UNIT-2

Gluconeogenesis (new formation of sugar).

The human brain and nervous system as well as the erythrocytes, renal medulla and embryonic tissues need glucose. Glucose from the blood is the sole or major fuel source. The brain alone requires about 120 gm of glucose each day-more than half of all the glucose stored as glycogen in muscle and liver. However, the supply of glucose from this source is not always sufficient between meals and during longer first fasts or after vigorous exercise, glycogen is depleted. **For these times, organisms need a method for synthesizing glucose from non carbohydrate precursors**. **This is accomplished by a pathway called gluconeogenesis which converts pyruvate and related 3 and 4 carbon compounds to glucose**.

The important precursors of glucose in animals are three carbon compounds such as lactate, pyruvate and glycerol as well as certain amino acids. In mammals gluconeogenesis takes place mainly in the liver and to a lesser extent in renal cortex epithelial cells that line the inside of the small intestine. The glucose produced passes into the blood to supply other tissues. After vigorous exercise, lactate produced by anaerobic glycolysis in skeletal muscles returns to the liver and is converted to glucose which moves back to the muscle and is converted to glycogen in a circuit called the cori cycle.

Gluconeogenesis from Pyruvate

1. Gluconeogenesis is not simply the reverse of glycolysis The end product of aerobic glycolysis is pyruvate. But glucose cannot be produced by reversing the glycolysis process because there are three irreversible steps in glycolysis.

2. Of the 10 reactions that constitute gluconeogenesis, 7 reversible steps are shared with glycolysis; the 3 irreversible steps are bypassed by the separate sets of enzymes.

The reactions have a ΔG close to zero, therefore easily reversible. However, under intracellular conditions, the overall ΔG of glycolysis is about -63 kJ/mol (-15 kcal/mol) and of gluconeogenesis about -16 kJ/mol (-3.83 kcal/mol), namely, both the pathways are **irreversible**

There are some important differences. Pyruvate is a common starting material for gluconeogenesis. First, the pyruvate is converted into oxaloacetate. Oxaloacetate then serves as a substrate for the enzyme phosphoenolpyruvate carboxykinase (PEPCK), which transforms oxaloacetate into phosphoenolpyruvate (PEP).

From this step, gluconeogenesis is nearly the reverse of glycolysis. PEP is converted back into 2-phosphoglycerate, which is converted into 3-phosphoglycerate.

Then, 3-phosphoglycerate is converted into 1,3 bisphosphoglycerate and then into glyceraldehyde-3-phosphate.

Two molecules of glyceraldehyde-3-phosphate then combine to form fructose-1-6-bisphosphate, which is converted into fructose 6-phosphate and then into glucose-6-phosphate. Finally, a series of reactions generates glucose itself. In gluconeogenesis (as compared to glycolysis), the enzyme hexokinase is replaced by glucose-6-phosphatase, and

the enzyme phosphofructokinase-1 is replaced by fructose-1,6-bisphosphatase. This helps the cell to regulate glycolysis and gluconeogenesis independently of each other.

Thus, the net requirements to make one glucose molecule are:

- Two pyruvate.
- Four ATP and two GTP.
- Two NADH.
- Six H_2O

Significance of Gluconeogenesis Pathway

1. Gluconeogenesis meets the needs of the body for glucose when sufficient carbohydrate is not available from the diet or glycogen reserves.
2. Glycogen stored in adipose tissue and in skeletal muscle is converted to glucose by glycogenolysis. However the stored glycogen may not be sufficient during heavy exercise, diabetic conditions,or during fasting etc. so during shortage, glucose is synthesized by gluconeogenesis process.
3. A continual supply of glucose is necessary as a source of energy especially for the nervous system and erythrocytes.
4. Gluconeogenesis mechanism is used to clear the products of the metabolism of other tissues from the blood, eg: Lactate, produced by muscle and erythrocytes and glycerol, which is continuously produced by adipose tissue.

Associated Disease

Deficiency in any of the gluconeogenic enzymes leads to hypoglycemia. Failure of gluconeogenesis may be fatal.

The bypass reaction that occur during conversion of pyruvate to glucose are

1. **Conversion of pyruvate to Phosphoenolpyruvate (PEP)**
2. **Conversion of Fructose-1,6-bisphosphate to Fructose-6-phosphate**

3. **Conversion of Glucose-6-phosphate to glucose**

Bypass step I: Conversion of Pyruvate to PEP:

- It is the first bypass reaction in gluconeogenesis
- The conversion of pyruvate to PEP occurs in both cytosol and mitochondria.
- First pyruvate is transported from cytosol into mitochondira or it is generated in mitochondria from alanine by transamination (urea cycle)
- Then pyruvate carboxylase) coenzyme-biotin) converts pyruvate to Oxaloacetate within mitochondria.

Pyruvate + HCO_3^- +ATP——————— Oxaloacetate + ADP + pi

- The mitochondrial membrane do not have transporter for Oxaloacetate. So, oxaloacetate is reduced to malate by mitochondrial enzyme malate dehydrogenase

Oxaloacetate + NADH + H^+——————— malate + NAD^+

- Malate leaves the mitochondria through special transporter and in cytosol it is reoxidized into oxaloacetate by the cytosolic enzyme malate dehydrogenase.

Malate + NAD^+————————- Oxaloacetate + NADH + H^+

- The oxaloacetate is then converted to Phosphoenol pyruvate (PEP) by an enzyme phosphoenolpyruvate carboxykinase. This reaction is Mg^{++} dependent and require GTP.

Oxaloacetate + GTP————————- PEP + GDP + CO_2

Bypass Step II: conversion of Fructose-1,6-bisphosphate to Fructose-6-phosphate

- This reaction is catalyzed by an enzyme fructose-1,6-bisphospatase (FBPase-1)which causes the irreversible hydrolysis of phosphate at C1.

Fructose-1,6-bisphosphate +H_2O————————fructose-6-phosphate + Pi

Bypass step III: conversion of glucose-6-phosphate to glucose

- This reaction is catalyzed by glucose-6-phosthatase which hydrolyses the phosphate at C6 yielding glucose.

Glucose-6-phosphate +H2o ———————— Glucose + Pi

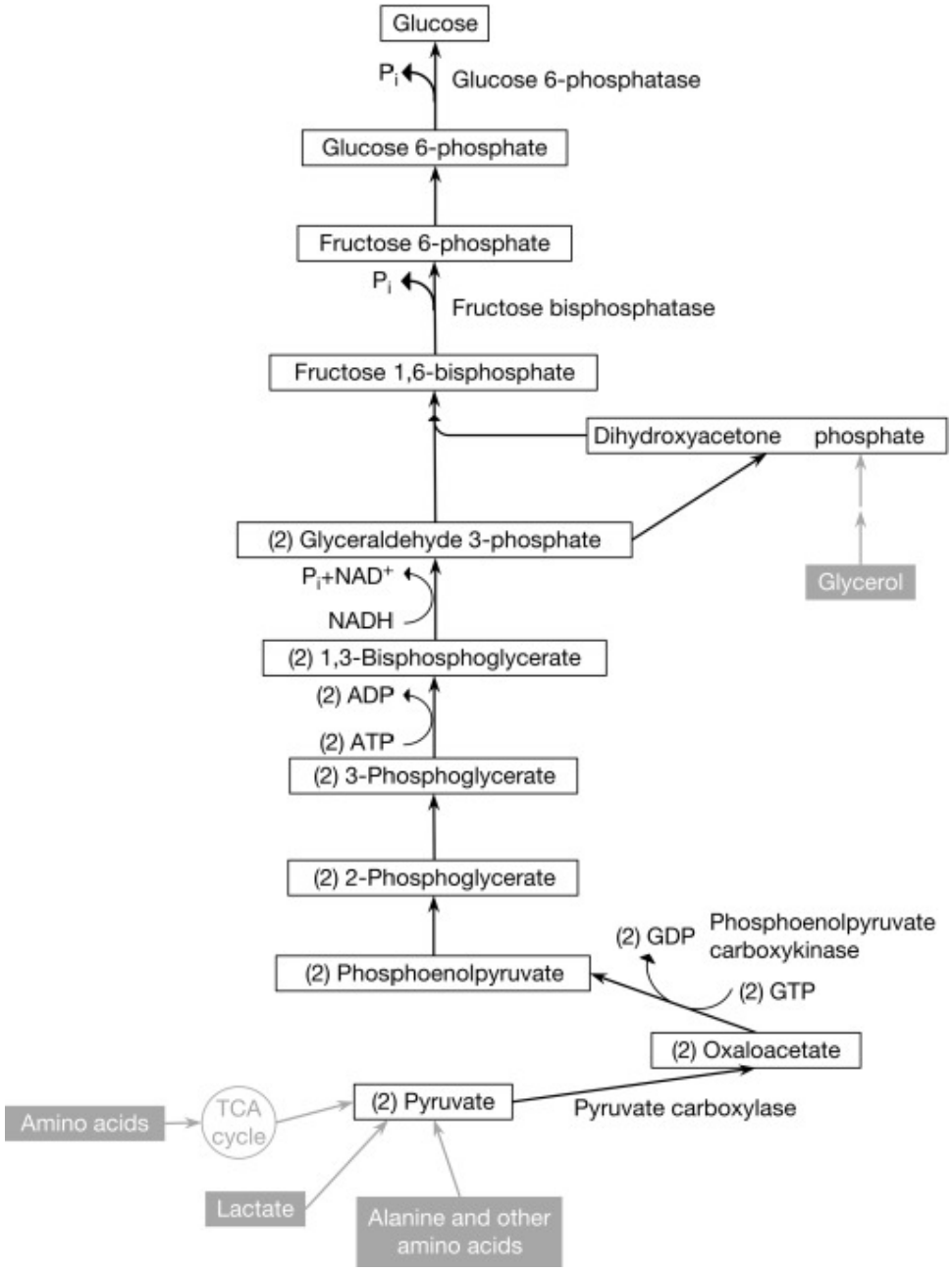
Other precursors such as lactate, intermediates of TCA cycle and some glucogenic aminoacids can also convert into glucose.

1. Conversion of lactate:(cori's cycle)

- Lactate generates during anaerobic respiration in Erythrocytes and in muscle during heavy exercise is converted into pyruvate by an enzyme lactate dehydrogenase.
- Pyruvate then enter into mitochondria from cytosol and convert into Oxaloacetate by the enzyme pyruvate carboxylase
- Oxaloacetate directly convert into PEP (phospoenolpyruvate) by an isoenzyme PEP carboxykinase within Mitochondria.
- PEP is then transported outside of mitochondria to continue gluconeogenesis.

2. conversio of TCA intermediate and aminoacids into glucos

- Citrate, isocitrate, alfa-ketoglutarate, succinyl coA, succinate, fumarate, malate etc all intermediates of TCA cycle are oxidized to oxaloacetate which then converts in glucose.
- The glucogenic aminoacids such as alanine, glutamine etc. are converted to pyruvate which in turn converts to glucose.


Glucose
P_i
Glucose 6-phosphatase
Glucose 6-phosphate
Fructose 6-phosphate
P_i
Fructose bisphosphatase
Fructose 1,6-bisphosphate
Dihydroxyacetone phosphate
(2) Glyceraldehyde 3-phosphate
Glycerol
P_i+NAD^+
NADH
(2) 1,3-Bisphosphoglycerate
(2) ADP
(2) ATP
(2) 3-Phosphoglycerate
(2) 2-Phosphoglycerate
(2) GDP
Phosphoenolpyruvate carboxykinase
(2) Phosphoenolpyruvate
(2) GTP
(2) Oxaloacetate
Amino acids
TCA cycle
(2) Pyruvate
Pyruvate carboxylase
Lactate
Alanine and other amino acids