Carbohydrate Metabolism

The fate of dietary components after digestion and absorption constitutes metabolism into three categories:

(1) **Anabolic pathways:** are those involved in the synthesis of compounds like Protein, triacylglycerol and glycogen. Anabolic pathways are endothermic.

(2) **Catabolic pathways:** are involved in the breakdown of larger molecules, commonly involving oxidative reactions; they are exothermic.

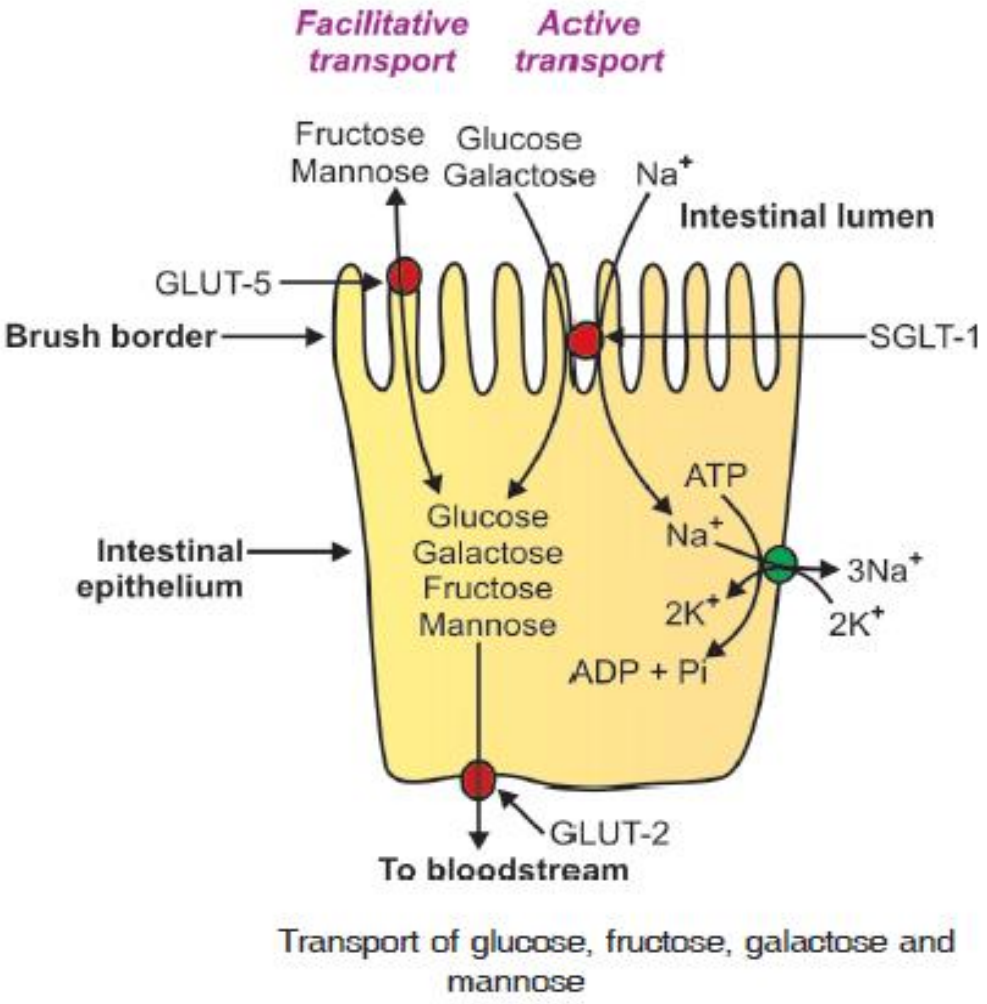
(3) **Amphibolic pathways:** acting as links between the anabolic and catabolic pathways for example the citric acid cycle.

Normal metabolism includes adaptation to periods of starvation, exercise, pregnancy, and lactation. Abnormal metabolism may result from nutritional deficiency, enzyme deficiency, abnormal secretion of hormones, or the actions of drugs and toxins. An important example of a metabolic disease is diabetes mellitus.

Carbohydrates Transporters

Carbohydrates transports through the plasma membrane of the intestinal cell. Glucose and Galactose is transported against its concentration gradient by GLUT-1. 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^+ .

Fructose and mannose are transported across the brush border by 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 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.



Transport of glucose, fructose, galactose and mannose

Metabolic fate of carbohydrate

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.

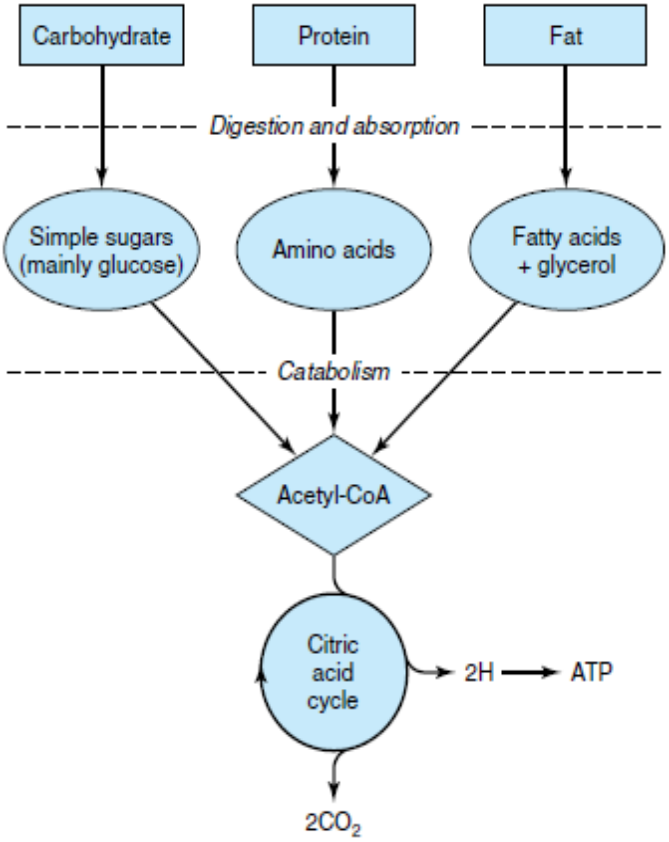
• **Gluconeogenesis:** Synthesis of glucose from noncarbohydrate substances such as lactate, glycerol, glucogenic amino acids, etc.

• **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.



Pathways for the catabolism of dietary carbohydrate, protein, and fat.

Glycolysis & the Oxidation of Pyruvate

Most tissues have requirement for glucose. Glycolysis, the major pathway for glucose metabolism, occurs in the cytosol of all cells. Erythrocytes, which lack mitochondria, are completely reliant on glucose as their metabolic fuel and metabolize it by anaerobic glycolysis.

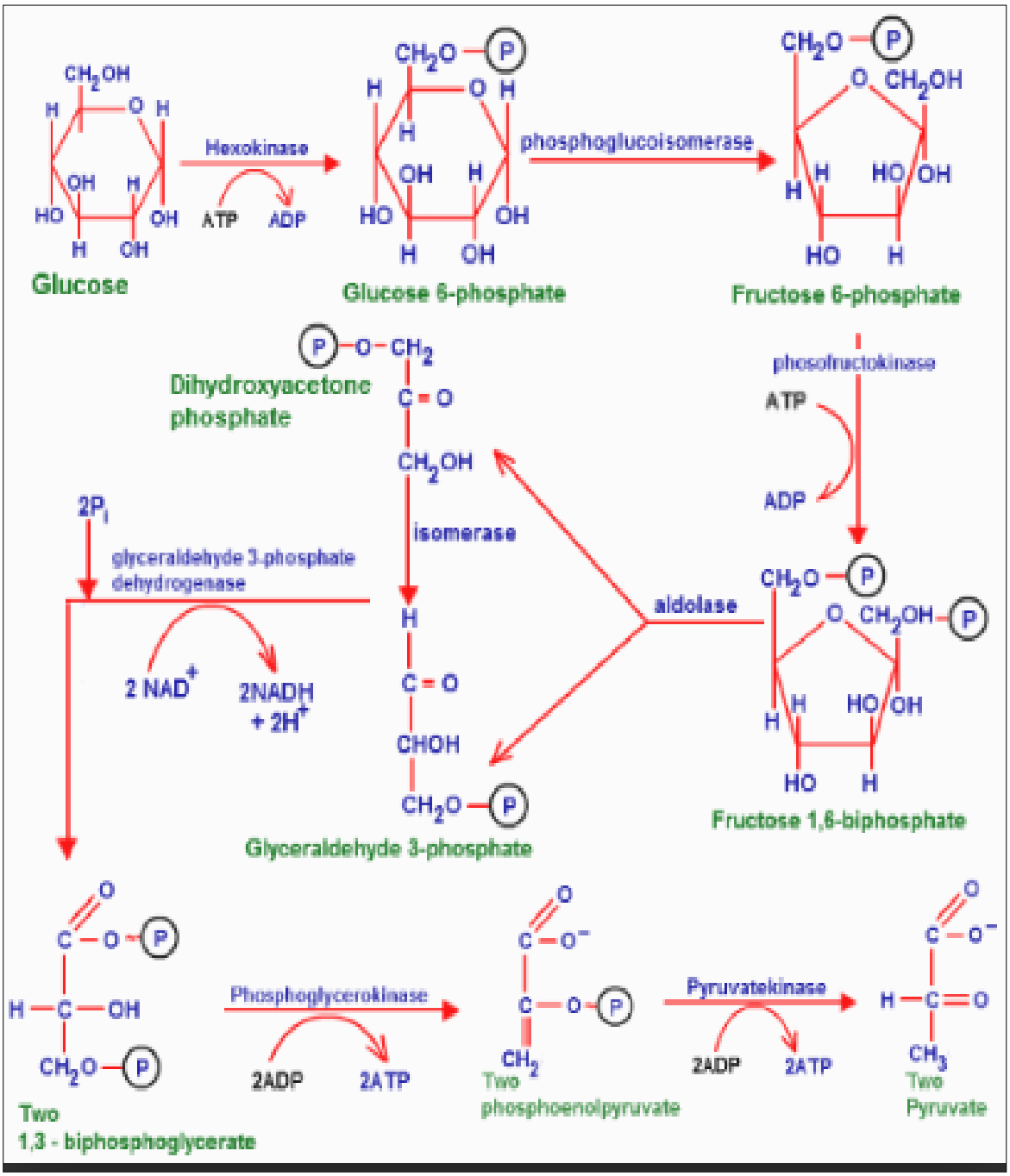
Glycolysis is the sequence of reactions that glucose oxidation into energy, and the major pathway for the utilization of glucose and is found in cytosol of all cells. Glycolysis is both the principal route for glucose metabolism and the main pathway for the metabolism of fructose, galactose, and other carbohydrates derived from the diet. The ability of glycolysis to provide ATP in the absence of oxygen is especially important because it allows skeletal muscle to perform at very high levels when oxygen supply is insufficient.

In fast-growing cancer cells, glycolysis proceeds at a higher rate than is required by the citric acid cycle, forming large amounts of pyruvate, which is reduced to lactate and exported. The lactate is used for gluconeogenesis in the liver, an energy-expensive process responsible for much of the hyper metabolism seen in cancer cachexia. Lactic acidosis results from several causes, including impaired activity of lactate dehydrogenase. Lactate dehydrogenase deficiency present with lactic acidosis, particularly after a glucose load, brain is a prominent tissue where these metabolic defects manifest themselves in neurologic disturbances. Muscle contracts in an anaerobic medium, ie, one from which oxygen is excluded, glycogen disappears and lactate appears as the principal end product that defect in muscle. All of the enzymes of glycolysis are cytosolic. Glucose enters glycolysis by phosphorylation to glucose- 6-phosphate, catalyzed by **hexokinase,** using ATP as the phosphate donor. Under physiological conditions, the phosphorylation of glucose to glucose-6-phosphate can be regarded as irreversible. Hexokinase is inhibited allosterically by its product, glucose-6-phosphate. Hexokinase has a high affinity (low *K*m) for glucose, and in the liver it is saturated undernormal conditions, and so acts at a constant rate to provide glucose-6-phosphate to meet the liver's needs. Liver cells also contain an isoenzyme of hexokinase, **glucokinase,** which has a *K*m very much higher than the normal intracellular concentration of glucose. glycolysis, it is converted to fructose 6-phosphate by **phosphohexose isomerase,** which involves an aldose-ketose isomerization. This reaction is followed

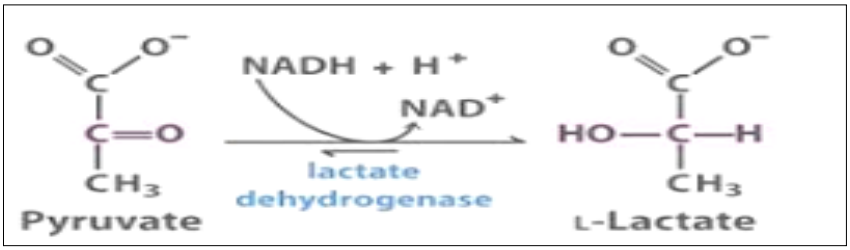
by another phosphorylation catalyzed by the enzyme **phosphofructokinase** (phosphofructokinase- 1) forming fructose 1,6-bisphosphate. The Phosphofructokinase reaction is irreversible under physiological conditions. Phosphofructokinase is both inducible and subject to allosteric regulation, and has a major role in regulating the rate of glycolysis. Fructose 1,6-bisphosphate is cleaved by **aldolase** (fructose 1,6-bisphosphate aldolase) into two triose phosphates, glyceraldehyde-3-phosphate and dihydroxyacetone phosphate, which are interconverted by the enzyme **phosphotriose isomerase**. Glycolysis continues with the oxidation of glyceraldehyde- 3-phosphate to 1,3-bisphosphoglycerate. The enzyme catalyzing this oxidation, **glyceraldehyde-3-phosphate dehydrogenase,** is NAD dependent. In the next reaction, catalyzed by **phosphoglycerate kinase,** phosphate is transferred from 1,3-bisphosphoglycerateonto ADP, forming ATP and phosphoenolpyrovate,and then to pyruvate by pyruvate **kinase**. The availability of oxygen now determines which of the two pathways is followed. Under **anaerobic conditions**, the NADH cannot be reoxidized through the respiratory chain, and pyruvate is reduced to lactate catalyzed by **lactate dehydrogenase**. This permits the oxidization of NADH, permitting another molecule of glucose to undergo glycolysis. Under **aerobic conditions,** pyruvate is transported into mitochondria and undergoes oxidative decarboxylation to acetyl-CoA then oxidation to CO2 in the citric acid cycle . The reducing equivalents from the NADH formed in glycolysis are taken up into mitochondria for oxidation via either the malate-aspartate shuttle or the glycerophosphate shuttle.

Significance of Glycolysis

Glycolysis is the principal route for glucose metabolism for the production of ATP molecules. It generates precursors for biosynthetic pathway, e.g. Pyruvate may be transaminated to amino acid alanine. In the liver, pyruvate provides acetyl-CoA for fatty acid biosynthesis.


Glucose
Hexokinase
ATP
ADP
Glucose 6-phosphate
phosphoglucoisomerase
Fructose 6-phosphate
Dihydroxyacetone phosphate
phosofructokinase
ATP
ADP
2Pi
glyceraldehyde 3-phosphate dehydrogenase
2 NAD+
2NADH + 2H+
isomerase
aldolase
Fructose 1,6-biphosphate
Glyceraldehyde 3-phosphate
Two 1,3 - biphosphoglycerate
Phosphoglycerokinase
2ADP
2ATP
Two phosphoenolpyruvate
Pyruvatekinase
2ADP
2ATP
Two Pyruvate

In anaerobic conditions, the reoxidation of NADH by and conversion of pyruvate to lactate :.



Tissues that function 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.

Regulation of Glycolysis

Glycolysis is regulated at 3 steps which are irreversibl. 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-l

- Phosphofructokinase-l is activated by:
- Fructose-6-phosphate(substrate)
- AMP (which signals low energy state)
- Phosphofructokinase-I is inhibited by ATP (which signals high energy).
- 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.

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

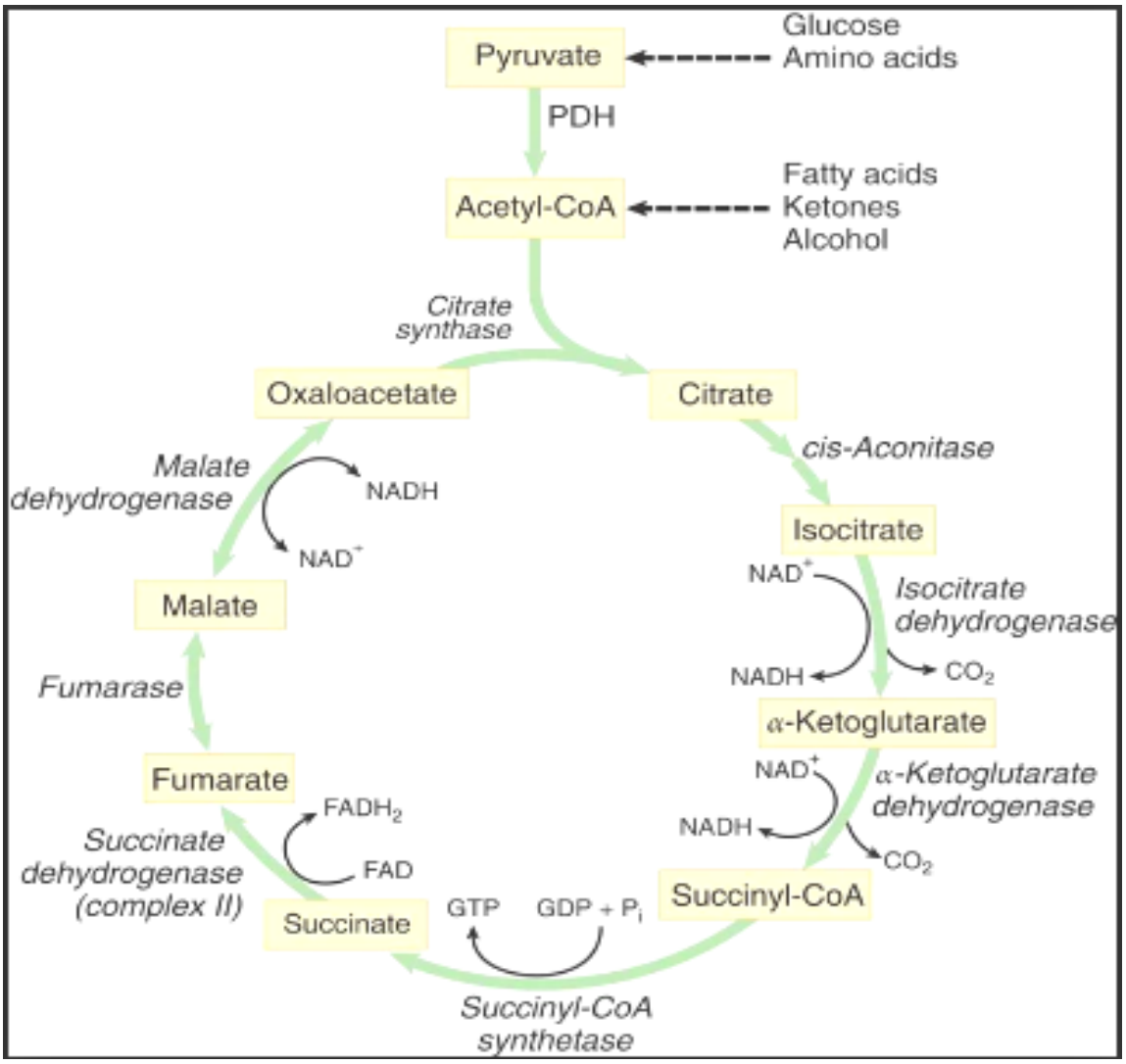
- Net production of ATP in aerobic glycolysis = Number of ATP produced minus number of ATPs consumed = 10 – 2 = 8
- *It is assumed that NADH formed in glycolysis uses malate shuttle to produce 6 ATPs
- Total ATP per molecule of glucose under anaerobic glycolysis = 2

Production of ATP in glycolysis

Citric Acid Cycle:

Citric acid cycle is also called Krebs cycle or tricarboxylic acid (TCA) cycle. It is called citric acid cycle because citrate was one of the first compounds known to participate. It is called Krebs cycle, because its reactions were formulated into a cycle by Sir Hans Krebs. The most common name for this pathway is, the tricarboxylic acid or TCA cycle, due to involvement of the tricarboxylatescitrate and isocitrate

The citric acid cycle is a series of reactions in mitochondria that oxidize acetyl residues (as acetyl-CoA) and reduce coenzymes that upon reoxidation are linked to the formation of ATP. The citric acid cycle is the final common pathway for the aerobic oxidation of carbohydrate, lipid, and protein because glucose, fatty acids, and most amino acids are metabolized to acetyl-CoA or intermediates of the cycle. It also has a central role in gluconeogenesis, lipogenesis, and interconversion of amino acids.



Calcaulation of ATP

As a result of oxidation of acetyl-CoA to H_2O and CO_2 by citric acid cycle, three molecules of NADH and one FADH are produced.

•Oxidation of 3NADH by electron transport chain results in the synthesis of 3*3= 9 ATP, whereas FADH generates 1*2= 2 ATP molecules.

•One molecule of ATP is generated at substrate level during the conversion of succinyl-CoA to succinate. Thus, a total of 12 ATP are generated from one molecule of acetyl-CoA.

Production of ATP in citric acid cycle

Reaction	*Reaction catalyzed by*	*No. of ATP formed per acetyl-CoA molecule*
Isocitrate to α-ketoglutarate	Isocitrate dehydrogenase	+3
α-Ketoglutarate to succinyl-CoA	α-Ketoglutarate dehydrogenase	+3
Succinyl-CoA to succinate	Succinyl thiokinase	+1
Succinate to fumarate	Succinate dehydrogenase	+2
Malate to oxaloacetate	Malate dehydrogenase	+3
Number of ATPs formed per acetyl-CoA molecule in citric acid cycle = 12		

Regulation of Citric Acid Cycle

Citric acid cycle is regulated at three steps. These are catalyzed by:

1. Citrate synthase
2. Isocitrate dehydrogenase
3. α-ketoglutarate dehydrogenase.

• Activities of these enzymes are dependent on the energy status of the cycle.

• Excess of ATP, NADH and succinyl-CoA, which signals high energy status of the cell, inhibit these enzymes.

• High level of ADP which signals low energy status of the cell stimulates the operation of the cycle.

Significance of Citric Acid Cycle

The primary function of the citric acid cycle is to provide energy in the form of ATP.

• Citric acid cycle is the final common pathway for the oxidation of carbohydrates, lipids, and proteins as glucose, fatty acids and many amino acids are all metabolized to acetyl-CoA or intermediates of the cycle.

• Citric acid cycle is an amphibolic process that has a dual function, it functions in both catabolism (of carbohydrates, fatty acids and amino acids) and anabolism.

Some metabolic pathways end in the constituent of the citric acid cycle while other pathways originate from the cycle, such as:

– Gluconeogenesis
– Transamination
– Fatty acid synthesis
– Heme synthesis.

Citric acid cycle with chemical reactions:

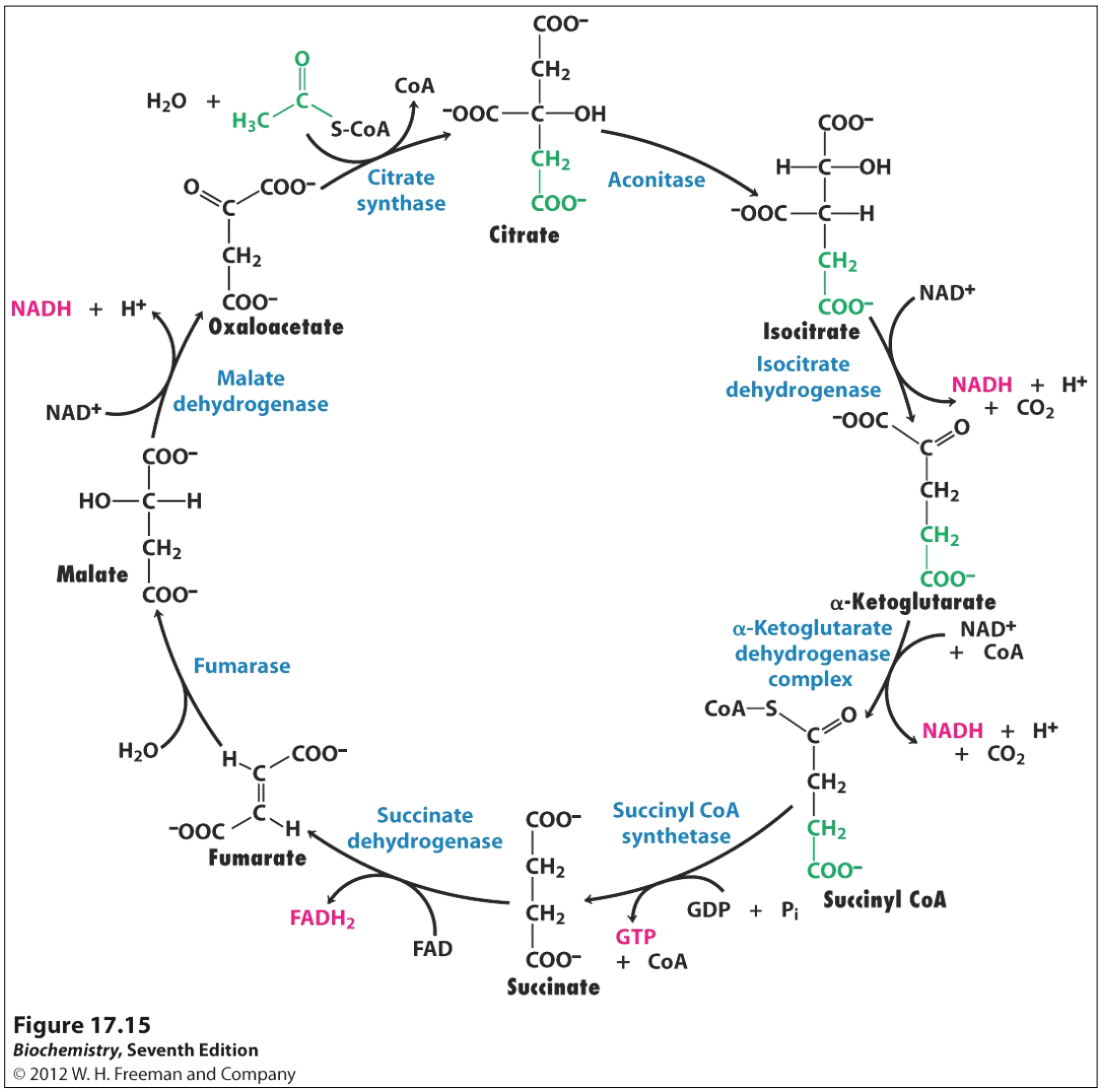


Figure 17.15
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