BIOCHEMISTRY- BP203T

UNIT: 1 METABOLISM OF CARBOHYDRATES

CLASS:6

TOPIC: GLUCONEOGENESIS

GLUCONEOGENESIS:

- The synthesis of glucose from noncarbohydrate compounds is known as gluconeogenesis.
- The major substrates/precursors for gluconeogenesis are lactate, pyruvate, glucogenic amino acids, propionate and glycerol.
- Location of gluconeogenesis Gluconeogenesis occurs mainly in the cytosol, although some precursors are produced in the mitochondria.
- Gluconeogenesis mostly takes place in liver (about 1 kg glucose synthesized everyday) and, to some extent, in kidney matrix (about one-tenth of liver capacity)

IMPORTANCE OF GLUCONEOGENESIS :

Glucose occupies a key position in the metabolism and its continuous supply is absolutely essential to the body for a variety of functions

1. Brain and central nervous system, erythrocytes, testes and kidney medulla are dependent on glucose for continuous supply of energy. Human brain alone requires about 120 g of glucose per day, out of about 160 g needed by the entire body.

2. Glucose is the only source that supplies energy to the skeletal muscle, under anaerobic conditions.

3. In fasting even more than a day, gluconeogenesis must occur to meet the basal requirements of the body for glucose and to maintain the intermediates of citric acid cycle. This is essential for the survival of humans and other animals.

4. Certain metabolites produced in the tissues accumulate in the blood, e.g. lactate, glycerol, propionate etc. Gluconeogenesis effectively clears them from the blood

REACTIONS OF GLUCONEOGENESIS :

Gluconeogenesis closely resembles the reversed pathway of glycolysis, although it is not the complete reversal of glycolysis.

Essentially, 3 (out of 10) reactions of glycolysis are irreversible.

The seven reactions are common for both glycolysis and gluconeogenesis (Fig.13.11).

The three irreversible steps of glycolysis are catalysed by the enzymes, namely hexokinase, phosphofructokinase and pyruvate kinase.

These three stages—bypassed by alternate enzymes specific to gluconeogenesis—are discussed

1. Conversion of pyruvate to phosphoenol pyruvate:

This takes place in two steps (Fig.13.12). Pyruvate carboxylase is a biotin— dependent mitochondrial enzyme that converts pyruvate to oxaloacetate in presence of ATP and CO2.

This enzyme regulates gluconeogenesis and requires acetyl CoA for its activity.

Oxaloacetate is synthesized in the mitochondrial matrix.

It has to be transported to the cytosol to be used in gluconeogenesis, where the rest of the pathway occurs.

Due to membrane impermeability, oxaloacetate cannot diffuse out of the mitochondria.

It is converted to malate and then transported to the cytosol. Within the cytosol, oxaloacetate is regenerated.

The reversible conversion of oxaloacetate and malate is catalysed by malate dehydrogenase, an enzyme present in both mitochondria and cytosol.

In the cytosol, phosphoenolpyruvate carboxykinase converts oxaloacetate to phosphoenol pyruvate.

GTP or ITP (not ATP) is used in this reaction and the CO2 (fixed by carboxylase) is liberated.

For the conversion of pyruvate to phosphoenol pyruvate, 2 ATP equivalents are utilized.

This is in contrast to only one ATP that is liberated in glycolysis for this reaction.

2. Conversion of fructose 1,6-bisphosphate to fructose 6-phosphate:

Phosphoenolpyruvate undergoes the reversal of glycolysis until fructose 1,6-bisphosphate is produced.

The enzyme fructose 1,6-bisphosphatase converts fructose 1,6-bisphosphate to fructose 6-phosphate.

This enzyme requires Mg2+ ions. Fructose 1,6- bisphosphatase is absent in smooth muscle and heart muscle.

This enzyme is also regulatory in gluconeogenesis.

3. Conversion of glucose 6-phosphate to glucose:

Glucose 6-phosphatase catalyses the conversion of glucose 6-phosphate to glucose.

The presence or absence of this enzyme in a tissue determines whether the tissue is capable of contributing glucose to the blood or not.

It is mostly present in liver and kidney but absent in muscle, brain and adipose tissue.

The overall summary of gluconeogenesis for the conversion of pyruvate to glucose is shown below

2 Pyruvate + 4ATP + 2GTP + 2NADH + 2H+ + 6H2O→ Glucose + 2NAD+ + 4ADP + 2GDP + 6Pi + 6H+

Glycolysis/gluconeogenesis