

Note (Study Glycolysis, fermentation and their regulation, Gluconeogenesis and glycogenolysis, Metabolism of galactose, TCA cycle and Amphibolic role of the cycle, and Glyoxalic acid cycle, HMP shunt in detail from U.B. Satyanarayana)

## CARBOHYDRATE METABOLISM

### Major pathways of carbohydrate metabolism

1. **Glycolysis (Embden-Meyerhof pathway):** The oxidation of glucose to pyruvate and lactate. (Located in cytosol)
2. **Citric acid cycle (Krebs cycle or tricarboxylic acid cycle):** The oxidation of acetyl CoA to CO<sub>2</sub>. Krebs cycle is the final common oxidative pathway for carbohydrates, fats or amino acids, through acetyl CoA. (Located in mitochondria)
3. **Gluconeogenesis:** The synthesis of glucose from non-carbohydrate precursors (e.g. amino acids, glycerol etc.). (Located in cytosol)
4. **Glycogenesis:** The formation of glycogen from glucose. (Located in cytosol)
5. **Glycogenolysis:** The breakdown of glycogen to glucose. (Located in cytosol)
6. **Hexose monophosphate shunt (pentose phosphate pathway or direct oxidative pathway):** This pathway is an alternative to glycolysis and TCA cycle for the oxidation of glucose (directly to carbon dioxide and water). (Located in cytosol)
7. **Uronic acid pathway:** Glucose is converted to glucuronic acid, pentoses and, in some animals to ascorbic acid (not in man). This pathway is also an alternative oxidative pathway for glucose.
8. **Galactose metabolism:** The pathways concerned with the conversion of galactose to glucose and the synthesis of lactose.
9. **Fructose metabolism:** The oxidation of fructose to pyruvate and the relation between fructose and glucose metabolism.

10. **Amino sugar and mucopolysaccharide metabolism:** The synthesis of amino sugars and other sugars for the formation of mucopolysaccharides and glycoprotein.

### Glucose transporters:

- In recent years, at least six glucose transporters (GLUT-1 to GLUT-5 and GLUT-7) in the cell membranes have been identified.
- For instance, GLUT-1 is abundant in erythrocytes whereas GLUT-4 is abundant in skeletal muscle and adipose tissue.
- Insulin increases the number and promotes the activity of GLUT-4 in skeletal muscle and adipose tissue.

## GLYCOLYSIS

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

- Glycolysis takes place in the cytosomal fraction of the cell.
- It occurs in the absence of oxygen (anaerobic) or in the presence of oxygen (aerobic).
- Lactate is the end product under anaerobic condition. In the aerobic condition, pyruvate is formed, which is then oxidized to CO<sub>2</sub> and H<sub>2</sub>O.

### Irreversible steps in glycolysis

- The three steps governed by the enzymes **hexokinase (or glucokinase), phosphofruktokinase and pyruvate kinase** in glycolysis are irreversible and mainly regulates glycolysis.

- The reversal of glycolysis, with alternate arrangements made at the three irreversible stages, leads to the synthesis of glucose from pyruvate (gluconeogenesis)

### Pasteur effect

- The inhibition of glycolysis by oxygen (aerobic condition) is known as Pasteur effect.

### Crabtree effect

- The phenomenon of inhibition of oxygen consumption by the addition of glucose to tissues having high aerobic glycolysis is known as Crabtree effect.
- Basically, this is opposite to that of Pasteur effect.

### CONVERSION OF PYRUVATE TO ACETYL CoA

Pyruvate is converted to acetyl CoA by oxidative decarboxylation.

This is an irreversible reaction, catalysed by a multi enzyme complex, known as **pyruvate dehydrogenase complex (PDH)**, which is found only in the mitochondria.

The enzyme PDH requires five cofactors (coenzymes), namely-

1. TPP
2. Lipoamide
3. FAD
4. Coenzyme A
5. NAD<sup>+</sup>

### KREB CYCLE

- Citric acid cycle essentially involves the oxidation of acetyl CoA to CO<sub>2</sub> and H<sub>2</sub>O.
- The name TCA cycle is used, since, at the outset of the cycle, tricarboxylic acids (**citrate, isocitrate and alpha-ketoglutarate**) participate.
- The enzymes of TCA cycle are located in mitochondrial matrix, in close proximity to the electron transport chain.

- There is no direct participation of oxygen in Krebs cycle. However, the cycle operates only under aerobic conditions. This is due to the fact that NAD<sup>+</sup> and FAD (from NADH and FADH<sub>2</sub>, respectively) required for the operation of the cycle can be regenerated in the respiratory chain only in the presence of O<sub>2</sub>.
- Therefore citric acid cycle is strictly aerobic in contrast to glycolysis which operates in both aerobic and anaerobic conditions.

### Inhibitors of Krebs cycle

| Enzyme                                | Inhibitor                       |
|---------------------------------------|---------------------------------|
| Aconitase                             | Fluoroacetate (non-competitive) |
| $\alpha$ -Ketoglutarate dehydrogenase | Arsenite (non-competitive)      |
| Succinat dehydrogenase                | Malonate (competitive)          |

### Metabolic Disorders:

#### 1. Lactic acidosis

It is due to reduction in oxygen supply which leads to shifting of aerobic glycolysis to anaerobic glycolysis resulting in accumulation of Lactic acid.

#### 2. Haemolysis:

HMP shunt is the only means of providing NADPH in the erythrocytes. Decreased activity of G6PD impairs the synthesis of NADPH in RBC. This results in the accumulation of methemoglobin and peroxides in erythrocytes leading to haemolysis.

#### 3. Wernicke-Korsakoff syndrome

An alteration in transketolase activity that reduces its affinity (by tenfold or so) with thiamine pyrophosphate. The symptoms of Wernicke-Korsakoff syndrome include mental disorder, loss of memory and partial paralysis

#### 4. Galactosemia

It is due to the deficiency of the enzyme galactose 1-phosphate uridylyltransferase during galactose metabolism.

## Generation of ATP in glucose metabolism

| Pathway    | Enzyme (method of ATP synthesis)   | No. of ATP synthesized |
|------------|--|------------------------|
| Glycolysis | Glyceraldehyde 3-phosphate dehydrogenase<br>( 2 NADH, ETC, oxidative phosphorylation ) | 6*                     |

|                          |   |           |
|--------------------------|---|-----------|
|                          | Phosphoglycerate kinase (substrate level phosphorylation)                             | 2         |
|                          | Pyruvate kinase (substrate level phosphorylation)                                     | 2         |
|                          | Two ATP are consumed in the reactions catalysed by hexokinase and phosphofructokinase | -2        |
|                          | <b>Net ATP synthesis in glycolysis in aerobic condition</b>                           | <b>8</b>  |
|                          | Pyruvate dehydrogenase (2 NADH, ETC, oxidative phosphorylation)                       | 6         |
| <b>Citric acid cycle</b> | Isocitrate dehydrogenase (2 NADH, ETC, oxidative phosphorylation)                     | 6         |
|                          | $\alpha$ -ketoglutarate dehydrogenase   | 6         |
|                          | Succinate thiokinase (substrate level dehydrogenase)                                  | 2         |
|                          | Succinate dehydrogenase (2 FADH, ETC, oxidative phosphorylation)                      | 4         |
|                          | Malate dehydrogenase (2 NADH, ETC, oxidative phosphorylation)                         | 6         |
|                          | <b>Total ATP per mole of glucose under aerobic condition</b>                          | <b>38</b> |
|                          | Total ATP per mole of glucose under anaerobic condition                               | 2         |

\*6 ATP are produced if NADH uses malate shuttle; only 4 ATP are produced if glycerol-phosphate shuttle operates, in which case total ATP synthesized per mole of glucose oxidation is 36 and not 38