WELCOME TO

Biochemistry | Chapter-8

Chapter-8

Metabolism (Study of cycle/pathways without chemical structures)

(BIOCHEMISTRY & CLINICAL PATHOLOGY)

Metabolism (Study of cycle/pathways without chemical structures)

Unit-1

- **Metabolism of Carbohydrates: Glycolysis, TCA cycle and glycogen metabolism, regulation of blood glucose level. Diseases related to abnormal metabolism of Carbohydrates.**

Unit-2

- **Metabolism of lipids:** Lipolysis, β-oxidation of Fatty acid (Palmitic acid) ketogenesis and ketolysis. Diseases related to abnormal metabolism of lipids such as Ketoacidosis, Fatty liver, Hypercholesterolemia

Unit-3

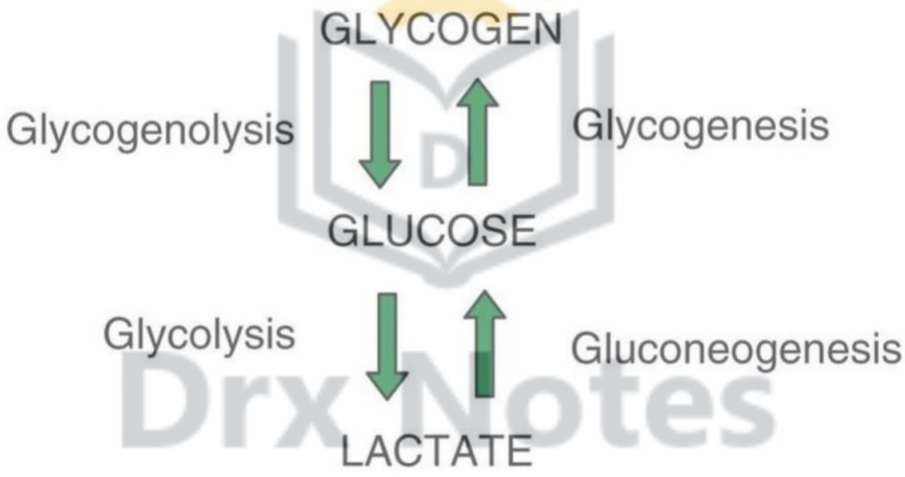
- **Metabolism of Amino acids (Proteins):** General reactions of amino acids and its significance– Transamination, deamination, Urea cycle and decarboxylation. Diseases related to abnormal metabolism of amino acids, Disorders of ammonia metabolism, phenylketonuria, alkaptonuria and Jaundice.
- **Biological oxidation:** Electron transport chain and Oxidative phosphorylation

Unit-1

Metabolism of carbohydrates.

Introduction—The major pathways of carbohydrate metabolism either begin or end with glucose. An understanding of the pathways and their regulation is necessary because of the important role played by glucose in the body. Glucose is the major form in which carbohydrate absorbed from the intestinal tract is presented to cells of the body. Glucose is the only fuel used to any significant extent by a few specialized cells and the major fuel used by the brain. Indeed, glucose is so important to these specialized cells and the brain that several of the major tissues of the body work together to ensure a continuous supply of this essential substrate.

Relationship of glucose to the major pathways of carbohydrate metabolism.

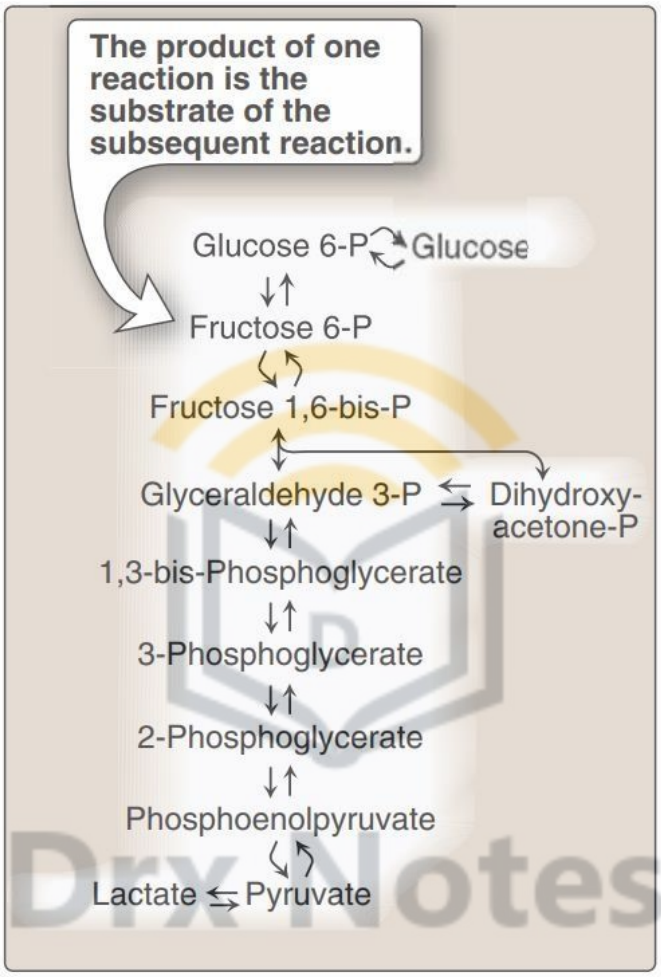


Glycolysis

- Glycolysis, a pathway used by all cells of the body to extract part of the chemical energy inherent in the glucose molecule. This pathway also converts glucose to pyruvate and sets the stage for complete oxidation of glucose to CO_2 and H_2O.

- In contrast to glycolysis, which produces ATP, gluconeogenesis requires ATP and is therefore an energy requiring process.

Metabolic pathway of glycolysis.



Reactions of glycolysis.

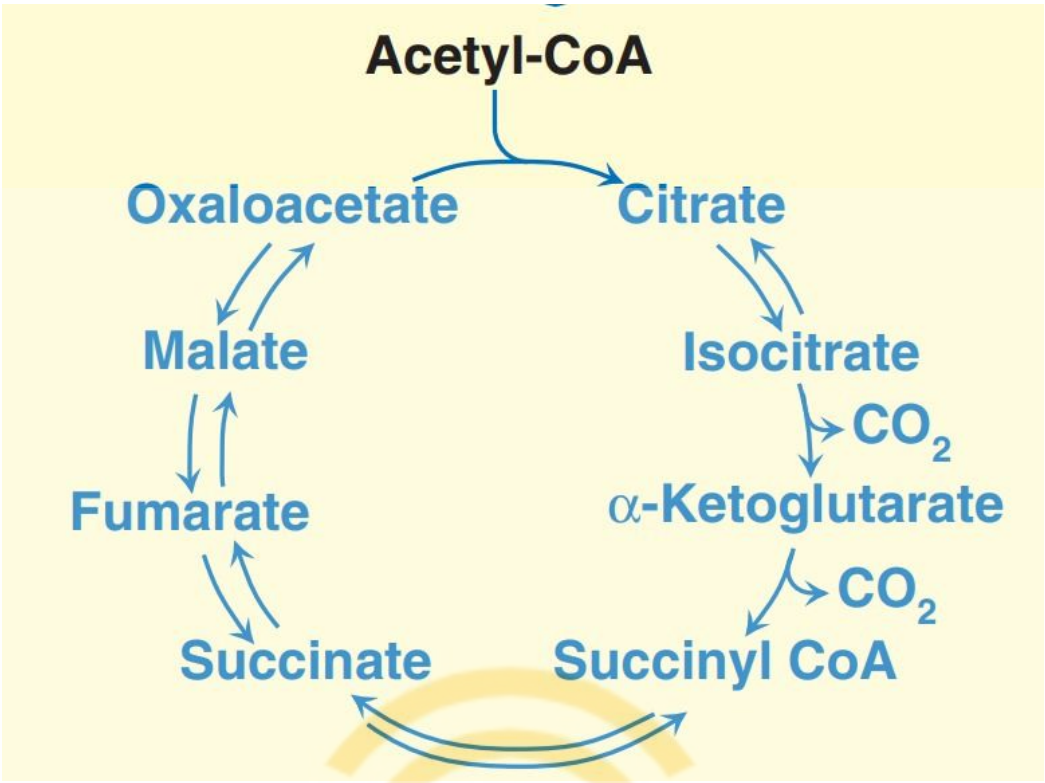
The conversion of glucose to pyruvate occurs in two stages. The first five reactions of glycolysis correspond to an energy investment phase in which the phosphorylated forms of intermediates are synthesized at the expense of ATP. The subsequent reactions of glycolysis constitute an energy generation phase in which a net of two molecules of ATP are formed by substrate-level phosphorylation per glucose molecule metabolized.

1. **Phosphorylation of glucose—** Phosphorylated sugar molecules do not readily penetrate cell membranes, because there are no specific transmembrane carriers for these compounds, and because they are too polar to diffuse through the lipid core of membranes. Mammals have several isozymes of the enzyme hexokinase that catalyse the phosphorylation of glucose to glucose 6-phosphate.
2. **Isomerization of glucose 6-phosphate—**The isomerization of glucose 6-phosphate to fructose 6-phosphate is catalysed by phosphoglucose isomerase.
3. **Phosphorylation of fructose 6-phosphate—** The irreversible phosphorylation reaction catalysed by phosphor fructokinase-1 (PFK-1) is the most important control point and the rate-limiting and committed step of glycolysis.
4. **Cleavage of fructose 1,6-bisphosphate—**Aldolase cleaves fructose 1,6-bisphosphate to dihydroxy acetone phosphate and glyceraldehyde 3-phosphate.
5. **Isomerization of dihydroxyacetone phosphate—**Triose phosphate isomerase interconverts dihydroxyacetone phosphate and glyceraldehyde 3-phosphate (see Figure 8.16). Dihydroxy -acetone phosphate 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 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 catalysed by phosphoglycerate kinase.
8. **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
9. **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 high energy enol phosphate

10. **Formation of pyruvate producing ATP—**The conversion of PEP to pyruvate is catalysed by pyruvate kinase, the third irreversible reaction of glycolysis. The equilibrium of the pyruvate kinase reaction favours the formation of ATP
11. **Reduction of pyruvate to lactate—**Lactate, formed by the action of lactate dehydrogenase, is the final product of anaerobic glycolysis in eukaryotic cells.
12. **Energy yield from glycolysis—**Despite the production of some ATP during glycolysis, the end products, pyruvate or lactate, still contain most of the energy originally contained in glucose. The TCA cycle is required to release that energy completely
    - 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
    - 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.

TCA cycle

- The tricarboxylic acid cycle (TCA cycle, also called the Krebs cycle or the citric acid cycle) plays several roles in metabolism. It is the final pathway where the oxidative metabolism of carbohydrates, amino acids, and fatty acids converge, their carbon skeletons being converted to CO_2. This oxidation provides energy for the production of the majority of ATP in most animals, including humans.
- The cycle occurs totally in the mitochondria and is, therefore, in close proximity to the reactions of electron transport which oxidize the reduced coenzymes produced by the cycle.
- The TCA cycle is an aerobic pathway, because O_2 is required as the final electron acceptor. Reactions such as the catabolism of some amino acids generates intermediates of the cycle and are called anaplerotic reactions.



Reaction of TCA cycle.

1. **Oxidative decarboxylation of pyruvate—**Pyruvate, the end product of aerobic glycolysis, must be transported into the mitochondrion before it can enter the TCA cycle. This is accomplished by a specific pyruvate transporter that helps pyruvate cross the inner mitochondrial membrane. Once in the matrix, pyruvate is converted to acetyl CoA by the pyruvate dehydrogenase complex, which is a multienzyme complex. Strictly speaking, the pyruvate dehydrogenase complex is not part of the TCA cycle proper, but is a major source of acetyl CoA—the two-carbon substrate for the cycle.
2. **Synthesis of citrate from acetyl CoA and oxaloacetate—**The condensation of acetyl CoA and oxaloacetate to form citrate (a tricarboxylic acid) is catalysed by citrate synthase. This aldol condensation has an equilibrium far in the direction of citrate synthesis
3. **Isomerization of citrate—** Citrate is isomerized to isocitrate by aconitase, an Fe-S protein.
4. **Oxidation and decarboxylation of isocitrate—**Isocitrate dehydrogenase catalyses the irreversible oxidative decarboxylation of isocitrate yielding

the first of three NADH molecules produced by the cycle, and the first release of CO2

5. **Oxidative decarboxylation of α-ketoglutarate—**The conversion of α-ketoglutarate to succinyl CoA is catalysed by the α-ketoglutarate dehydrogenase complex, a multimolecular aggregate of three enzymes. The mechanism of this oxidative decarboxylation is very similar to that used for the conversion of pyruvate to acetyl CoA by the PDH complex. The reaction releases the second CO2 and produces the second NADH of the cycle. The coenzymes required are thiamine pyrophosphate, lipoic acid, FAD, NAD+, and CoA.
6. **Cleavage of succinyl CoA—** Succinate thiokinase (also called succinyl CoA synthetase—named for the reverse reaction) cleaves the high-energy thioester bond of succinyl. This reaction is coupled to phosphorylation of guanosine diphosphate (GDP) to guanosine triphosphate (GTP). GTP and ATP are energetically interconvertible by the nucleoside diphosphate kinase reaction
7. **Oxidation of succinate—**Succinate is oxidized to fumarate by succinate dehydrogenase, as FAD (its coenzyme) is reduced to FADH2. Succinate dehydrogenase is the only enzyme of the TCA cycle that is embedded in the inner mitochondrial membrane.
8. **Hydration of fumarate—**Fumarate is hydrated to malate in a freely reversible reaction catalysed by fumarase (also called fumarate hydratase).
9. **Oxidation of malate—**Malate is oxidized to oxaloacetate by malate dehydrogenase. This reaction produces the third and final NADH of the cycle.

Glycogen metabolism.

- Glycogen metabolism refers to the process by which glycogen is synthesized, stored, and broken down in the body. Glycogen is a complex carbohydrate made up of glucose molecules that is primarily stored in the liver and muscle tissue.
- The synthesis of glycogen, also known as glycogenesis, occurs when glucose molecules are joined together through a process called glycosylation. This process is catalysed by the enzyme glycogen synthase and requires the presence of a primer molecule called glycogenin.

- Glycogen is broken down through a process called glycogenolysis, which occurs when the body needs energy. The breakdown of glycogen is catalysed by the enzyme glycogen phosphorylase, which cleaves off individual glucose molecules from the glycogen chain. These glucose molecules are then converted into glucose-6-phosphate and can be further metabolized to produce energy.
- Control of glycogen metabolism—The regulation of glycogen metabolism is tightly controlled by hormones such as insulin and glucagon. Insulin promotes the synthesis of glycogen, while glucagon stimulates the breakdown of glycogen to release glucose into the bloodstream. The regulation of glycogen metabolism is critical for maintaining blood glucose levels and providing energy to the body.

Regulation of blood glucose level

The regulation of blood glucose level is a complex process involving various hormones and physiological mechanisms. The main hormones involved in this process are insulin, glucagon, and epinephrine.

- **Insulin—**Insulin is a hormone produced by the pancreas that helps regulate glucose levels in the blood. It stimulates the uptake of glucose from the blood into cells, where it can be used for energy or stored as glycogen. Insulin also promotes the conversion of excess glucose into fat for storage.
- **Glucagon—**Glucagon, another hormone produced by the pancreas, has the opposite effect of insulin. It stimulates the liver to break down glycogen into glucose and release it into the bloodstream, thereby increasing blood glucose levels.
- **Epinephrine—**Epinephrine, also known as adrenaline, is a hormone produced by the adrenal glands in response to stress or exercise. It increases blood glucose levels by stimulating the liver to release glucose and by reducing the uptake of glucose by muscles.

Diseases related to abnormal metabolism of Carbohydrates.

- Glucose metabolism is defective in two very common metabolic diseases, obesity and diabetes, which contribute in development of a number of major medical problems, including
- Atherosclerosis,
- Hypertension,
- Small vessel disease,
- Kidney disease, and blindness etc.

NOTE—Three stages of catabolism of substrate.