GLUCONEOGENESIS

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Gluconeogenesis Definition:

- Gluconeogenesis (GNG) is a metabolic pathway that results in the formation of new glucose molecule from carbohydrate or non-carbohydrate precursor.

- The important precursors are lactate, pyruvate and glycerol as well as certain amino acids.

- It is a ubiquitous process, present in plants, animals, fungi, bacteria, and other microorganisms.

Location of Gluconeogenesis:

In vertebrates, gluconeogenesis takes place mainly in the liver and, to a lesser extent, in the cortex of the kidneys and intestine; not in skeletal muscle. The first reaction (catalyzed by pyruvate carboxylase) takes place in the mitochondria, whereas the rest of the reactions occur in the cytosol.

Features of Gluconeogenesis:

- Gluconeogenesis is the production of glucose from non-sugar precursors.

- It mainly occurs in the liver, and involves the synthesis of glucose from compounds that are not carbohydrates.

- When a cell is growing on a hexose such as glucose, and obtaining glucose for polysaccharide synthesis, there is no problem.

- However, when the cell is growing on other carbon compounds, glucose must be synthesized. This process is called as gluconeogenesis.

- Gluconeogenesis uses phosphoenolpyruvate, which is one of the intermediates of glycolysis, as starting material and travels backwards through the glycolytic pathway to form glucose.

- However, it involves several enzymatic steps that do not occur in glycolysis; thus, glucose is not generated by a simple reversal of glycolysis alone.

- The major precursors for gluconeogenesis are lactate, amino acids (which form pyruvate or TCA cycle intermediates), and glycerol (which forms DHAP).

- The synthesis of 1 mole of glucose from 2 moles of lactate requires energy equivalent to about 6 moles of ATP.

- It is one of two primary mechanisms - the other being degradation of glycogen (glycogenolysis) - used by humans and many other animals to maintain blood glucose levels, avoiding low levels (hypoglycemia).

- In ruminants, because dietary carbohydrates tend to be metabolized by rumen organisms, gluconeogenesis occurs regardless of fasting, low-carbohydrate diets, exercise, etc.

- In many other animals, the process occurs during periods of fasting, starvation, low-carbohydrate diets, or intense exercise.

- In humans, substrates for gluconeogenesis may come from any non-carbohydrate sources that can be converted to pyruvate or intermediates of glycolysis.

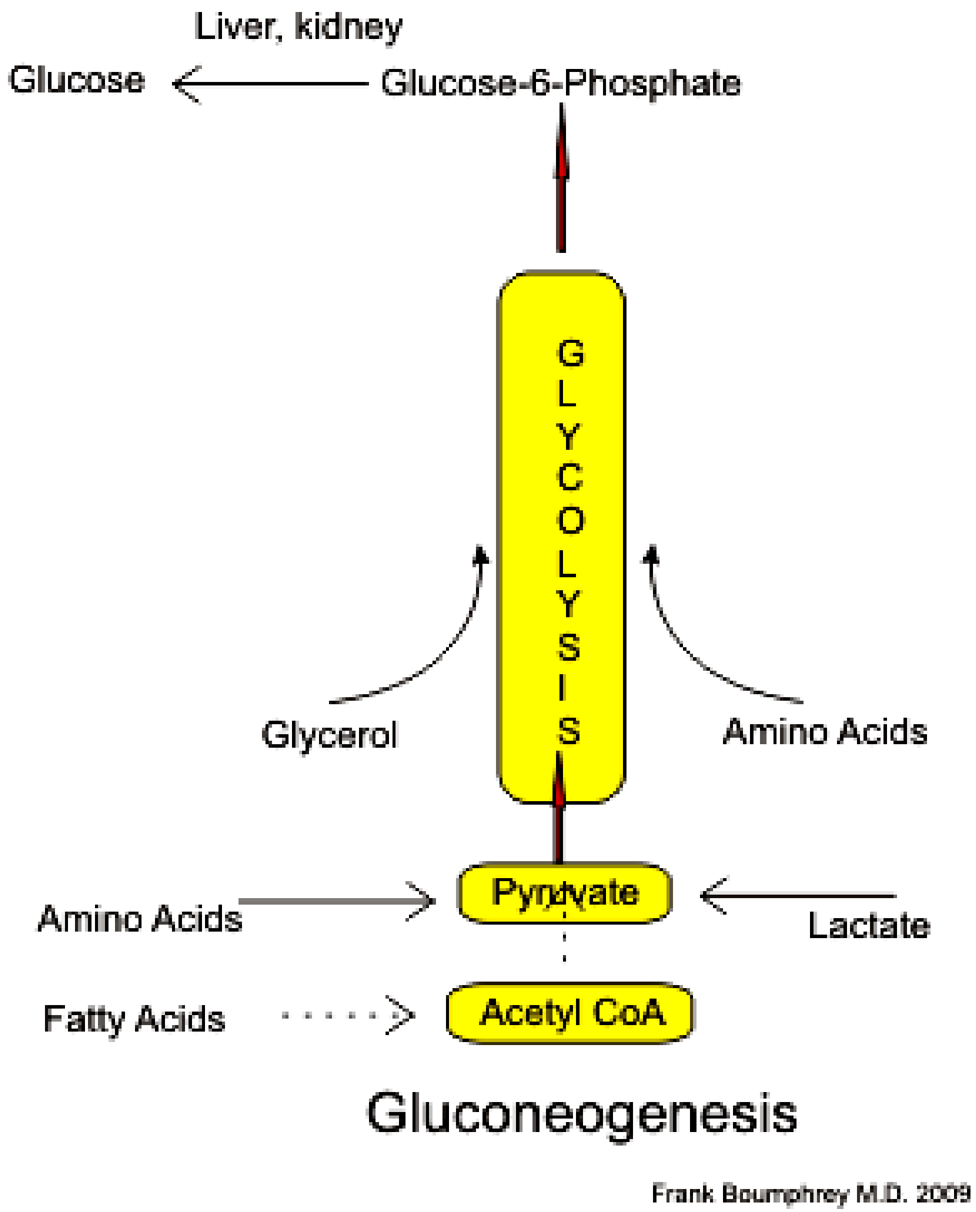
- For the breakdown of proteins, these substrates include glucogenic amino acids (although not ketogenic amino acids);

from breakdown of lipids (such as triglycerides), they include glycerol, odd-chain fatty acids (although not even-chain fatty acids, see below); and from other parts of metabolism they include lactate from the Cori cycle.

❖ Under conditions of prolonged fasting, acetone derived from ketone bodies can also serve as a substrate, providing a pathway from fatty acids to glucose.

- Although most gluconeogenesis occurs in the liver, the relative contribution of gluconeogenesis by the kidney is increased in diabetes and prolonged fasting.

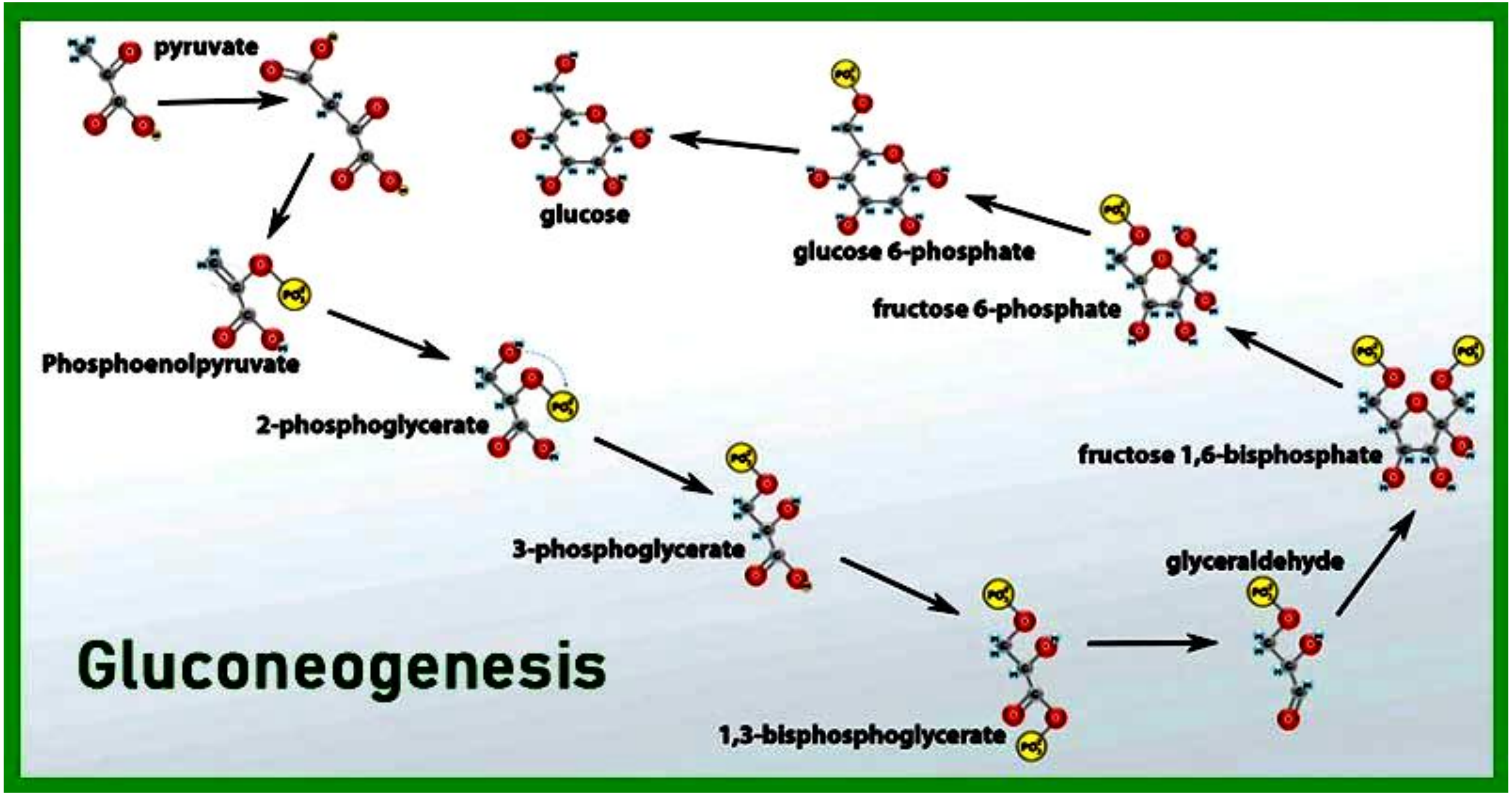
- The gluconeogenesis pathway is highly endergonic until it is coupled to the hydrolysis of ATP or GTP, effectively making the process exergonic.


Liver, kidney
Glucose
Glucose-6-Phosphate
GLYCOLYSIS
Glycerol
Amino Acids
Pyruvate
Amino Acids
Lactate
Fatty Acids
Acetyl CoA
Gluconeogenesis
Frank Boumphrey M.D. 2009

Gluconeogenesis from Pyruvate:

- The end product aerobic glycolysis is pyruvate. But glucose cannot be produced by reversing the glycolysis process because there are three irreversible steps in glycolysis.

- Gluconeogenesis pathway leading from pyruvate to glucose-6-phosphate requires 4 molecules of ATP and 2 molecules of GTP to proceed spontaneously. These ATPs are supplied from fatty acid catabolism via beta oxidation.

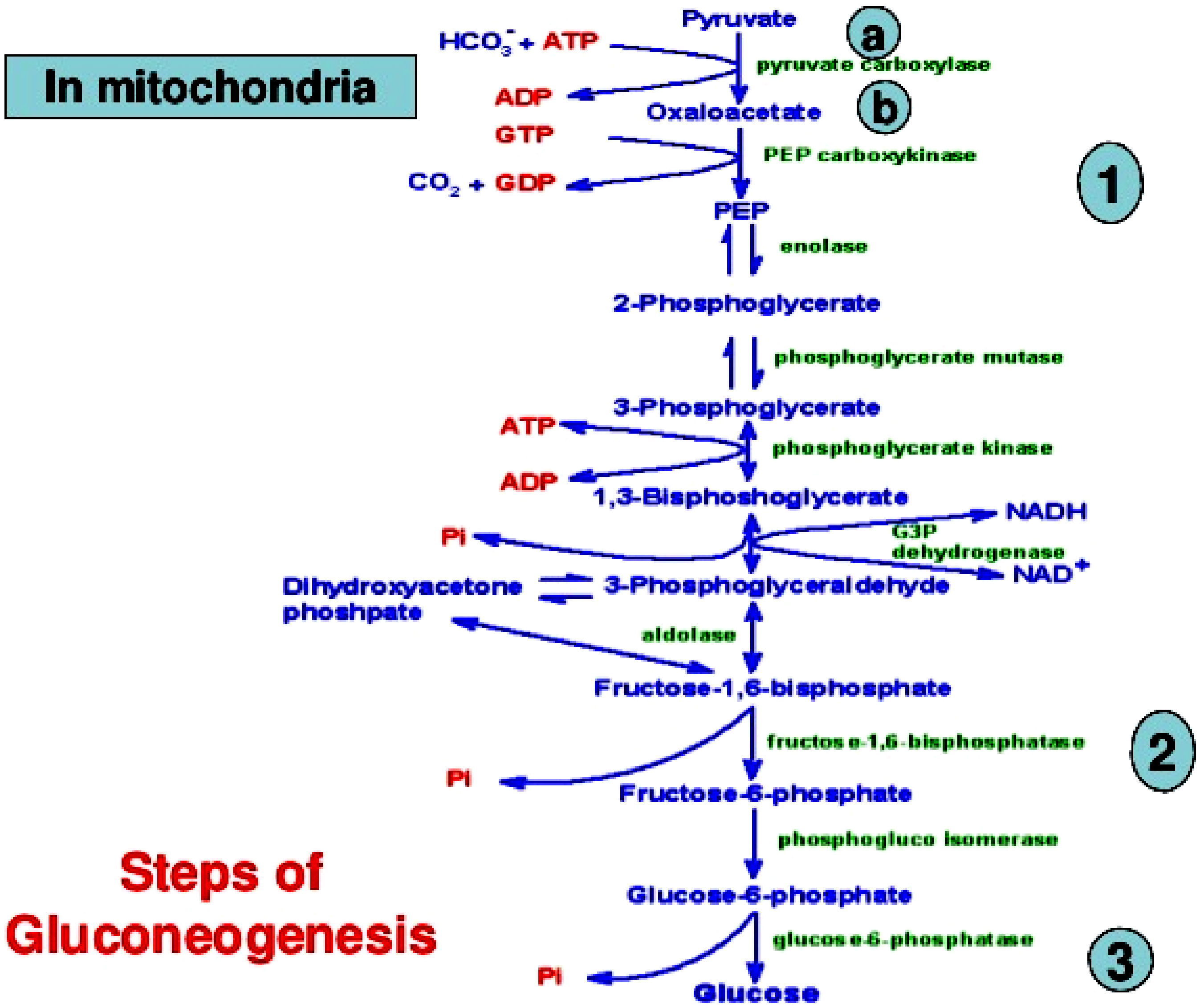

pyruvate
glucose
glucose 6-phosphate
fructose 6-phosphate
Phosphoenolpyruvate
2-phosphoglycerate
fructose 1,6-bisphosphate
3-phosphoglycerate
glyceraldehyde
Gluconeogenesis
1,3-bisphosphoglycerate

Steps in Gluconeogenesis:

- Pyruvate carboxylase converts pyruvate to oxaloacetate in the mitochondrion.
- Oxaloacetate is converted to malate or aspartate, which travels to the cytosol and is reconverted to oxaloacetate.
- Phosphoenolpyruvate carboxykinase converts oxaloacetate to phosphoenolpyruvate.
- Phosphoenolpyruvate forms fructose 1,6-bisphosphate by reversal of the steps of glycolysis.

- Fructose 1,6-bisphosphatase converts fructose 1,6-bisphosphate to fructose-6-phosphate, which is converted to glucose-6-phosphate.
- Glucose-6-phosphatase converts glucose-6-phosphate to free glucose, which is released into the blood.

Gluconeogenesis from pyruvate share 7 reversible steps of glycolysis and the 3 irreversible steps are bypassed by the separate sets of enzymes.


In mitochondria
Pyruvate
a
HCO_3^- + ATP
pyruvate carboxylase
ADP
Oxaloacetate
b
GTP
PEP carboxykinase
CO_2 + GDP
1
PEP
enolase
2-Phosphoglycerate
phosphoglycerate mutase
3-Phosphoglycerate
ATP
phosphoglycerate kinase
ADP
1,3-Bisphoshoglycerate
NADH
Pi
G3P
dehydrogenase
NAD^+
Dihydroxyacetone
phoshpate
3-Phosphoglyceraldehyde
aldolase
Fructose-1,6-bisphosphate
fructose-1,6-bisphosphatase
2
Pi
Fructose-6-phosphate
phosphogluco isomerase
Steps of
Gluconeogenesis
Glucose-6-phosphate
glucose-6-phosphatase
3
Pi
Glucose

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

Reactions involved in Gluconeogenesis:

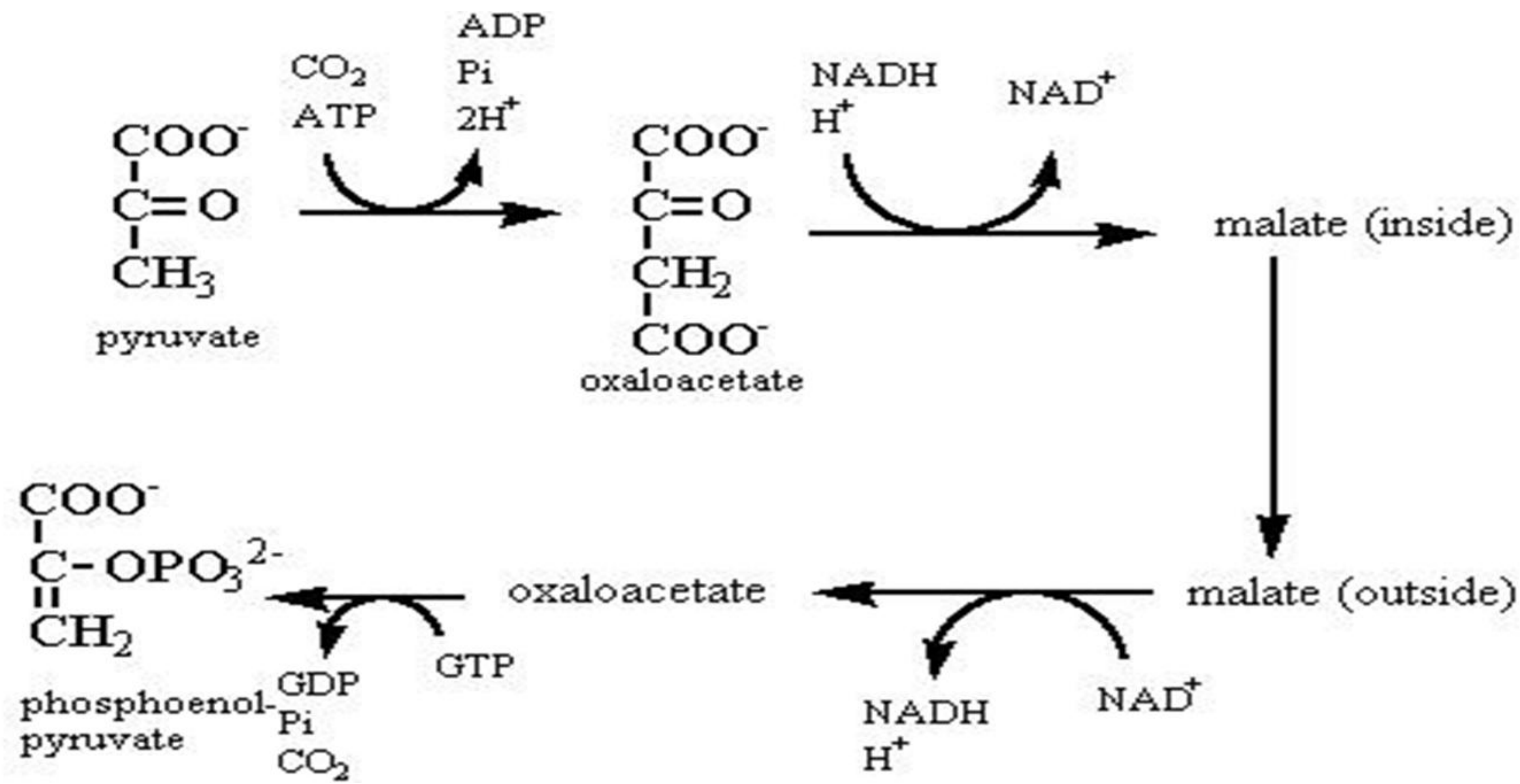
1. Conversion of pyruvate to phosphoenolpyruvate:

In the liver, pyruvate is converted to phosphoenolpyruvate.

- Pyruvate (produced from lactate, alanine, and other amino acids) is first converted to oxaloacetate by pyruvate carboxylase, a mitochondrial enzyme that requires biotin and ATP.

- Oxaloacetate cannot directly cross the inner mitochondrial membrane. Therefore, it is converted to malate or to aspartate, which can cross the mitochondrial membrane and be reconverted to oxaloacetate in the cytosol.
- Oxaloacetate is decarboxylated by phosphoenolpyruvate carboxykinase to form phosphoenolpyruvate. This reaction requires GTP.

- Phosphoenolpyruvate is converted to fructose 1,6-bisphosphate by reversal of the glycolytic reactions.



- 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+

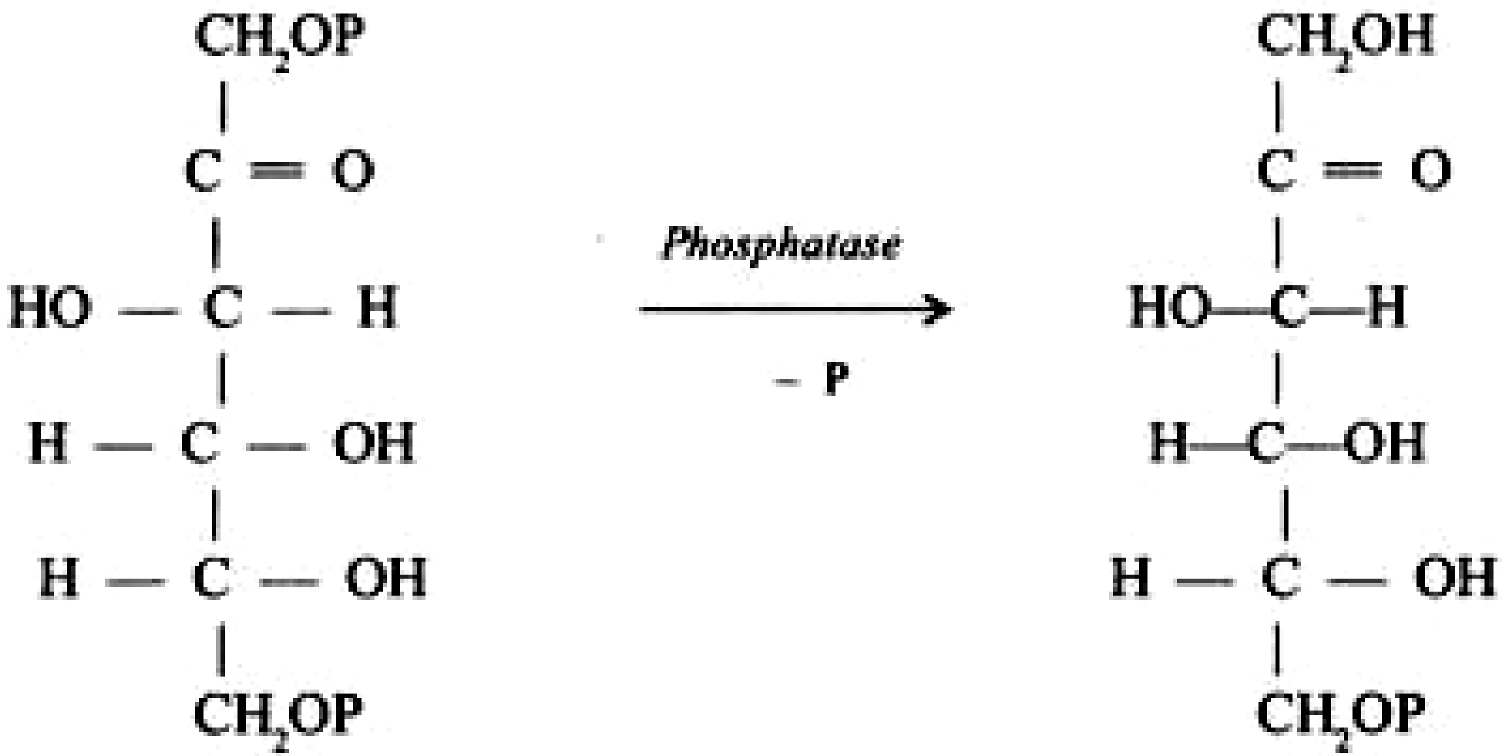
- Malate leaves the mitochondria through special transporter and in cytosol it is reoxidized into oxaloacetate by the cytosolic enzyme malate dehydrogenase.
- Malate + NAD+———————————- Oxaloacetate + NADH + H+

- 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

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

- Fructose-1, 6-bisphosphate is converted to fructose-6-phosphate in a reaction that releases inorganic phosphate and is catalyzed by fructose-1, 6-bisphosphatase.

- Fructose-6-phosphate is converted to glucose 6- phosphate by the same isomerase used in glycolysis.

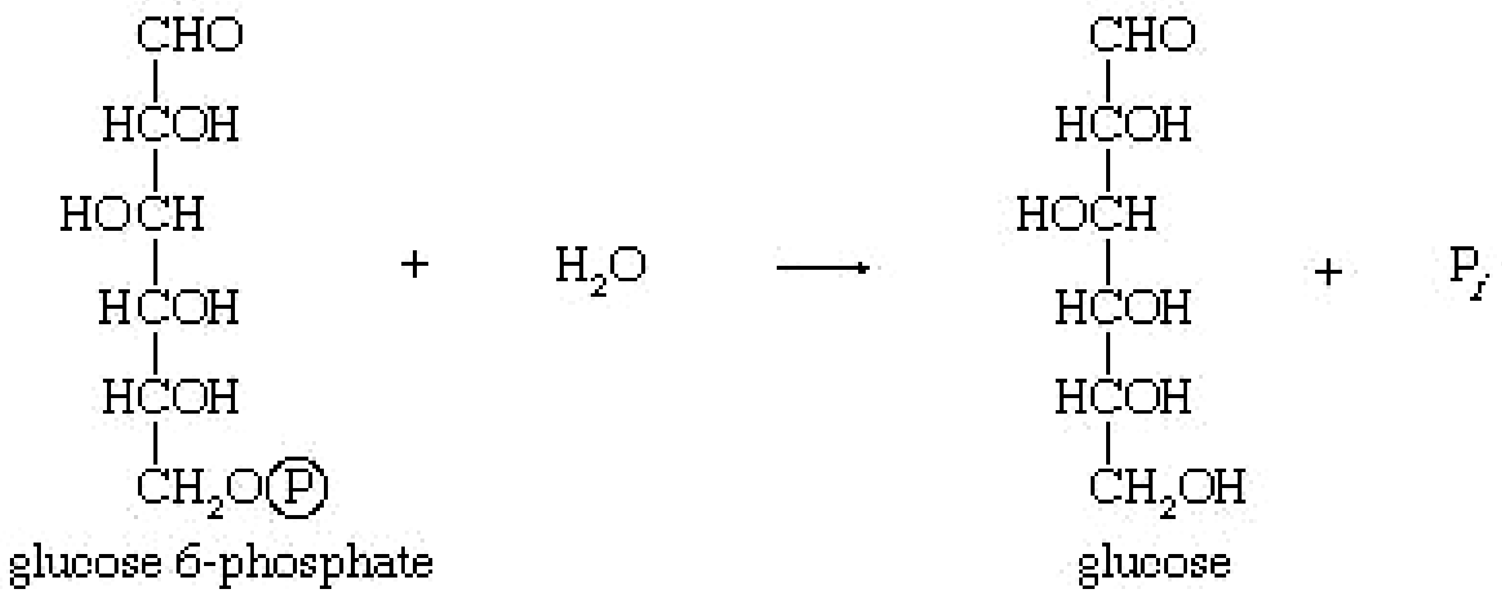


Fructose 1, 6-bisphosphate   Fructose 6-phosphate

- 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 +H2O————————fructose-6-phosphate + Pi

3. Conversion of glucose-6-phosphate to glucose:

- Glucose-6-phosphate releases inorganic phosphate, which produces free glucose that enters the blood. The enzyme involved is glucose 6-phosphatase.



[60]

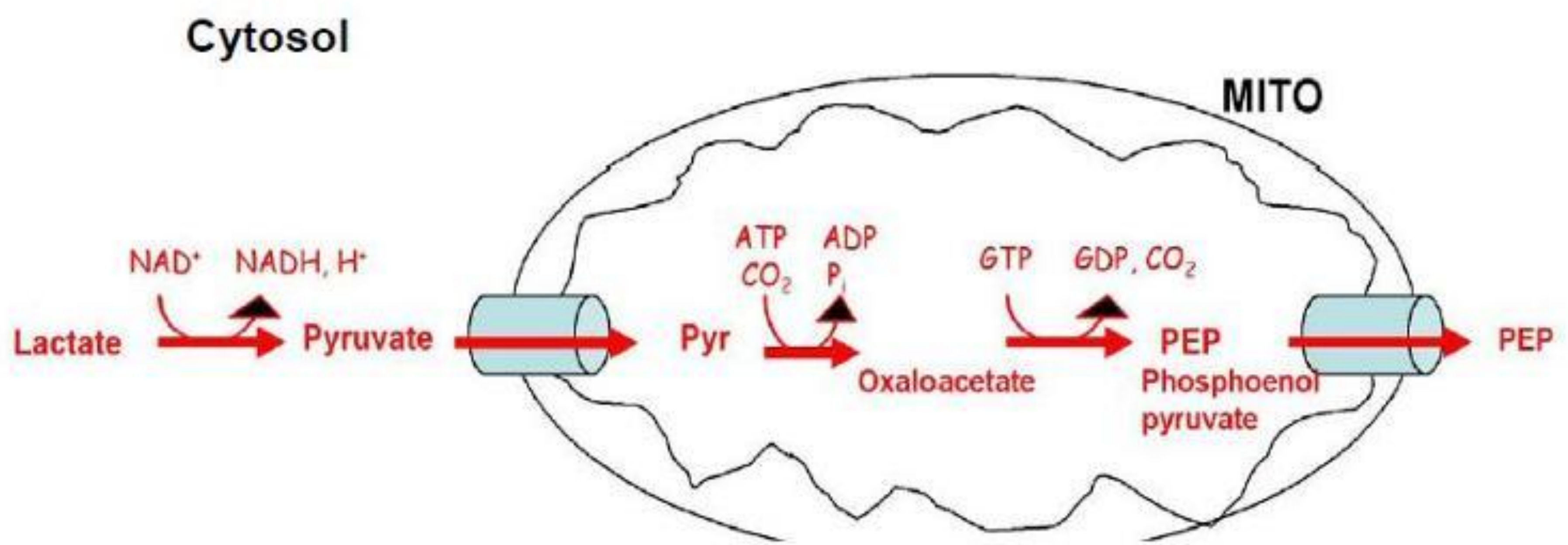
- This reaction is catalyzed by glucose-6-phosthatase which hydrolyses the phosphate at C6 yielding glucose.
- Glucose-6-phosphate +H_2O ——————— Glucose + Pi

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

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

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

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



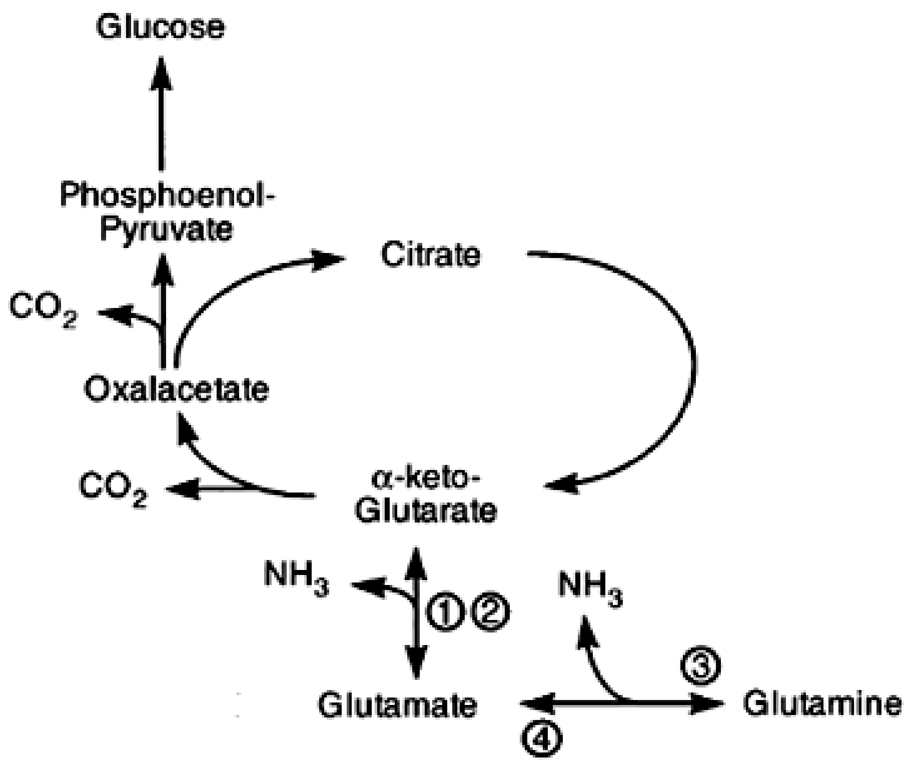
- Lactate generates during anaerobic respiration in Erythrocytes and in muscle during heavy exercise is converted into pyruvate by an enzyme lactate dehydrogenase.

- 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. Conversion of TCA intermediate and aminoacids into glucose:



- 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.

Significance of Gluconeogenesis Pathway:

- Gluconeogenesis meets the needs of the body for glucose when sufficient carbohydrate is not available from the diet or glycogen reserves.

- Glucose is universal building molecule and provides energy to all cells. Mainly brain cell and nervous tissue as well as erythrocytes, testes, renal medulla require glucose as sole source of energy.

- 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.

- A continual supply of glucose is necessary as a source of energy especially for the nervous system and erythrocytes.

- 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.

THANK YOU