

CHAPTER 12

Carbohydrate Metabolism

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INTRODUCTION

The major source of carbohydrates is found in plants. Glucose is the universal fuel for human cells. The glucose concentrations in the body are maintained within limits by various metabolic processes.

DIGESTION, ABSORPTION AND TRANSPORT OF CARBOHYDRATES

Digestion of Carbohydrates

The principal sites of carbohydrate digestion are the **mouth** and **small intestine**. The dietary carbohydrate consists of:

- **Polysaccharides:** Starch, glycogen and cellulose
- **Disaccharides:** Sucrose, maltose and lactose
- **Monosaccharides:** Mainly glucose and fructose.

Monosaccharides need no digestion prior to absorption, whereas disaccharides and polysaccharides must be hydrolyzed to simple sugars before their absorption (**Figure 12.1**).

Digestion in Mouth

Digestion of carbohydrates begins in the mouth. Salivary glands secrete **α -amylase (ptyalin)**, which initiates the hydrolysis of a starch. During mastication, salivary α -amylase acts briefly on dietary starch in random manner breaking some α -(1 \rightarrow 4) bonds, α -amylase hydrolyzes starch into dextrins.

Digestion in Stomach

Carbohydrate digestion halts temporarily in the stomach because the high acidity inactivates the salivary α -amylase.

Digestion in Intestine

Further digestion of carbohydrates occurs in the small intestine by **pancreatic enzymes**. There are two phases of intestinal digestion.

1. Digestion due to pancreatic **α -amylase**
2. Digestion due to intestinal enzymes : **sucrase, maltase, lactase, isomaltase**.

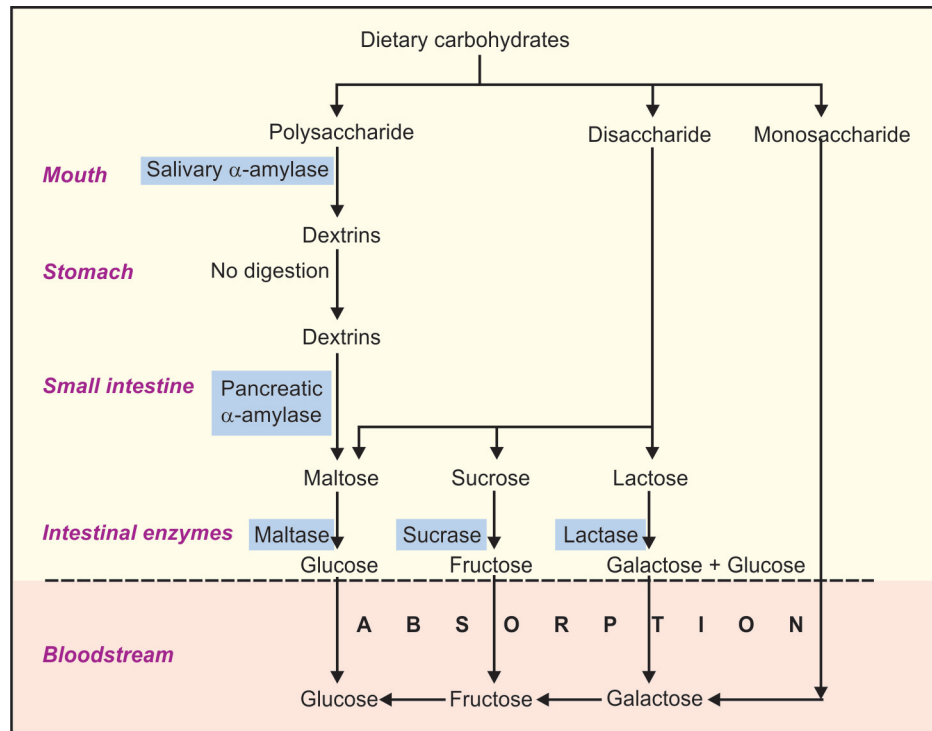


Figure 12.1: Flow sheet of digestion of carbohydrates

Digestion due to pancreatic α -amylase

- The function of pancreatic α -amylase is to degrade dextrins further into a mixture of maltose, isomaltose and α -limit dextrin.
- The α -limit dextrins are smaller oligosaccharides containing 3 to 5 glucose units.

Digestion due to intestinal enzymes

Enzymes responsible for the final phase of carbohydrate digestion are located in the brush-border membrane. The enzymes and the reactions they catalyze are as follows:

• Maltose	Maltase	→	Glucose + Glucose
• Isomaltose	Isomaltase	→	Glucose + Glucose
• Sucrose	Sucrase	→	Glucose + Fructose
• Lactose	Lactase	→	Glucose + Galactose
• α -Limit dextrin	Dextrinase	→	Glucose + Maltose

The end products of carbohydrate digestion are *glucose*, *fructose* and *galactose* which are readily absorbed through the intestinal mucosal cells into the bloodstream.

Absorption of Carbohydrates

Carbohydrates are absorbed as monosaccharides from the intestinal lumen. Two mechanisms are responsible for the absorption of monosaccharides:

- Active transport against a concentration gradient, i.e. from a low glucose concentration to a higher concentration.
- Facilitative transport, with concentration gradient, i.e. from a higher concentration to a lower one.

Active Transport

The transport of glucose and galactose across the brush-border membrane of mucosal cells occurs by an *active transport*. Active transport is an energy requiring process that requires a specific transport protein and the presence of sodium ions (**Figure 12.2**).

- A sodium dependent glucose transporter (SGLT-1) binds both glucose and Na^+ at separate sites and

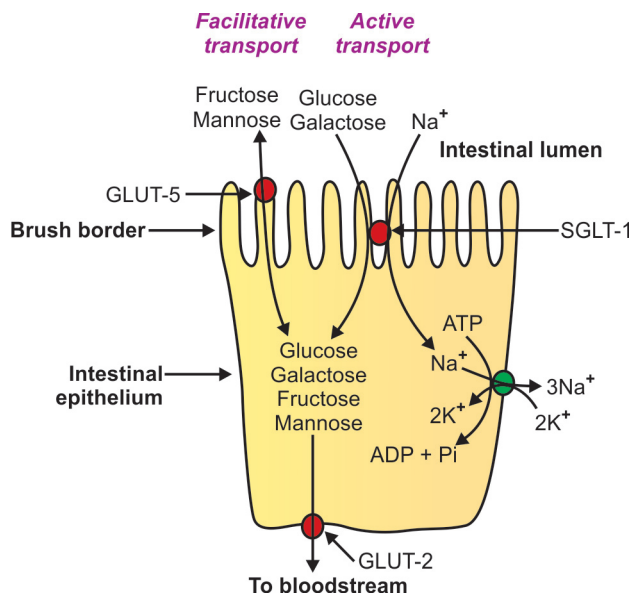


Figure 12.2: Transport of glucose, fructose, galactose and mannose

transports them both through the plasma membrane of the intestinal cell.

- The Na⁺ is transported down its concentration gradient (higher concentration to lower concentration) and at the same time glucose is transported against its concentration gradient.
- The free energy required for this active transport is obtained from the hydrolysis of ATP linked to a **sodium pump** that expels Na⁺ from the cell in exchange of K⁺ (**Figure 12.2**).

Facilitative Transport

- **Fructose** and **mannose** are transported across the brush border by a Na⁺ independent facilitative diffusion process, requiring specific glucose transporter, GLUT-5.
- Movement of sugar in facilitative diffusion is strictly from a higher concentration to a lower one until it reaches an equilibrium.
- The same transport can also be used by glucose and galactose if the concentration gradient is favorable.

Transport of Carbohydrates

The sodium independent transporter, GLUT-2 that facilitates transport of sugars out of the mucosal cells, thereby entering the portal circulation and being transported to the liver.

Lactose Intolerance

- Intolerance to lactose (the sugar of milk) not to milk. This is the most common disorder due to deficiency of enzyme *lactase*.
- In this condition, lactose accumulates in the gut which undergoes bacterial fermentation in the large intestine with the production of H₂ and CO₂ gases and low molecular weight acids like acetic acid, propionic acid and butyric acid which are osmotically active.
- Abdominal cramps and flatulence results from the accumulation of gases and the osmotically active products that draw water from the intestinal cells into the lumen resulting in *diarrhea* and *dehydration*.
- Treatment for this disorder is simply to remove lactose from the diet.

METABOLIC FATE OF CARBOHYDRATES

The major metabolic pathways of carbohydrates are :

- **Glycolysis:** The oxidation of glucose to pyruvate and lactate.
- **Citric acid cycle:** (Krebs cycle or tricarboxylic acid cycle) oxidation of acetyl-CoA to CO₂ and water.
- **Gluconeogenesis:** Synthesis of glucose from non-carbohydrate substances such as lactate, glycerol, glucogenic amino acids, etc.
- **Glycogenesis:** Synthesis of glycogen from glucose.
- **Glycogenolysis:** Breakdown of glycogen to glucose.
- **Hexose monophosphate Shunt (HMP Shunt):** It is an alternative pathway for oxidation of glucose. Some pentoses can also be oxidized through this pathway.
- **Uronic acid pathway:** Glucose is oxidized to glucuronic acid.
- **Galactose metabolism:** Galactose is converted to glucose.
- **Fructose metabolism:** Fructose is converted to glucose or metabolized in liver.

GLYCOLYSIS

Definition

Glycolysis is the sequence of reactions that converts glucose into pyruvate in the presence of oxygen (aerobic) or lactate in the absence of oxygen (anaerobic) with the production of ATP. This pathway is also called *Embden Meyerhof pathway*.

It is a unique pathway since it can utilize oxygen if available, or it can function in the total absence of oxygen.

Location

Glycolysis is the major pathway for the utilization of glucose and is found in **cytosol** of all cells.

Reactions of Glycolysis (Figure 12.3)

The breakdown of glucose (6-carbon compound) to two moles of pyruvate (3-carbon compound) is brought about by sequential action of ten enzymes which can be

divided into two phases.

1. Ist phase: Energy requiring phase or preparative phase
2. IInd phase: Energy generating phase.

Ist phase: Energy requiring phase or preparative phase

1. Glucose is phosphorylated to glucose-6-phosphate by **hexokinase** or **glucokinase** and ATP is required as a phosphate donor. Hexokinase and glucokinase are isoenzymes. The difference

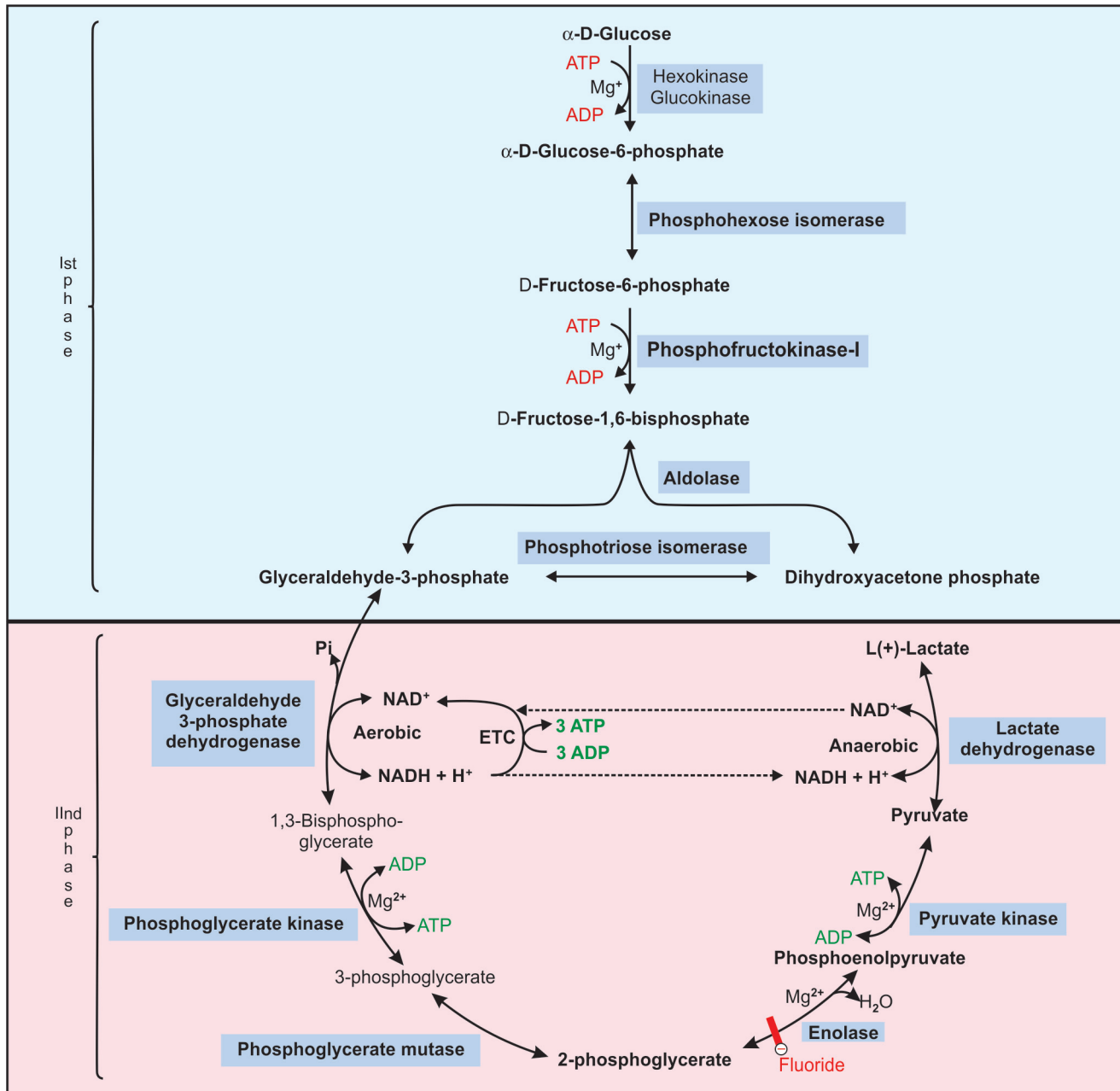


Figure 12.3: The reactions of glycolysis

Table 12.1: Difference between hexokinase and glucokinase

Hexokinase	Glucokinase
Present in extrahepatic tissue	Present in liver
High affinity for its substrate glucose (low K_m)	Low affinity for its substrate glucose (high K_m)
Inhibited by its product glucose-6-phosphate	No inhibition by its product glucose-6-phosphate
Its function is to ensure supply of glucose for the tissues, irrespective of blood glucose concentration	Its function is to remove glucose from the blood, when the blood glucose level increases (following meal)
Catalyze the phosphorylation of other hexoses like fructose, galactose, etc.	Specific for glucose
Its activity is not affected by insulin	It is an inducible enzyme that increases its synthesis in response to insulin

between glucokinase and hexokinase is given in **Table 12.1**. This is an **irreversible** reaction.

- Conversion of glucose-6-phosphate to fructose-6-phosphate by an enzyme *phosphohexose isomerase* which involve isomerization and is freely **reversible** reaction.
- Fructose-6-phosphate to fructose 1, 6-bisphosphate, second phosphorylation reaction requiring ATP catalyzed by an enzyme *phosphofructokinase-I*. This step is **irreversible** under physiological conditions. **Phosphofructokinase-I** is **regulatory enzyme of glycolysis**.
- Fructose-1,6-bisphosphate is cleaved by *aldolase* to two three carbon compounds, glyceraldehyde-3-phosphate and dihydroxy acetone phosphate (DHAP).
- DHAP is isomerized to glyceraldehyde-3-phosphate by the enzyme *phosphotriose isomerase*, so that, 2-molecules of glyceraldehyde-3-phosphate are formed from one molecule of glucose.

IInd phase: Energy generating phase

- Oxidation of glyceraldehyde-3-phosphate to 1,3-bisphosphoglycerate by *glyceraldehyde-3-phosphate dehydrogenase*, is a NAD dependent reversible reaction. The reducing equivalents NADH+H⁺ formed, are reoxidized by electron transport chain, to generate 3 ATP molecules per NADH+H⁺.
- 1, 3-bisphosphoglycerate to 3-phosphoglycerate is catalyzed by *phosphoglycerate kinase*. This is the step in glycolysis that generates ATP at **substrate level phosphorylation**. Since two molecules of glyceraldehyde-3-phosphate are formed per molecule of

glucose undergoing glycolysis, two molecules of ATP are generated at this stage per molecule of glucose.

- 3-phosphoglycerate to 2-phosphoglycerate is a reversible reaction catalyzed by *phosphoglycerate mutase*.
- 2-phosphoglycerate to phosphoenol pyruvate. This reaction is catalyzed by *enolase*. *Enolase is inhibited by fluoride, a property that can be used when it is required to prevent glycolysis in blood prior to the estimation of glucose*.
- Phosphoenol pyruvate to pyruvate is an **irreversible** reaction catalyzed by **pyruvate kinase**. This is the second step in glycolysis that generates ATP at **substrate level phosphorylation**. Enol pyruvate formed in this reaction is converted spontaneously to the keto form of pyruvate.

Under aerobic condition, pyruvate is taken up into mitochondria and after conversion to acetyl-CoA is oxidized to CO₂ and H₂O by citric acid cycle.

Anaerobic Glycolysis

- In anaerobic conditions, the reoxidation of NADH (formed in the glyceraldehyde-3-phosphate step) by respiratory chain is prevented and gets reoxidized by conversion of pyruvate to lactate by **lactate dehydrogenase (Figure 12.3)**.
- Tissues that function under hypoxic conditions produce lactate, e.g. skeletal muscle, smooth muscle and erythrocytes.
- In erythrocytes even under aerobic conditions, glycolysis terminates in lactate because of absence of mitochondria.

Regulation of Glycolysis

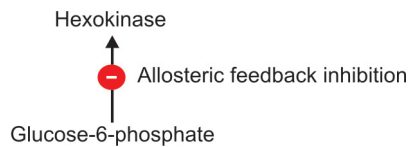
Glycolysis is regulated at 3 steps which are *irreversible*.

These reactions are catalyzed by:

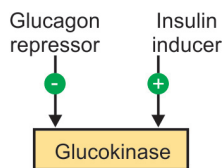
1. Hexokinase and glucokinase
2. Phosphofructokinase-I
3. Pyruvate kinase.

Hexokinase and glucokinase

- Hexokinase is an allosteric enzyme, that is inhibited by its product glucose-6-phosphate.

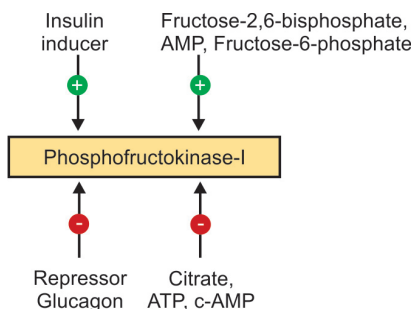


- Liver glucokinase is an inducible enzyme that increases its synthesis in response to insulin and decreases in response to glucagon.



Phosphofructokinase-I

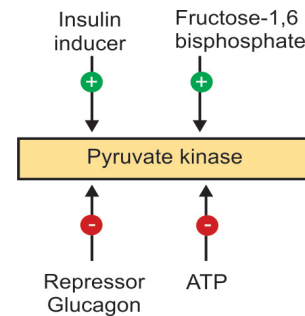
- Phosphofructokinase-I is activated by:
 - Fructose-6-phosphate (substrate)
 - AMP (which signals low energy state)
 - Fructose 2,6-bisphosphate.
- Phosphofructokinase-I** is inhibited by **citrate**, **c-AMP** and **ATP** (which signals high energy state slowing down the glycolysis).
- Phosphofructokinase-I is an inducible enzyme that increases its synthesis in response to **insulin** and decreases in response to **glucagon**.



Pyruvate kinase

- Pyruvate kinase is an inducible enzyme that increases in concentration with high insulin levels and decreases with glucagon.

- It is activated by fructose-1, 6-bisphosphate and inactivated by ATP.



Significance of Glycolysis

- Glycolysis is the principal route for glucose metabolism for the production of ATP molecules.
- An important biochemical significance is the ability of glycolysis to provide ATP in the absence of oxygen and allows tissues to survive anoxic episodes.
- It generates precursors for biosynthetic pathway, e.g.
 - Pyruvate may be transaminated to amino acid alanine. In the liver, pyruvate provides substrate, acetyl-CoA for fatty acid biosynthesis.
 - Glycerol-3-phosphate, which is required for the synthesis of triacylglycerol is derived from glycolytic pathway.
- In erythrocytes, glycolysis supplies 2,3-BPG which is required for the transport of oxygen by Hb.

Energetics of Glycolysis

- The details of ATP generation in glycolysis are given in **Table 12.2**. Under aerobic conditions, 8 molecules of ATP are produced.
- In anaerobic glycolysis, on the other hand, only 2 moles of ATP are produced per molecule of glucose.

RAPOPORT LUEBERING CYCLE

In Rapoport luebering cycle, production of ATP by substrate phosphorylation from 1,3-BPG is bypassed in the erythrocyte by taking a diversion pathway (**Figure 12.4**).

- In rapoport lubering cycle 1,3-BPG is converted to 2,3-BPG by an enzyme *bisphosphoglycerate mutase*.
- Then 2,3-BPG is converted to 3-phosphoglycerate by *2,3-bisphosphoglycerate phosphatase*, with a loss of high energy phosphate (energy is dissipated as heat) and there is no net production of ATP when glycolysis takes this route.

Table 12.2: Production of ATP in glycolysis aerobically

Reaction	Reaction catalyzed by	Number of ATP formed or consumed/ glucose molecule
Glucose to glucose-6-phosphate	Hexokinase, glucokinase	– 1
Fructose-6-phosphate to fructose 1,6-bisphosphate	Phosphofructokinase-I	– 1
Glyceraldehyde-3-phosphate to 1,3-bisphosphoglycerate	Glyceraldehyde-3-phosphate dehydrogenase	+6*
1, 3-bisphosphoglycerate to 3-phosphoglycerate	Phosphoglycerate kinase	+2
Phosphoenolpyruvate to pyruvate	Pyruvate kinase	+ 2

- Net production of ATP in aerobic glycolysis = Number of ATP produced minus number of ATPs consumed = $10 - 2 = 8$
- *It is assumed that NADH formed in glycolysis uses malate shuttle to produce 6 ATPs
- Total ATP per molecule of glucose under anaerobic glycolysis = 2

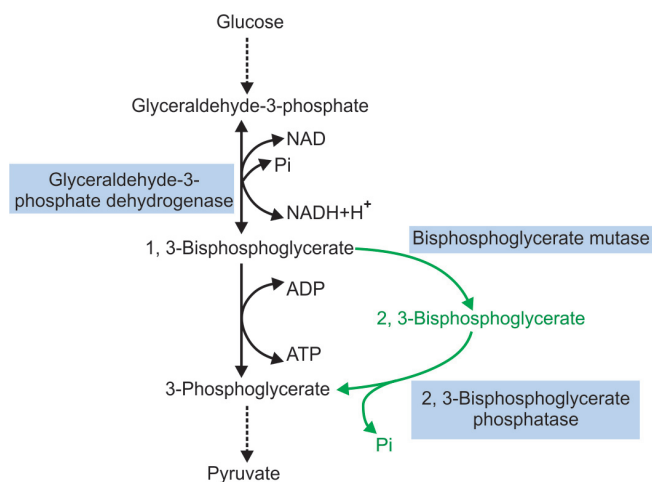


Figure 12.4: Rapoport Luebering cycle of erythrocytes shown in green color

Significance of Rapoport Luebering Cycle

- It prevents accumulation of ATP not needed by the erythrocyte.
- It supplies 2,3-BPG required for the transport of oxygen by hemoglobin. 2,3-BPG regulates the binding and release of oxygen from hemoglobin.
- 2, 3-BPG present in erythrocytes acts as a buffer.

CONVERSION OF PYRUVATE TO ACETYL-CoA

- Pyruvate is converted to acetyl CoA by **oxidative decarboxylation**. This step occurs only in mitochondria. This is an irreversible reaction catalyzed by a multienzyme complex known as **pyruvate dehydrogenase complex (PDH)** (Figure 12.5).
- The enzyme pyruvate dehydrogenase requires five coenzymes, namely thiamine pyrophosphate (TPP), lipoate, coenzyme-A, FAD and NAD^+ .

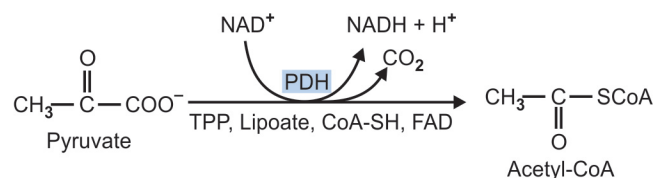


Figure 12.5: Oxidative decarboxylation of pyruvate by the pyruvate dehydrogenase (PDH) complex

Energetics in conversion of pyruvate to Acetyl CoA

As a result of oxidation of pyruvate to acetyl CoA catalyzed by pyruvate dehydrogenase, one molecule of NADH is produced for each molecule of pyruvate. Oxidation of NADH by electron transport chain results in synthesis of **3 ATP molecules**.

Significance

- The conversion of pyruvate to acetyl-CoA is a central step, linking the glycolytic pathway with citric acid cycle.