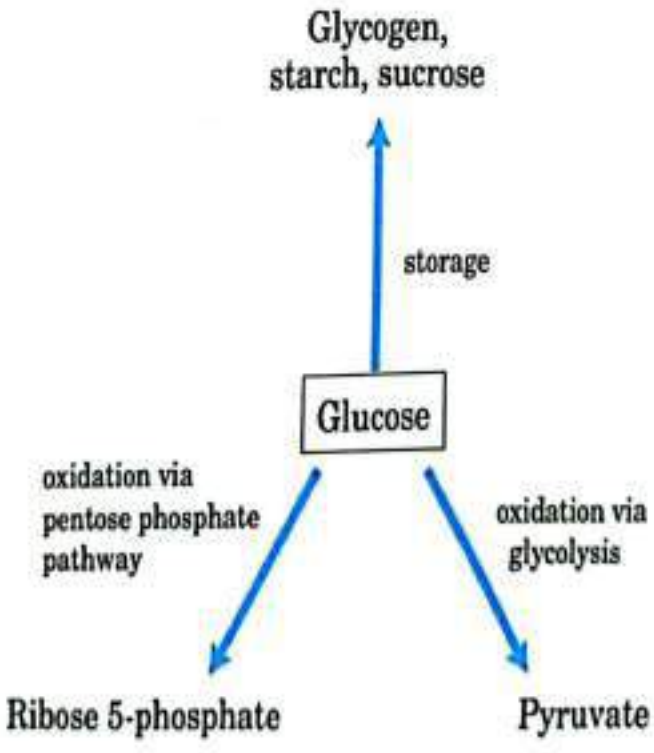


Fig. 1: **Major pathways of glucose utilization.** Although not the only possible fates for glucose, these three pathways are the most significant in terms of the amount of glucose that flows through them in most cells.

Glycolysis has two phases

The breakdown of the six-carbon glucose into two molecules of the three-carbon pyruvate occurs in ten steps (2-stages)

First stage:

The first five steps of which constitute the preparatory phase (Fig. 2a).

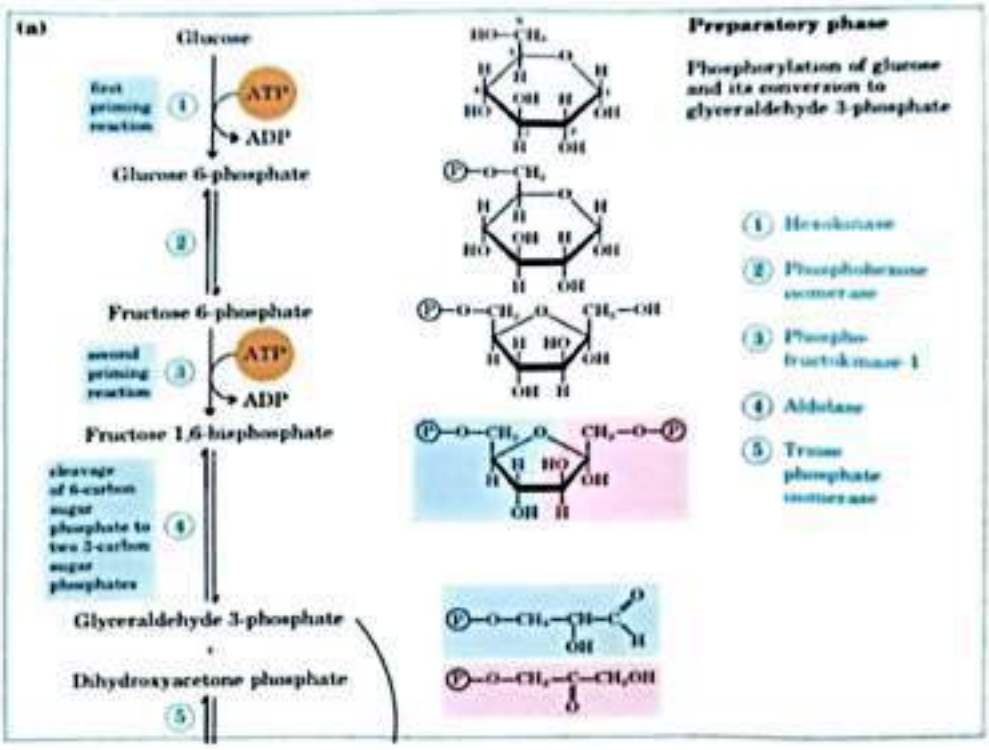
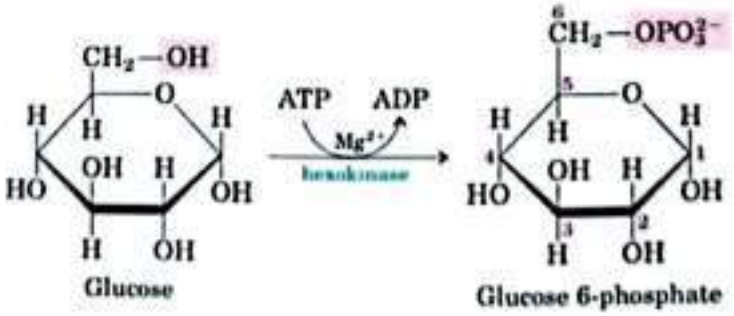
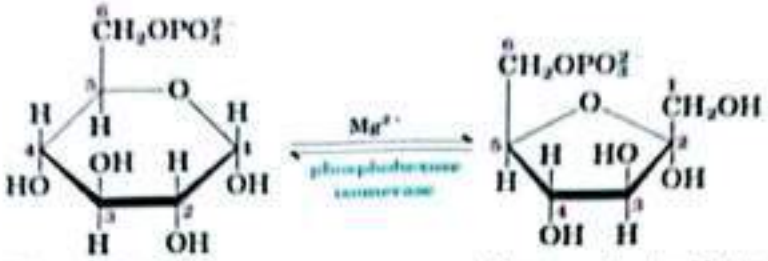


Figure 2a: Preparatory phase of glycolysis

In these reactions, glucose is first phosphorylated at the hydroxyl group on C-6 (step 1).



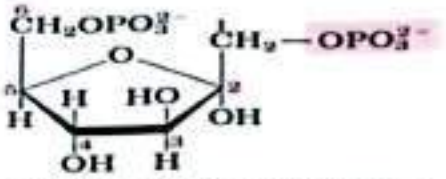
The D-glucose-6-phosphate thus formed is converted to D-fructose-6-phosphate (step 2) by phosphohexose isomerase and Mg^{+2} as a cofactor.



Glucose 6-phosphate — Fructose 6-phosphate

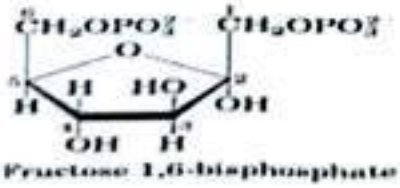
which is again phosphorylated, this time at C-1, to yield D-fructose-1,6-bisphosphate (step 3).

Fructose 6-phosphate

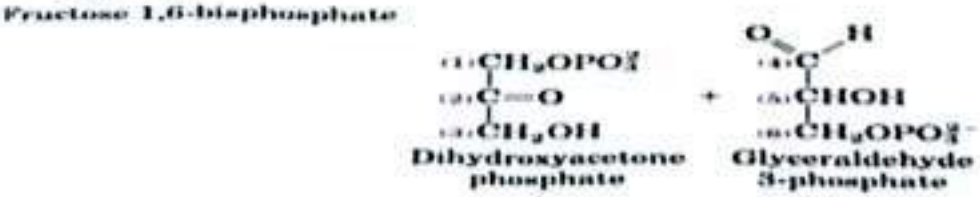


Fructose 1,6-bisphosphate

Fructose-1,6-bisphosphate is split to yield two three-carbon molecules, dihydroxyacetone phosphate and glyceraldehyde 3-phosphate (step 4); this is the "lysis" step that gives the pathway its name.

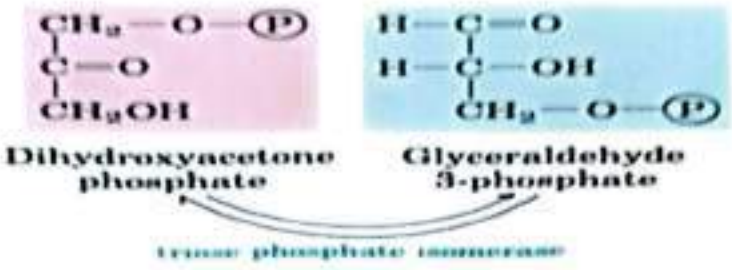


Fructose 1,6-bisphosphate



Dihydroxyacetone phosphate + Glyceraldehyde 3-phosphate

The dihydroxyacetone phosphate is isomerized to a second molecule of glyceraldehyde-3-phosphate (step 5).



Second stage:

The energy gain comes in the payoff phase of glycolysis (Fig. 2b).

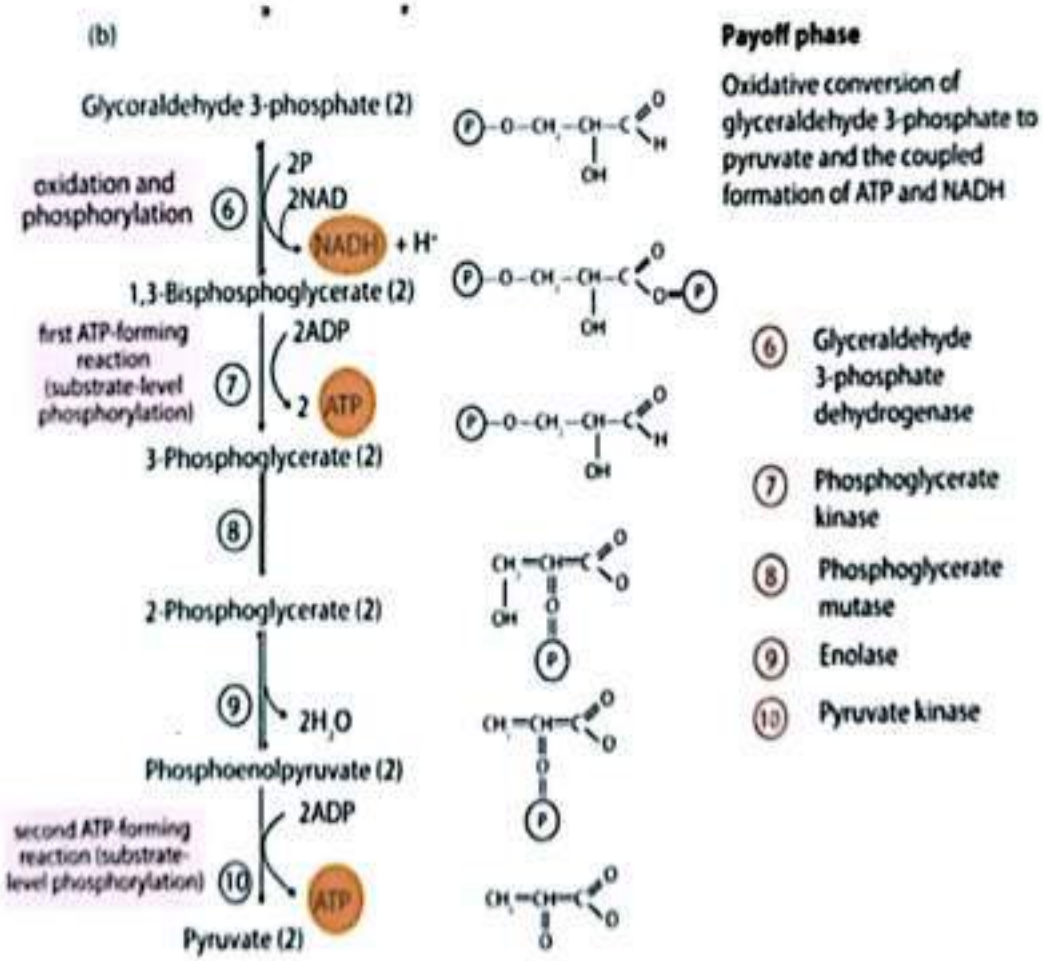
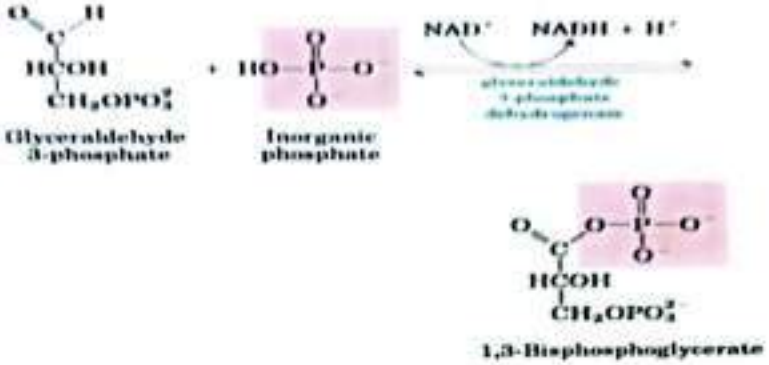
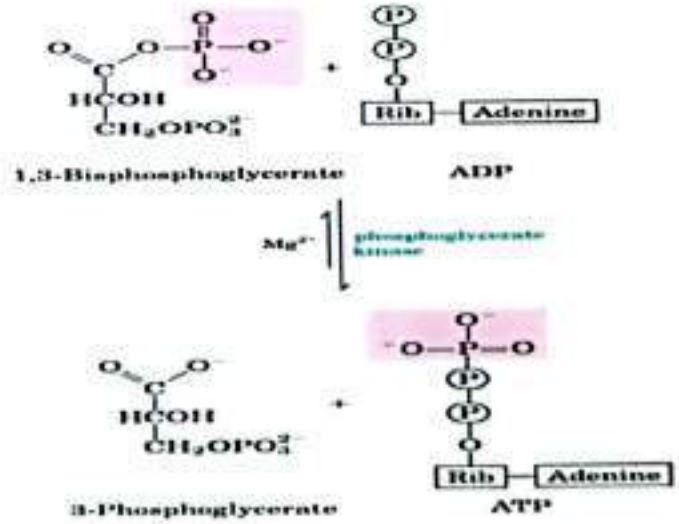


Figure 2b: payoff face of glycolysis

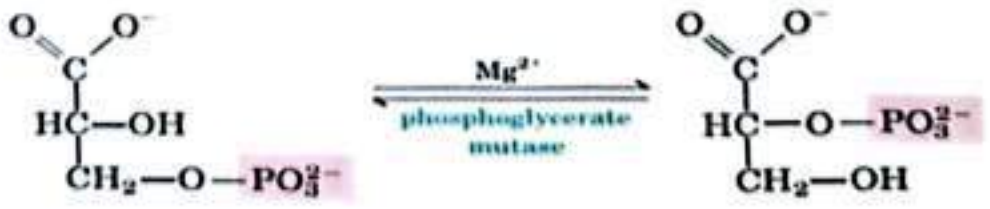
Each molecule of glyceraldehyde 3-phosphate is oxidized and phosphorylated by inorganic phosphate (not by ATP) to form 1,3-bisphosphoglycerate (step 6).



Energy is then released as the two molecules of 1,3-bisphosphoglycerate are converted to two molecules of 3-phosphoglycerate (steps 7).



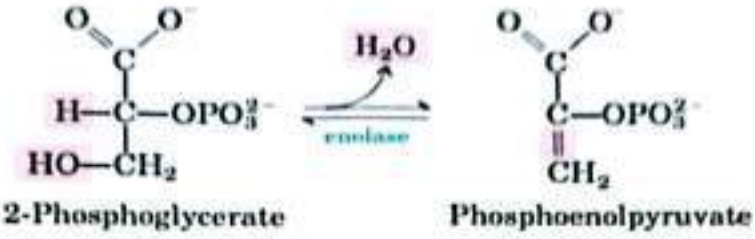
The step 8 of glycolysis involves conversion of 3-Phosphoglycerate to 2-Phosphoglycerate



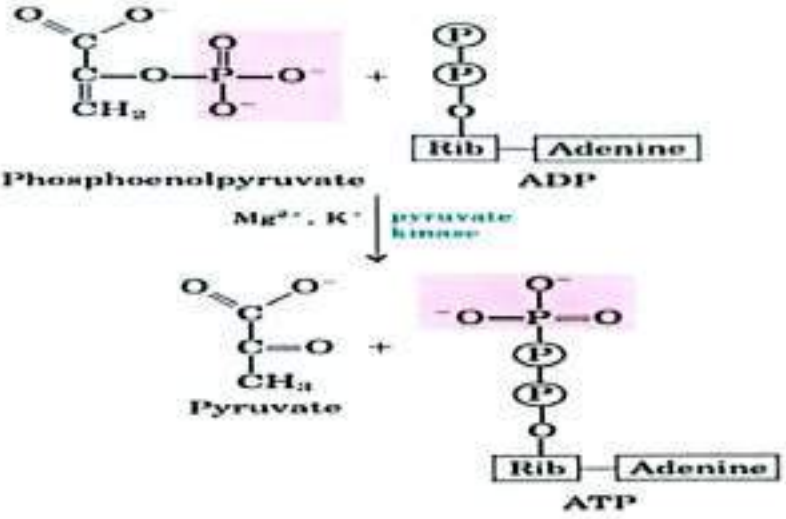
3-Phosphoglycerate

2-Phosphoglycerate

The step 9 of glycolysis involves dehydration of 2-Phosphoglycerate to Phosphoenolpyruvate



Final step (step 10) of glycolysis was transfer of the phosphoryl group from phosphoenolpyruvate to ADP to give pyruvate and ATP.



Much of this energy is conserved by the coupled phosphorylation of four molecules of ADP to ATP. The net yield is two molecules of ATP per molecule of glucose used, because two molecules of ATP were invested in the preparatory phase. Energy is also conserved in the payoff phase in the formation of two molecules of NADH per molecule of glucose.

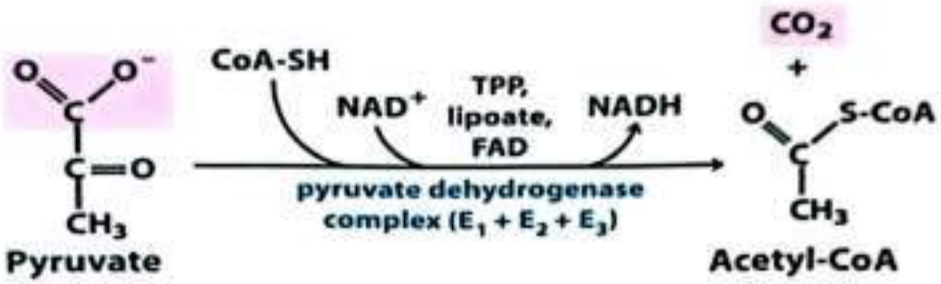
In the sequential reactions of glycolysis, three types of chemical transformations are particularly noteworthy:

(1) Degradation of the carbon skeleton of glucose to yield pyruvate,

(2) Phosphorylation of ADP to ATP by high-energy phosphate compounds formed during glycolysis, and

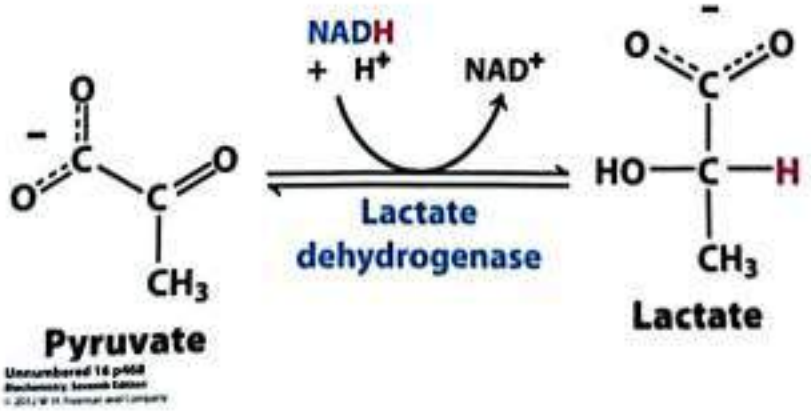
(3) Transfer of a hydride ion to NAD^+, forming NADH.

Fates of Pyruvate: With the exception of some interesting variations in the bacterial realm, the pyruvate formed by glycolysis is further metabolized via one of three catabolic routes. In aerobic organisms or tissues, under aerobic conditions, glycolysis is only the first stage in the complete degradation of glucose (Fig. 3). Pyruvate is oxidized, with loss of its carboxyl group as CO_2, to yield the acetyl group of acetyl coenzyme A



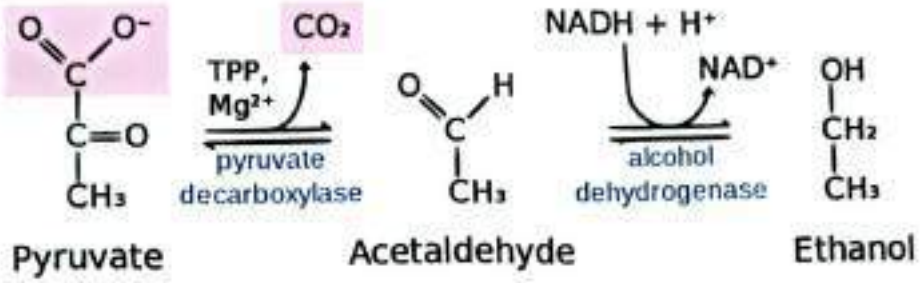
The acetyl group is then oxidized completely to CO_2 by the citric acid cycle. The electrons from these oxidations are passed to O_2 through a chain of carriers in the mitochondrion, to form H_2O. The energy from the electron-transfer reactions drives the synthesis of ATP in the mitochondrion.

The second route for pyruvate is its reduction to lactate via lactic acid fermentation. When vigorously contracting skeletal muscle must function under low oxygen conditions (hypoxia), NADH cannot be reoxidized to NAD^+, but NAD^+ is required as an electron acceptor for the further oxidation of pyruvate. Under these conditions pyruvate is reduced to lactate, accepting electrons from NADH and thereby regenerating the NAD^+ necessary for glycolysis to continue.



Certain tissues and cell types (retina and erythrocytes, for example) convert glucose to lactate even under aerobic conditions, and lactate is also the product of glycolysis under anaerobic conditions in some microorganisms (Fig. 3).

The third major route of pyruvate catabolism leads to ethanol. In some plant tissues and in certain invertebrates, protists, and microorganisms such as brewer's yeast, pyruvate is converted under hypoxic or anaerobic conditions into ethanol and CO_2, a process called ethanol (alcohol) fermentation.



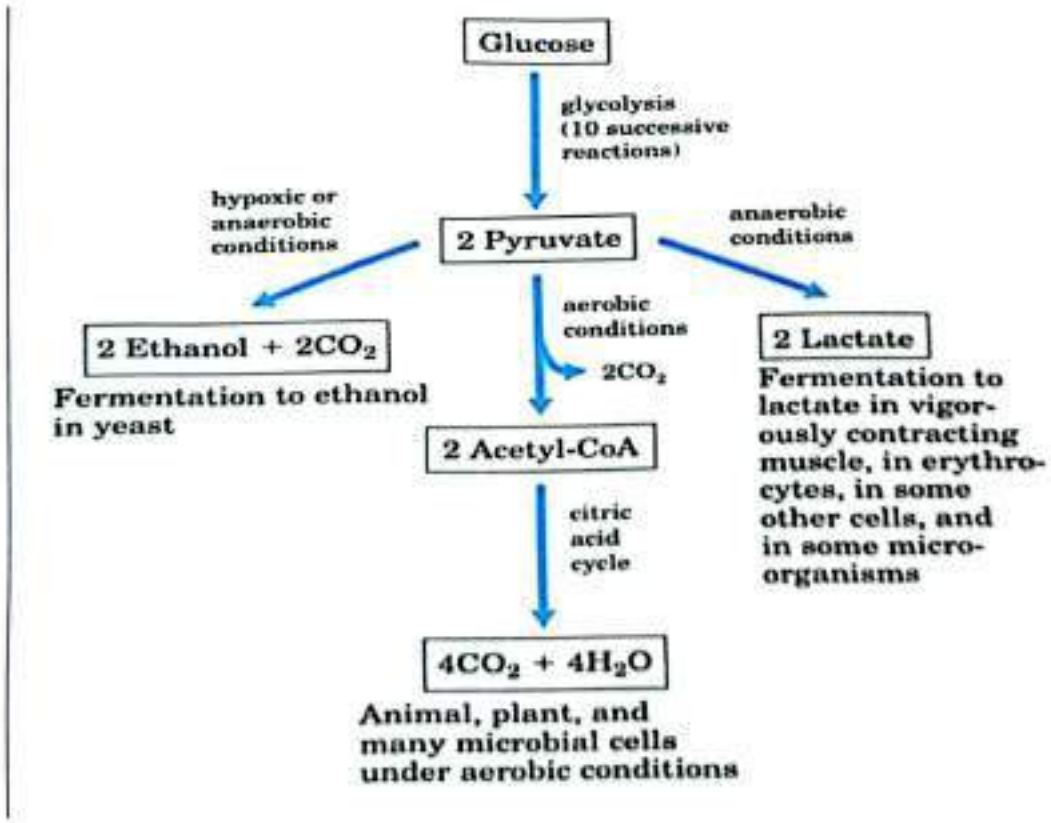
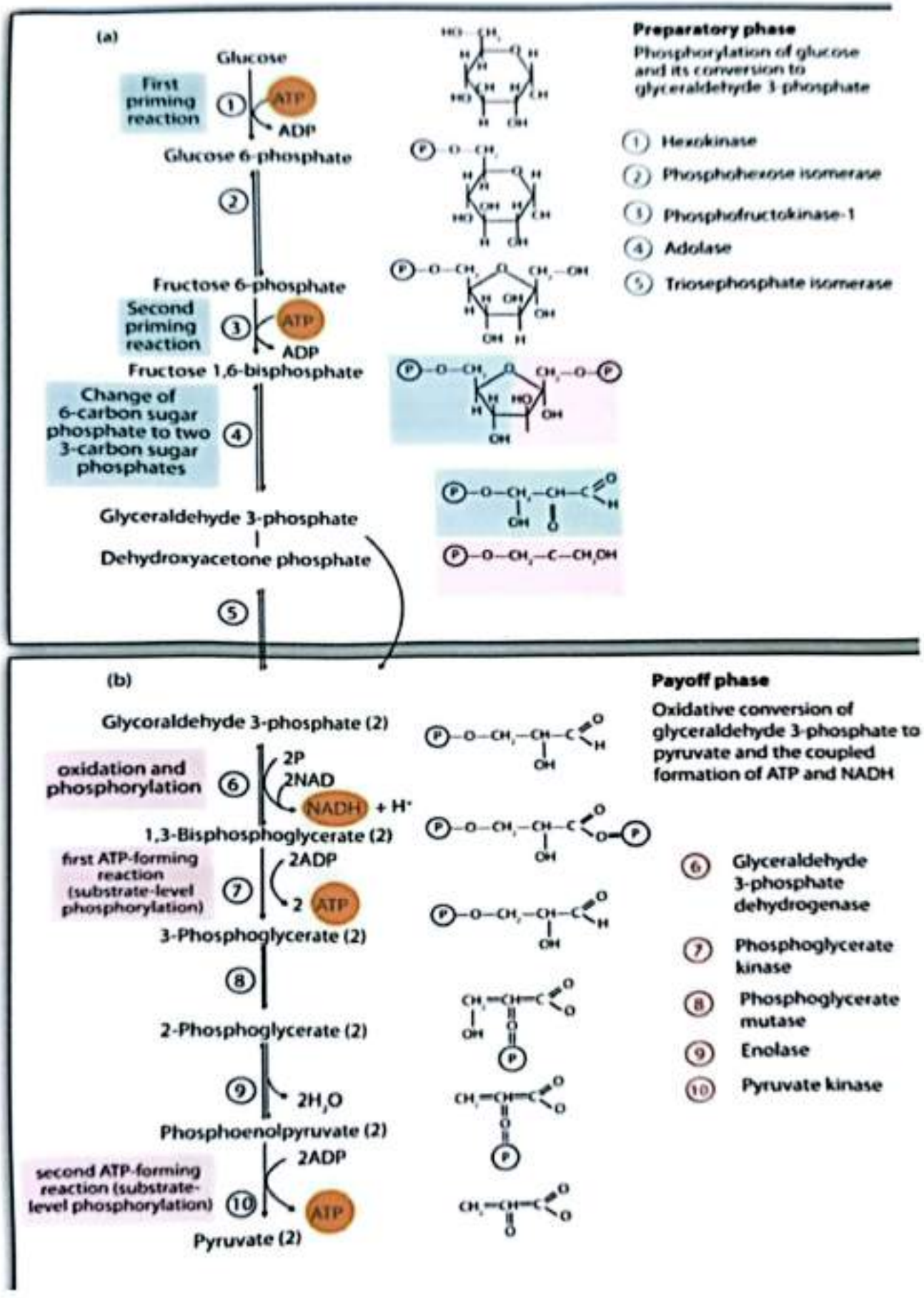


Figure 3: Three possible catabolic fates of the pyruvate formed in glycolysis



Pathway of entry of different sugar into glycolysis

Disaccharides must be hydrolyzed to monosaccharides before entering cells. Intestinal disaccharides and dextrins are hydrolyzed by enzymes attached to the outer surface of the intestinal epithelial cells:

$$\text{Dextrin} + n\text{H}_2\text{O} \xrightarrow[\text{dextrinase}]{} n \text{ D-glucose}$$

$$\text{Maltose} + \text{H}_2\text{O} \xrightarrow[\text{maltase}]{} 2 \text{ D-glucose}$$

$$\text{Lactose} + \text{H}_2\text{O} \xrightarrow[\text{lactase}]{} \text{D-galactose} + \text{D-glucose}$$

$$\text{Sucrose} + \text{H}_2\text{O} \xrightarrow[\text{sucrase}]{} \text{D-fructose} + \text{D-glucose}$$

$$\text{Trehalose} + \text{H}_2\text{O} \xrightarrow[\text{trehalase}]{} 2 \text{ D-glucose}$$

Hexoses can enter the glycolysis pathway from different places, as shown in Figure 4

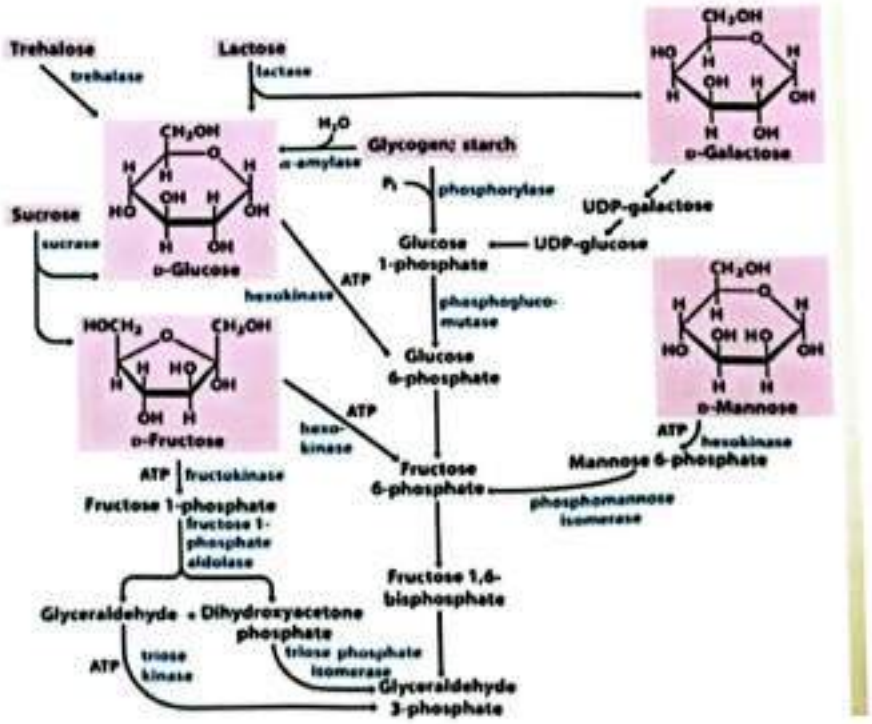
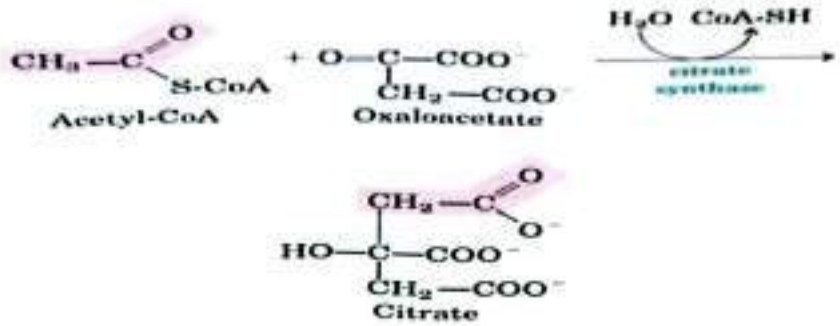


Figure 4 :Entry of glycogen, starch, disaccharides, and hexoses into the preparatory stage of glycolysis

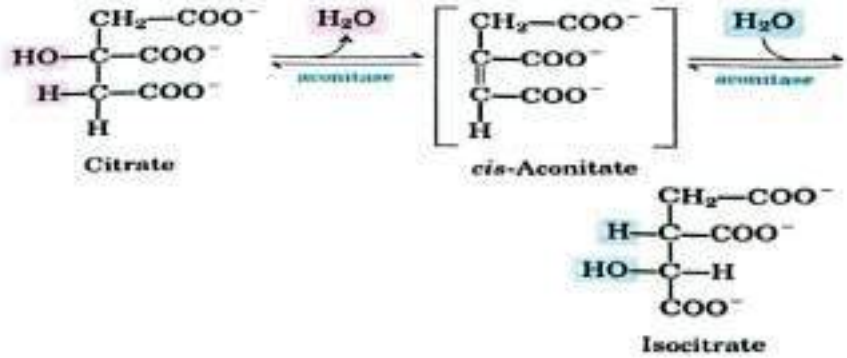
Citric acid cycle

The citric acid Cycle has eight steps, this cycle takes place inside the mitochondria, which is the highest source of energy release, and takes place according to the following steps

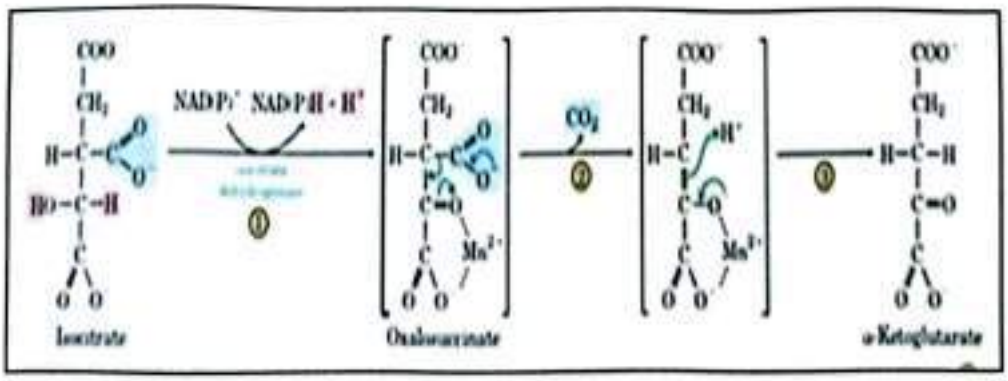
1-Formation of Citrate



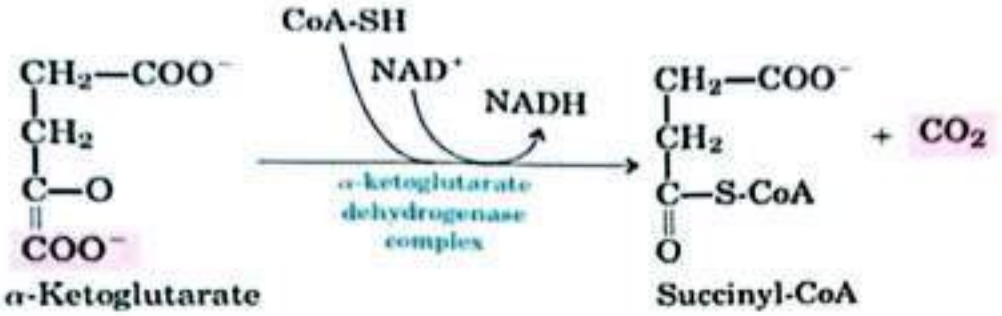
2-Formation of Isocitrate via cis-Aconitate



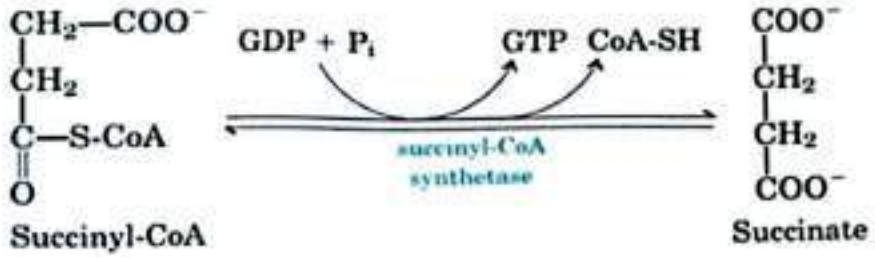
3-Oxidation of Isocitrate to α-Ketoglutarate and CO_2



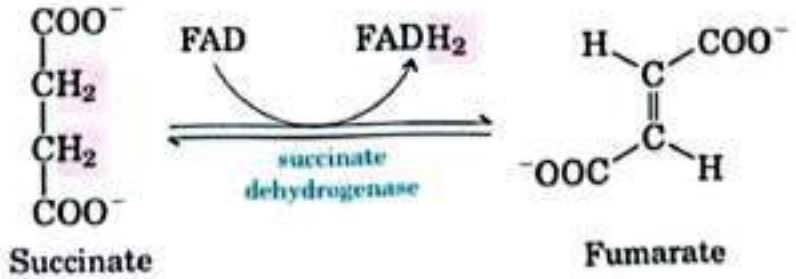
4-Oxidation of α-Ketoglutarate to Succinyl-CoA and CO_2



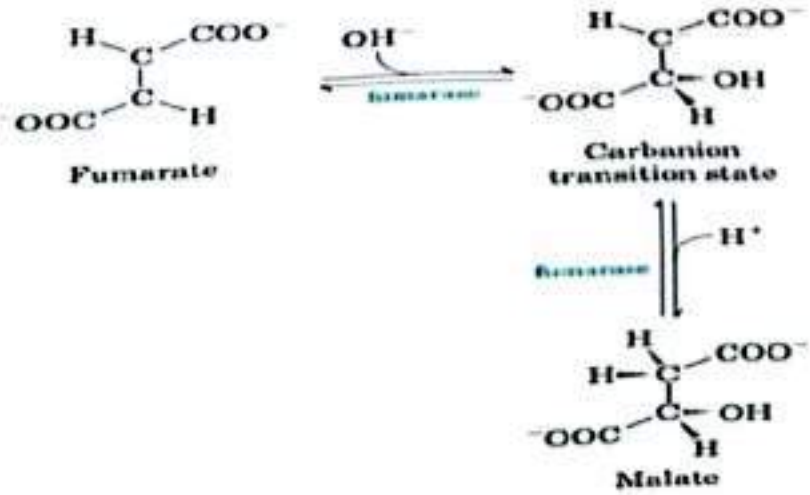
5-Conversion of Succinyl-CoA to Succinate



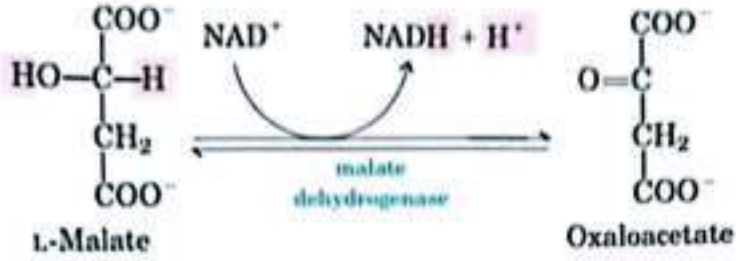
6-Oxidation of Succinate to Fumarate



7-Hydration of Fumarate to Malate



8-Oxidation of Malate to Oxaloacetate



KREBS CYCLE (CITRIC ACID CYCLE)

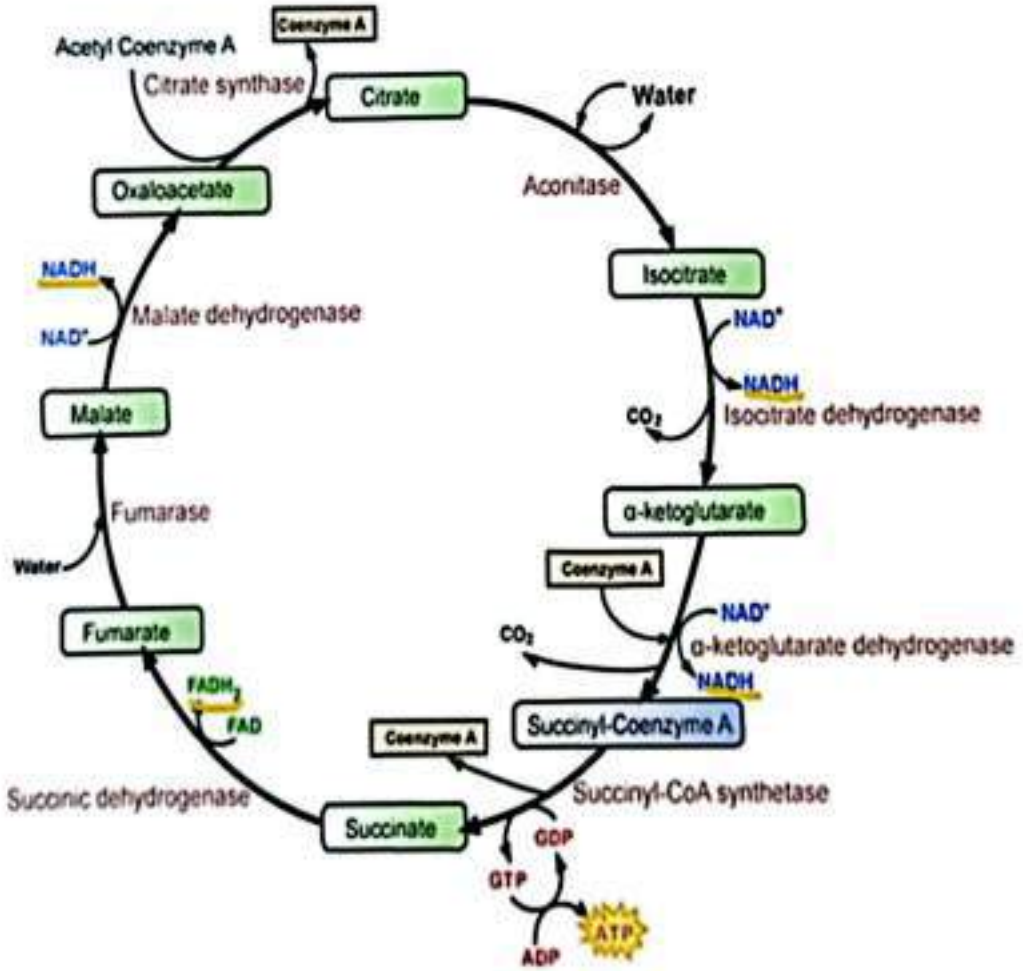


Figure 5 : TCA Cycle

Routes of NADH crossing the mitochondrial wall

NADH molecules produced from glycolysis in the cytoplasm cannot cross the mitochondrial wall to release energy, so they depend on two known pathways, the malate pathway and the glycerol phosphate pathway, and the type of pathway depends on the type of tissue.

Malate and Glycerol phosphate Shuttle

The fate of NADH molecules from glycolysis in aerobic cells is to cross the mitochondrial envelope through two pathways, the malate shuttle and the glycerol phosphate shuttle, depending on the type of tissue in which the glycolysis takes place. The malate shuttle occurs in the cells of the liver, heart, and kidneys, and the glycerol phosphate shuttle occurs in the muscle and brain cells.

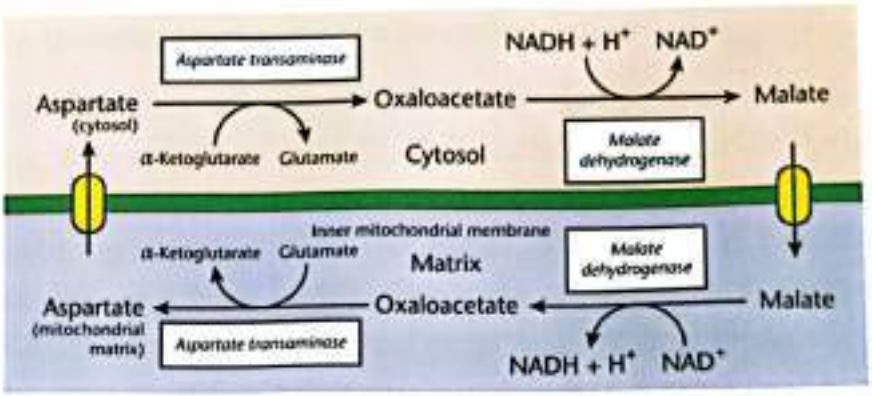


Figure 6: Malate Shuttle

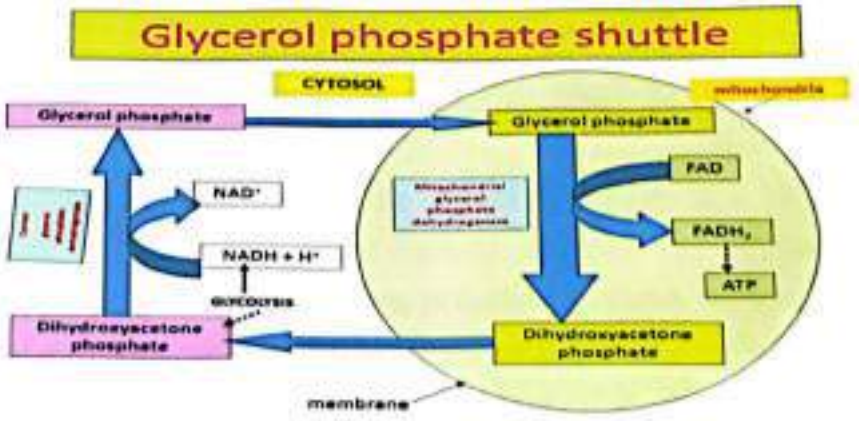


Figure 7: Glycerol phosphate shuttle

Types of phosphorylation

There are two different types of phosphorylation

1- Phosphorylation at the level of the substrate: It occurs when a phosphate group is transferred from the substrate to ADP to obtain ATP. An example of this is the reactions in the process of glycolysis, where the compounds 1,3-diphosphoglycerate and phosphoenolpyruvate are formed, which interact with ADP to form ATP, as well as the compound Succinyl CoA. In the TCA cycle, which is used to convert GDP to GTP, the latter is converted to ATP

2- Oxidative phosphorylation: It occurs at the expense of a large amount of energy resulting from the transfer of electrons through the respiratory chain from NADH to oxygen.

Electron transport and oxidative phosphorylation

It was found when glycolysis and during the TCA cycle, we got the reduction equivalents of NADH and FADH, and in order to continue working in the course of the cycles, the cell must oxidize these equivalents to be used again as we know that chemical oxidation is the removal of electrons and vice versa (Reduction is the reception of electrons). Thus, when NADH is oxidized, there must be an acquired or acceptor of electrons, and these reactions are called oxidation-reduction reactions.

In aerobic conditions, the cell acts as a final acceptor of electrons resulting from the oxidation of NADH, as in the following equation:

$$NADH + H^+ + 1/2O_2 \longrightarrow NAD^+ + H_2O$$

This process is accompanied by the release of energy in a large amount (-52.5 mole\kcal) and this is done through a series and several enzymatic stages. Each stage is an oxidation-reduction process associated with the release of specific energy. The enzymes responsible for this together form the respiratory chain or the chain of transmission of electrons, and these electrons It is transmitted by the compounds that make up this chain.

The enzymes that make up the respiratory chain are in the mitochondrial inner membrane structure in eukaryotic cells while this chain is attached to the plasma cell membrane in prokaryotic cells.

The cell benefits from the energy resulting from the flow of electrons in the respiratory chain through the phosphorylation of ADP to ATP, and this process associated with the transfer of electrons is called oxidative phosphorylation

The CO_2 leaves the cell as the final product of the cellular respiration process, while the hydrogen atoms (or their electron equivalent) flow through the respiratory chain to molecular oxygen, which is the final electron acceptor (for hydrogen atoms) in the respiration process. The respiratory chain can be illustrated by the following diagram:

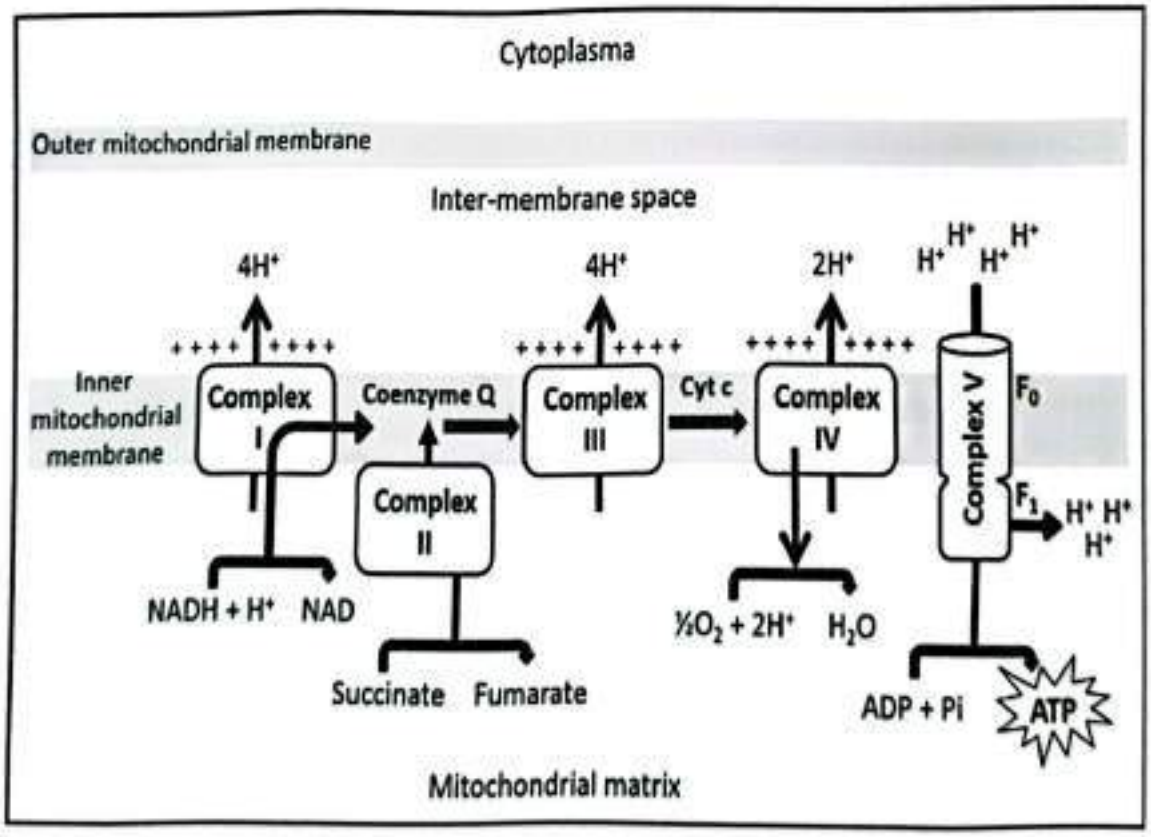


Figure 8: Respiratory chain and oxidative phosphorylation

Calculation of energy

Flavin adenine dinucleotide
Nicotinamide adenine dinucleotide

2NADH + 2ATP 2NADH 2 (3NADH + 1 $FADH_2$ + 1ATP)

Glucose ----------> 2 pyruvate ---------> 2Acetyl Co-A----------> TCA

Each of NADH gives 2.5 or 1.5 ATP according to the type of tissue

- In brain + muscles = 1.5
- In heart + liver + kidney = 2.5 Each of $FADH_2$ gives 1.5 ATP .

Calculation of energy

From glycolysis [2ATP + 3ATP or 5ATP]= **5** or **7 ATP**

From conversion of pyruvate to Acetyl CoA = 5 ATP

From TCA = 2*[(3*2.5)+(1*1.5)+(1 ATP)]= 20 ATP

The total energy is either 30 or 32 ATP

Pentose Phosphate Pathway of Glucose Oxidation

In most animal tissues, the major catabolic fate of glucose 6-phosphate is glycolytic breakdown to pyruvate, much of which is then oxidized via the citric acid cycle, ultimately leading to the formation of ATP. Glucose 6-phosphate does have other catabolic fates, however, which lead to specialized products needed by the cell. Of particular importance in some tissues is the oxidation of glucose 6-phosphate to pentose phosphates by the pentose phosphate pathway (also called the phosphogluconate pathway or the hexose monophosphate pathway; Fig. (14). In this oxidative pathway, NADP is the electron acceptor, yielding NADPH. Rapidly dividing cells, such as those of bone marrow, skin, and intestinal mucosa, use the pentoses to make RNA, DNA, and such coenzymes as ATP, NADH, $FADH_2$, and coenzyme A. In other tissues, the essential product of the pentose phosphate pathway is not the pentoses but the electron donor NADPH, needed for reductive biosynthesis or to counter the damaging

effects of oxygen radicals. Tissues that carry out extensive fatty acid synthesis (liver, adipose, lactating mammary gland) or very active synthesis of cholesterol and steroid hormones (liver, adrenal gland, gonads) require the NADPH provided by the pathway. Erythrocytes and the cells of the lens and cornea are directly exposed to oxygen and thus to the damaging free radicals generated by oxygen.

The first reaction of the pentose phosphate pathway (Fig. 9) is the oxidation of glucose 6-phosphate by glucose 6-phosphate dehydrogenase (G6PD) to form 6-phosphogluconolactone, an intramolecular ester. NADP is the electron acceptor, and the overall equilibrium lies far in the direction of NADPH formation. The lactone is hydrolyzed to the free acid 6-phosphogluconate by a specific lactonase, then 6-phosphogluconate undergoes oxidation and decarboxylation by 6-phosphogluconate dehydrogenase to form ribulose-5-phosphate. This reaction generates a second molecule of NADPH. Phosphopentose isomerase converts ribulose-5-phosphate to its aldose isomer, ribose-5-phosphate. The net result is the production of NADPH, a reductant for biosynthetic reactions, and the ribose 5-phosphate, is a precursor for nucleotide synthesis.

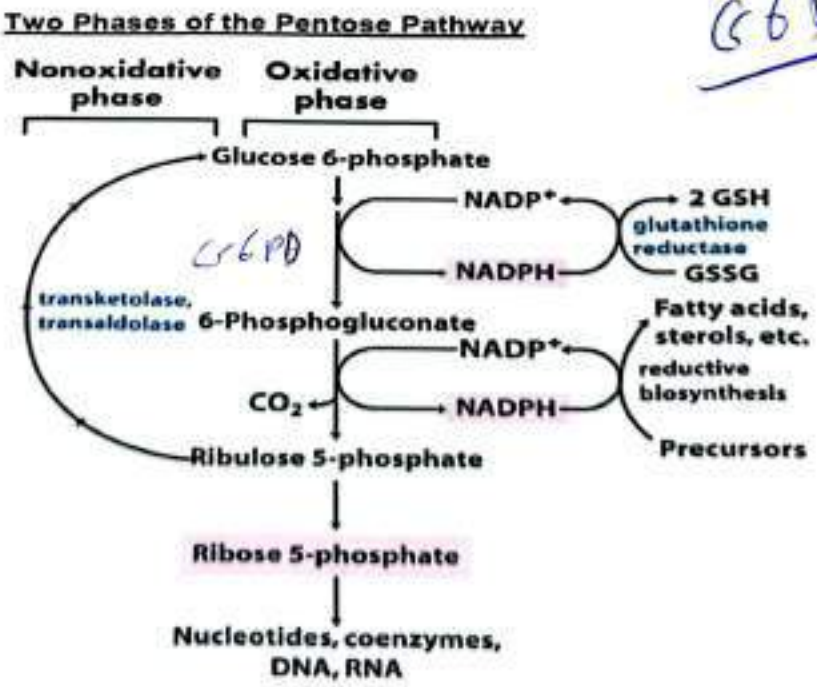


Figure 9: Pentose phosphate pathway

Gluconeogenesis

The central role of glucose in metabolism arose early in evolution, and this sugar remains the nearly universal fuel and building block in modern organisms, from microbes to humans. In mammals, some tissues depend almost completely on glucose for their metabolic energy. For the human brain and nervous system, as well as the erythrocytes, testes, renal medulla, and embryonic tissues, glucose from the blood is the sole or major fuel source. The brain alone requires about 120 g of glucose each day—more than half of all the glucose stored as glycogen in muscle and liver. However, the supply of glucose from these stores is not always sufficient; between meals and during longer fasts, or after vigorous exercise, glycogen is depleted. For these times, organisms need a method for synthesizing glucose from noncarbohydrate precursors. This is accomplished by a pathway called gluconeogenesis ("formation of new sugar"), which converts pyruvate and related three- and four-carbon compounds to glucose. Gluconeogenesis occurs in all animals, plants, fungi, and microorganisms. The reactions are essentially the same in all tissues and all species. The important precursors of glucose in animals are three-carbon compounds such as lactate, pyruvate, and glycerol, as well as certain amino acids (Fig. 7). In mammals, gluconeogenesis takes place mainly in the liver, and to a lesser extent in renal cortex. The glucose produced passes into the blood to supply other tissues.

Glucose is the primary fuel material for the functioning of the brain and muscle structure. During fasting, the liver has enough glycogen stores to supply the body with glucose for a period of 12-24 hours. The biodegradation of amino acids) and the process of glucose formation occurs in the liver and kidneys and in the epithelial cells of the intestine, where there are special enzymes necessary for the process of generating glucose in these organs. The main pathway for the formation of glucose from α-keto acids is the pathway of converting pyruvate to glucose, and this is the inverse outcome of the glycolysis process. From the eleven reactions of glycolysis, there are 8 of them reverse that can be used to generate glucose,

but there are 3 non-reversible reactions, so there are side reactions (replacement) to complete the process of generating glucose.

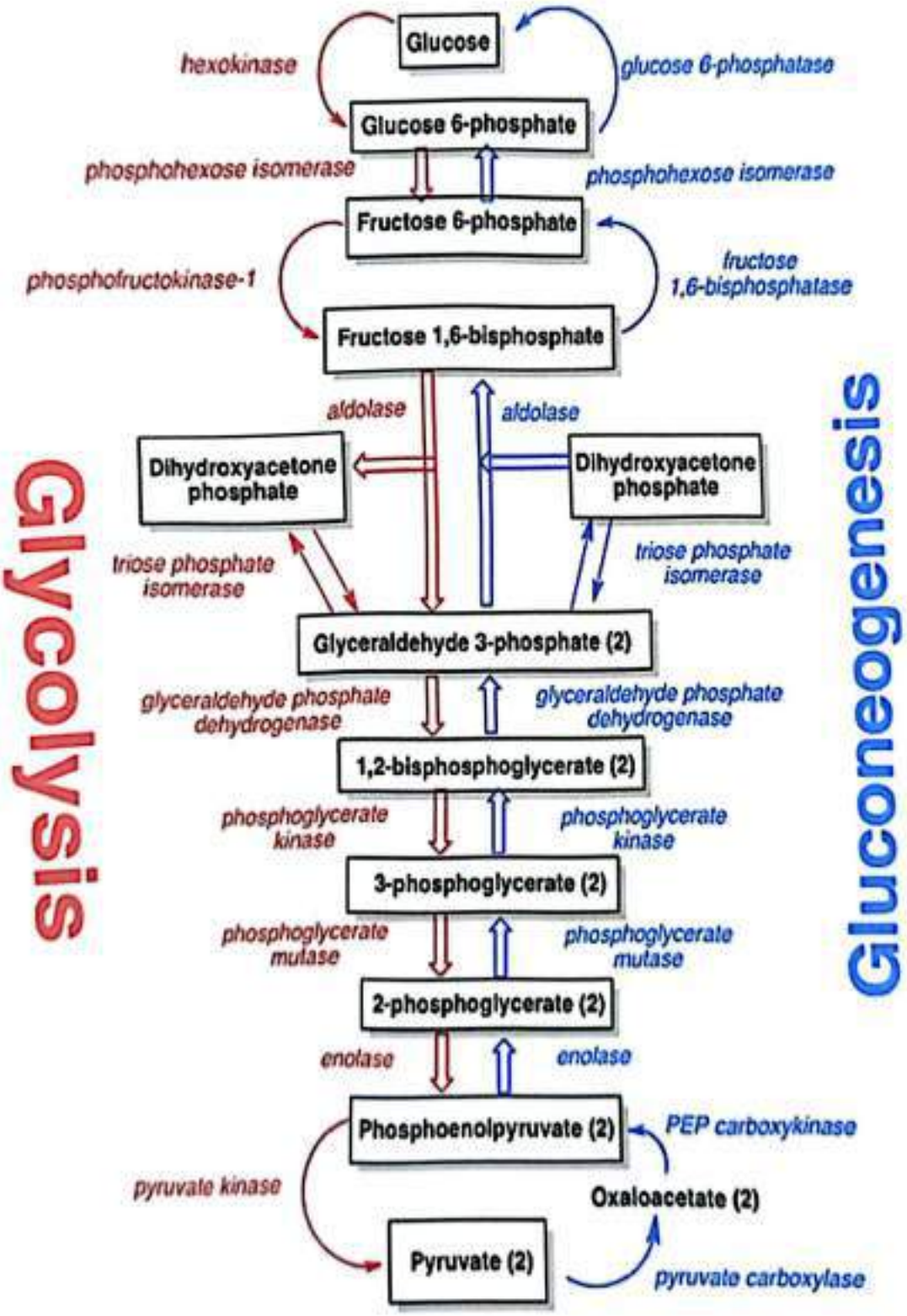


Figure 10 : Glycolysis and gluconeogenesis

Glycogenesis

The process of generating glycogen from glucose units occurs mainly in the liver and muscles and is not the opposite of the process of glycogenolysis. 5 enzymes participate in this process, which takes place as follows:

Glucose is converted to glucose-6-phosphate by the hexokinase enzyme, and glucose-6-phosphate is converted to glucose-1-phosphate by the enzyme phosphoglucomutase, then glucose-1-phosphate is activated by its union with uridine triphosphate (UTP) to form the active compound uridine diphosphate-glucose (UDPG) and pyrophosphate by the action of the enzyme uridine diphosphate-glucose pyrophosphorylase. The activated glucose molecules in the form of uridine diphosphate-glucose are the primary material for building glycogen, as they bind with the glucose unit of (UDPG) with a glucose unit from the non-reducing end of the glycogen chain to be elongated (the starting chain) by the action of the enzyme glycogen synthase under the influence of the hormone epinephrine, The branching enzyme Amylo (1-4) ⟶ (1-6) trans-glucosidase works to form the (1-6) glycosidic bond which is necessary for the branching structure of glycogen straight glucose.

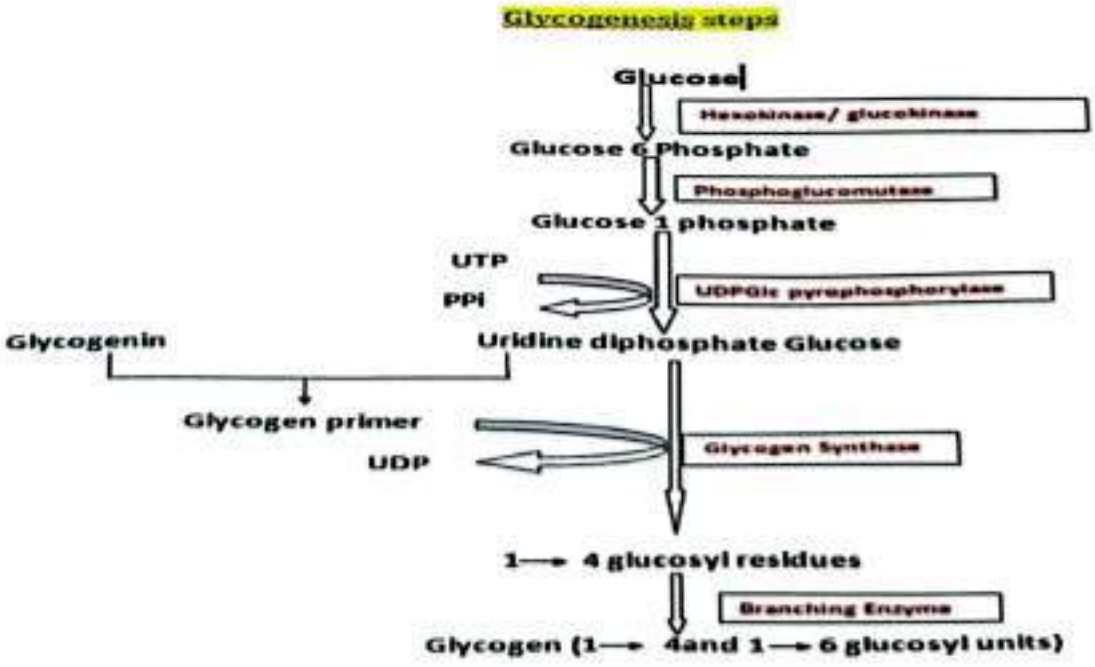


Figure 11: Glycogenesis

Two ATP molecules are consumed to add one glucose unit, the first to build glucose-6-phosphate and the second to regenerate the UTP consumed in this process, as in the following equation.

$$UDP + ATP \longrightarrow UTP + ADP$$

Glycogenolysis

Glycogenolysis means the breakdown (catabolism) of glycogen (in the liver and muscles) into glucose units in the liver or glucose-6-phosphate in the muscles. Glucose is released from the liver into the blood in order to raise the level of glucose in the blood during fasting, for example, while glucose-6-phosphate enters the glucose pathway in the muscles for the purpose of releasing the energy needed for muscle contraction. In the liver, the initial reaction takes place by the action of the enzyme glycogen phosphorylase, whereby it attacks the α(1-4) glycosidic bond of the non-reducing end of the glycogen chain, thus producing glucose-1-phosphate.

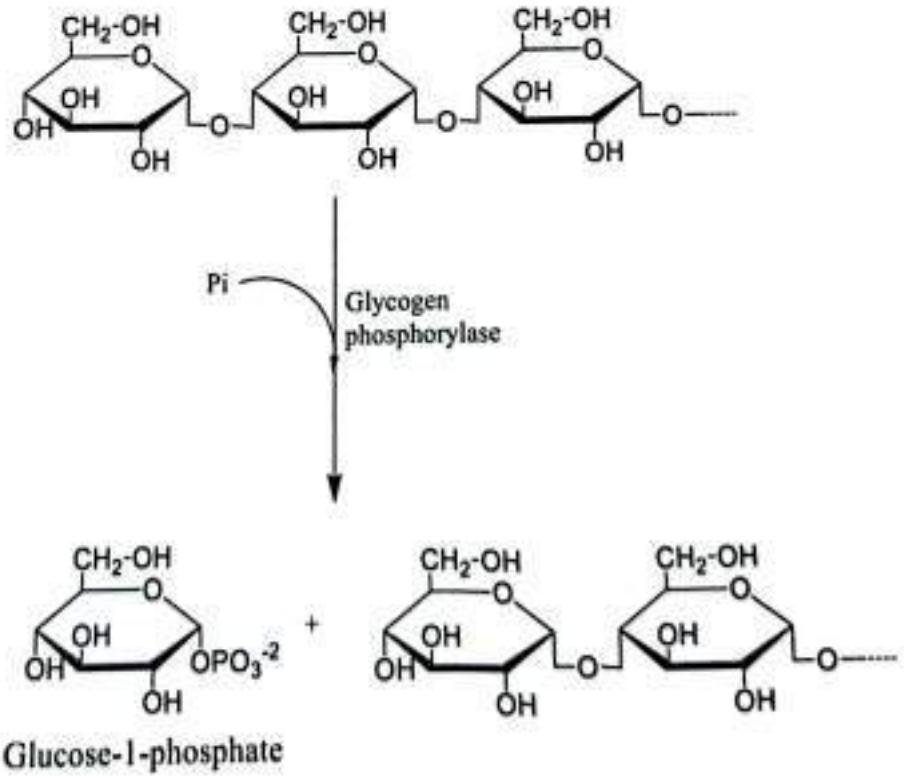


Figure 12: Glycogenolysis