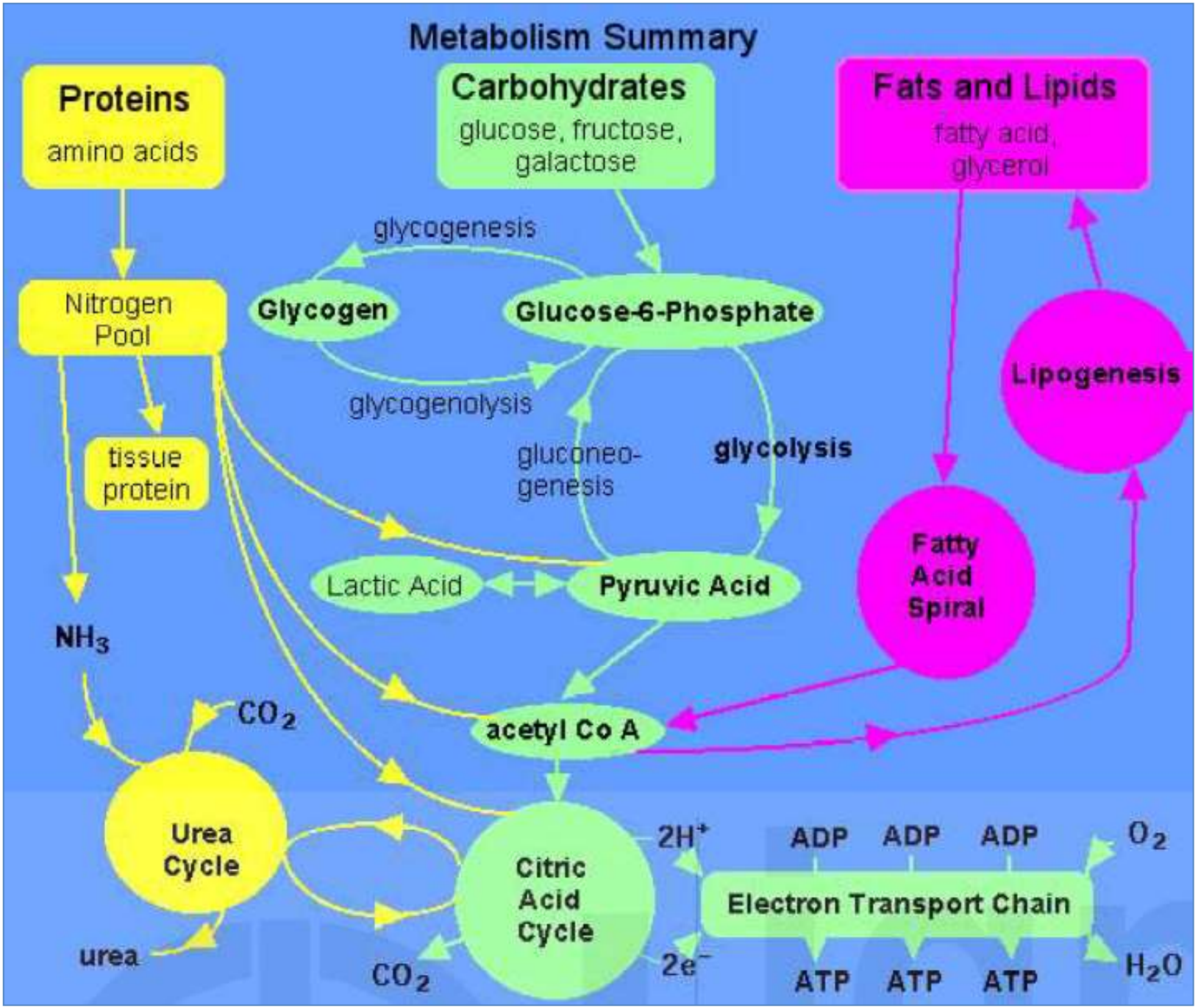
# CARBOHYDRATE METABOLISM

## GLUCONEOGENESIS
## GLYCOGENOLYSIS
## AND
## GLYCOGENESIS

***Dr. R. Prasad,***
***Assistant Professor,***
***Department of Zoology,***
***Eastern Karbi Anglong College***


Metabolism Summary
Proteins
amino acids
Carbohydrates
glucose, fructose, galactose
Fats and Lipids
fatty acid, glycerol
glycogenesis
Nitrogen Pool
Glycogen
Glucose-6-Phosphate
Lipogenesis
glycogenolysis
tissue protein
gluconeo-genesis
glycolysis
Fatty Acid Spiral
Lactic Acid
Pyruvic Acid
NH3
CO2
acetyl Co A
Urea Cycle
Citric Acid Cycle
2H+
ADP ADP ADP
O2
Electron Transport Chain
urea
CO2
2e-
ATP ATP ATP
H2O

In Unit 5, we studied that carbohydrates are broken down into monosaccharides which are absorbed into the blood stream. In the liver and muscles, most of the glucose is changed into glycogen by the process of *glycogenesis* (anabolism). Glycogen is stored in the liver and muscles until needed at some later time when glucose levels are low. If blood glucose levels are low, then epinephrine and glucagon hormones are secreted to stimulate the conversion of glycogen to glucose. This process is called *glycogenolysis* (catabolism). If glucose is needed immediately upon entering the cells to supply energy, it begins the metabolic process called *glycolysis* (catabolism). The end products of glycolysis are pyruvic acid and ATP. Since glycolysis releases relatively little ATP, further reactions continue to convert pyruvic acid to acetyl CoA and then citric acid in the citric acid cycle. The majority of the ATP is made from oxidations in the citric acid cycle in connection with the electron transport chain.

During strenuous muscular activity, pyruvic acid is converted into lactic acid rather than acetyl CoA. During the resting period, the lactic acid is converted back to pyruvic acid. The pyruvic acid in turn is converted back to glucose by the process called *gluconeogenesis* (anabolism). If the glucose is not needed at that moment, it is converted into glycogen by glycogenesis. These processes are

# GLUCONEOGENESIS

Gluconeogenesis (i.e synthesis of new glucose) is the synthesis of carbohydrate from non-carbohydrate, source. The major substrates for gluconeogenesis are the glucogenic amino acids, lactate, glycerol and (important in ruminant) propionate. We shall get to know about them later in sub-section 6.6.2. Liver and kidney are the major tissues involved in gluconeogenesis due to the availability of the necessary enzymes.

But, first, what is the significance of gluconeogenesis? Read the next sub-section and find out.

## Functions of Gluconeogenesis

The significance of gluconeogenesis include:

1) During starvation or during periods of limited carbohydrate intake, when the levels of liver glycogen are low, gluconeogenesis is important in maintaining adequate blood sugar concentration since a continual supply of glucose is necessary as a source of energy for the nervous system and the erythrocytes.

2) Even when most of the energy requirement of the organism is met by the supply of fat, there is always a certain basal requirement for glucose which is provided by gluconeogenesis.

3) During extended exercise, when high catecholamine levels have mobilized carbohydrate and lipid reserves, the gluconeogenic pathway allows the use of lactate from glycolysis and of glycerol from fat break down.

4) During metabolic acidosis, gluconeogenesis in the kidney allows the excretion of an increased number of protons.

5) Gluconeogenesis also allows the use of dietary protein in carbohydrate pathway after disposal of the amino acid nitrogen as urea.

6) Gluconeogenesis is important to human beings everyday, making it possible for us to make it through the night and from meal to meal without nibbling on a source of carbohydrate continuously.

So, you would have realized that the production of glucose from other substrates is necessary for use as fuel. Hence, it is important for us to learn about these substrates and their reactions in gluconeogenesis. The next sub-section presents a discussion on these substrates.

## Gluconeogenesis – Substrates

Earlier in this section, you may recall reading that the major substrates for gluconeogenesis are the glucogenic amino acids, lactate, glycerol etc. Let us get to know about these substrates and their role in gluconeogenesis. We start with lactate as a substrate.

A) *Lactate*

Lactate is transported to the liver in the Cori cycle (lactic acid cycle) and is converted to pyruvate as shown in Figure 6.6. Hepatic gluconeogenesis then converts lactate back to glucose. Glucose is then free to circulate back to peripheral tissue to re-enter anaerobic glycolysis. This is the Cori cycle. It functions to:

- maintain glucose substrate for vital tissues, and
- prevent excessive acidosis due to an excess of lactate.

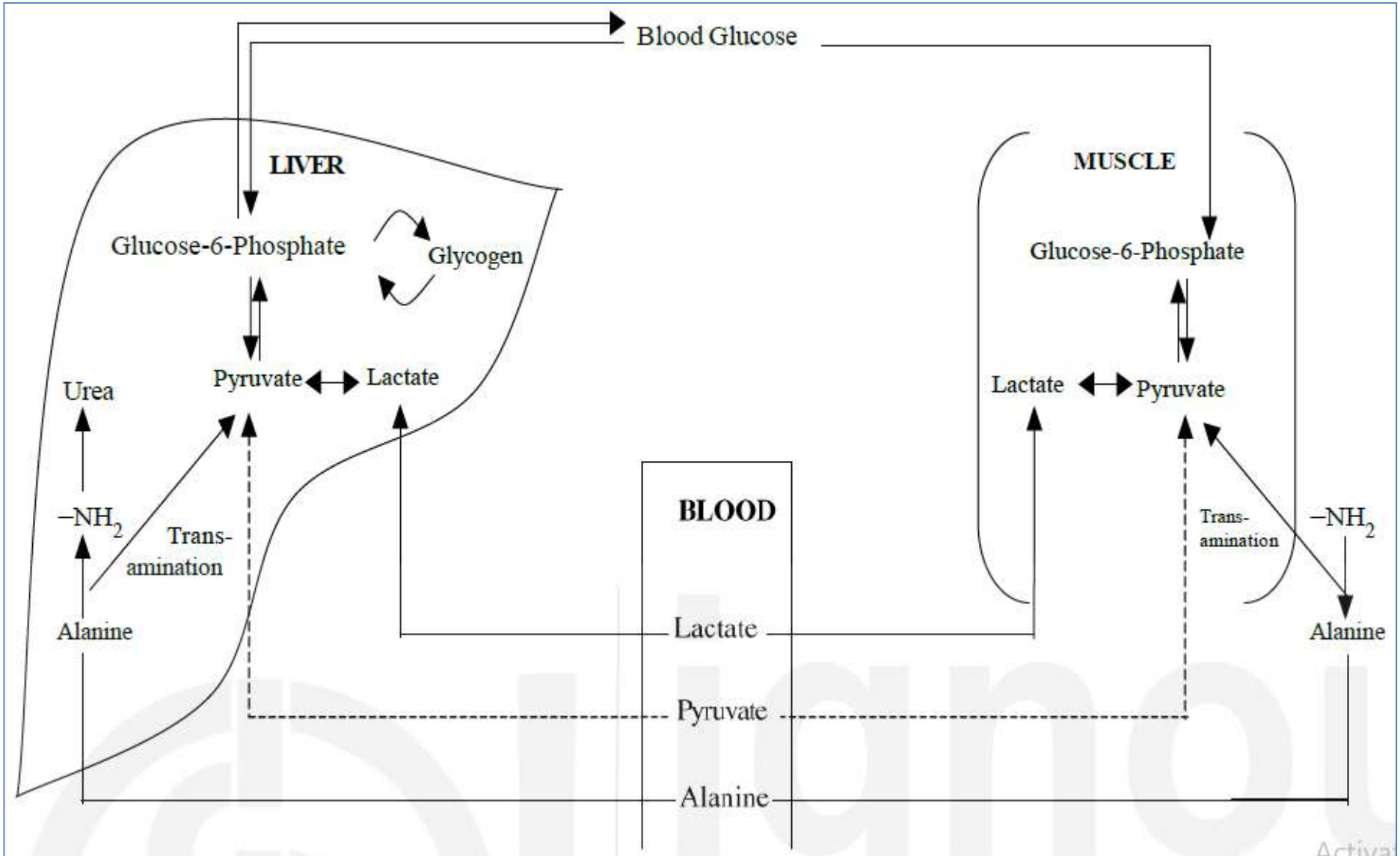



**Figure 6.6 : The Cori cycle and Alanine cycle**

B) *Glycerol*

The process includes:

1) Glycerol is formed in the adipose tissue by lipolysis of triacylglycerol when metabolic fuel is scarce.

2) Glycerol is released into the blood and taken up by the liver, where it is first converted to glycerol-3-phosphate by *glycerokinase* and ATP.

3) Glycerol-3-phosphate is oxidized to dihydroxyacetone phosphate by *glycerol-3-phosphate dehydrogenase* in presence of $NAD^+$. Dihydroxyacetone phosphate is then converted to glucose.

C) *Amino acids*

Figure 6.7 illustrates the citric acid cycle intermediates from the amino acids. Here, as you can see:

1) the glucogenic amino acids are converted to the intermediates of citric acid cycle either by transamination or deamination, and

2) these intermediates are converted to oxaloacetate and finally converted to glucose by the enzymes of gluconeogenesis.

Another important substrate, particularly in ruminant is propionate. Let us learn about it.

D) *Propionic acid*

Propionic acid is formed as a residual unit (propionyl CoA) in *β-oxidation* of odd-carbon fatty acids. The conversion of propionate to succinyl CoA involves a long process as given herewith and illustrated in Figure 6.8.

1) Propionate is first activated by thiokinase with ATP and CoA to form propionyl CoA.
2) Propionyl CoA undergoes $CO_2$ fixation reaction to form D-methyl malonyl CoA catalyzed by *propionyl CoA carboxylase* and biotin is required as a coenzyme.
3) D-methyl malonyl CoA is converted to L-methyl malonyl CoA by *methyl malonyl CoA racemase.*
4) L-methyl malonyl CoA is isomerised to succinyl CoA by *methyl malonyl CoA isomerase* which requires vitamin $B_{12}$ as a coenzyme.
5) Succinyl CoA enters citric acid cycle and is converted to oxaloacetate and then further to glucose via gluconeogenic pathway.

## Gluconeogenic Pathway

The metabolic pathways in connection with gluconeogenesis are the modification of the EM pathway and citric acid cycle. The synthesis of glucose from substrates is essentially a reversal of glycolysis. However, *Krebs* pointed out that energy barriers obstruct a simple reversal of glycolysis and must be bypassed for gluconeogenesis to be completed. These reactions are:

i) Between pyruvate and phosphoenolpyruvate (PEP)
ii) Between fructose 1,6 bisphosphate and fructose 6-phosphate
iii) Between glucose-6-phosphate and glucose, and
iv) Between glucose-1-phosphate and glycogen.

You may recall reading about these reactions in the glycolysis pathway. To help you understand the process, a summary of the gluconeogenesis pathway with gluconeogenesis enzyme names in red and names of reversible glycolysis enzymes in blue is presented in Figure 6.9. The above mentioned reactions are circumvented by the special reactions highlighted in Figure 6.9 (Under A, B and C) and also discussed herewith.

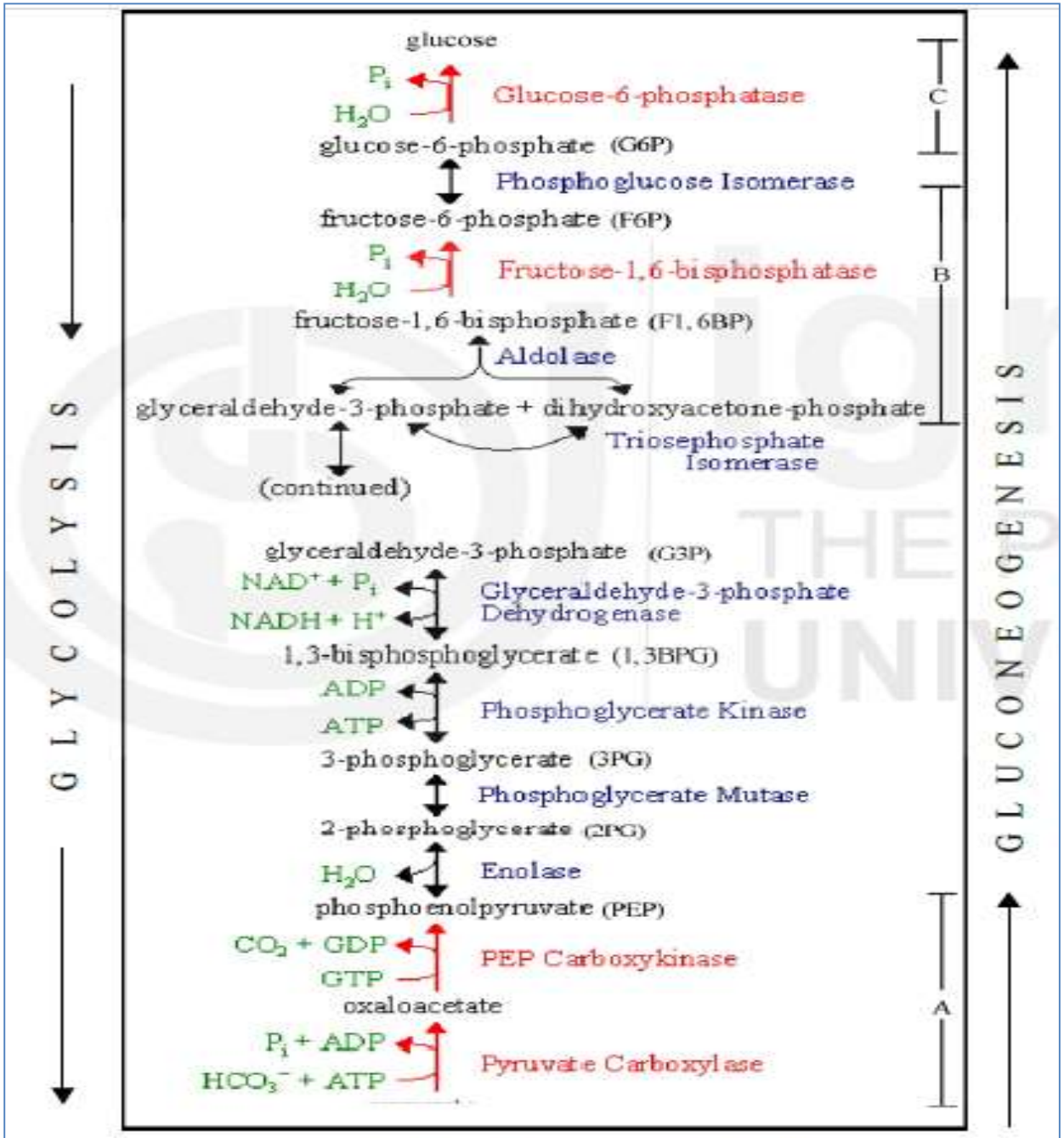



**Figure 6.9 : Summary of the gluconeogenesis pathway**

A) *Pyruvate* and *Phosphoenolpyruvate* (Look at Figure 6.9, A)

1) *Pyruvate carboxylation:* In this reaction, pyruvate, $CO_2$ and ATP are converted to oxaloacetate, ADP and Pi catalysed by the enzyme *pyruvate carboxylase* and the cofactors required are biotin and $Mg^{++}$ ions. This reaction occurs in the mitochondrial matrix.

2) *Conversion of oxaloacetate to phosphoenolpyruvate:* In this reaction, oxaloacetate and guanosine triphosphate (GTP) are converted to PEP, $CO_2$ and guanosine diphosphate (GDP). This reaction is catalyzed by *phosphoenolpyruvate carboxykinase* (PEPCK) which requires $Mn^{++}$ for its activation. In humans, this enzyme is equally distributed between mitochondria and the cytosol.

In mitochondria,

Pyruvate + ATP + $Mg^{++}$

*Pyruvate Carboxylase* | Biotin, $Mg^{++}$

↓

Oxaloacetate + ADP + Pi

In mitochondria or cytosol,

Oxaloacetate + GTP

PEPCK ↓ | ↑ $Mn^{++}$

Phosphoenolpyruvate (PEP) + $CO_2$ + GDP

With the help of the above 2 enzymes and LDH, lactate can also be converted to PEP.

3) *Oxaloacetate to Malate:* Oxaloacetate cannot permeate mitochondrial membrane well and it must be transported across the membrane in the form of malate.

This reaction is catalyzed by malate dehydrogenase.

$$\text{Oxaloacetate} + \text{NADH} + \text{H}^+ \rightleftharpoons \text{Malate} + \text{NAD}^+$$

a) In the mitochondria, a mitochondrial *malate dehydrogenase* catalyses the above reaction, and

b) In the cytosol, a cytosolic *malate dehydrogenase* catalyses the reverse reaction which regenerates oxaloacetate so it can be converted to PEP. Look at Figure 6.10.

$$\text{Malate} + \text{NAD}^+ \longrightarrow \text{Oxaloacetate} + \text{NADH} + \text{H}^+$$

c) In this process, malate also serves to transfer reducing equivalents from the mitochondria to the cytosol. The NADH formed is used in gluconeogenesis.

B) *Fructose-1,6-bisphosphate* and *Fructose-6-phosphate:* (Look at Figure 6.9, B)

The conversion of fructose-1,6- bisphosphate to fructose-6-phosphate is catalysed by *fructose-1,6-bisphosphatase* which is the major regulatory enzyme in gluconeogenesis. This enzyme is present in liver, kidney and striated muscle but absent from adipose tissue, heart muscle and smooth muscle. Fructose-1,6 bisphosphatase is an allosteric enzyme, activated by citrate and inhibited by AMP and fructose-1,6-bisphosphate.

These allosteric effects are exactly the opposite of those observed with phosphofructokinase, the regulatory enzyme in glycolysis. This is an example of reciprocal control of opposing metabolic pathways.

C) *Glucose-6-phosphate to Glucose:* (Look at Figure 6.9, C)

Glucose-6-phosphate is converted to glucose by *glucose-6-phosphatase* which is present in intestine, liver and kidney but absent from muscle and adipose tissue.

D) *Glucose-1-phosphate to Glycogen*

The conversion of glucose-1-phosphate to glycogen is through UDPG and glycogen synthase. We shall learn about this later in section under glycogen synthesis.

The conversion of 2 moles of pyruvate and 1 mole of glucose uses 4 moles of ATP and 2 moles of GTP, the total equivalent of 6 moles of high energy phosphate since GTP, like ATP, possesses high energy phosphate bonds.

Overall, each pathway i.e. glycolysis and gluconeogenesis may be summarized as follows:

*Glycolysis:*

$$\text{glucose} + 2NAD^+ + 2ADP + 2P_i \longrightarrow 2 \text{ pyruvate} + 2NADH + 2ATP$$

*Gluconeogenesis:*

$$2 \text{ pyruvate} + 2 NADH + 4ATP + 2GTP \longrightarrow \text{glucose} + 2NAD^+ + 4ADP + 2GDP + 6P_i$$