# GLUCONEOGENESIS

Defined as biosynthesis of glucose from non-carbohydrate precursors.

Gluconeogenesis is the biosynthesis of new glucose from non-carbohydrate substances such as

- ✓ pyruvate
- ✓ lactate
- ✓ Glycosylated amino acids
- ✓ Propionic acid derived from odd chain fatty acids
- ✓ Glycerol part of fat.

It takes place mainly in liver and to a lesser extent in renal cortex. The cycle is partly in mitochondrial and partly in cytoplasmic

**Sources for Gluconeogenesis**

Alanine: It is produced from other amino acids derived from tissue protein break down

Glycerol: lipid mobilization from adipose tissue & lipolysis

Lactate: anaerobic glycolysis in tissues such as working muscle or RBCs

Propionate: from odd chain length fatty acids

The one which is helping when body really needs glucose is Glucogenic Aminoacids especially Alanine

**Cori's cycle**

The cycle involving synthesis of glucose in liver from the skeletal muscle lactate and the reuse of glucose by the muscle for energy purpose is known as cori cycle

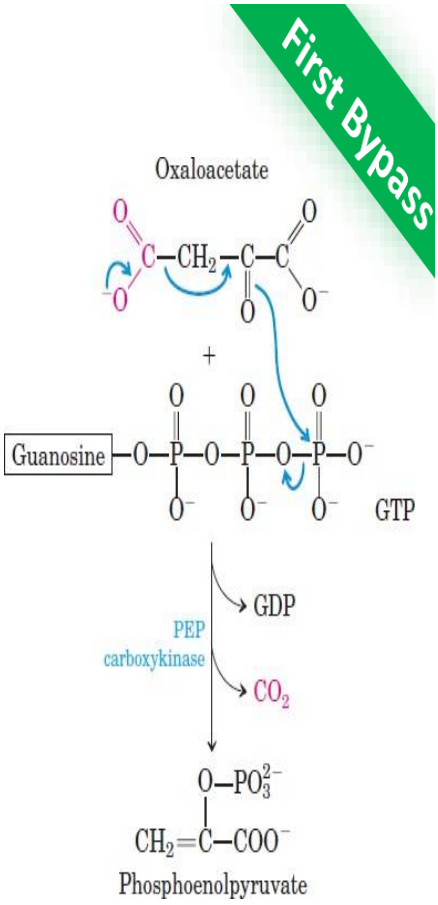
- ➢ Transferring lactate from tissue to liver and synthesis of glucose is known as cori's cycle.

**Effects**

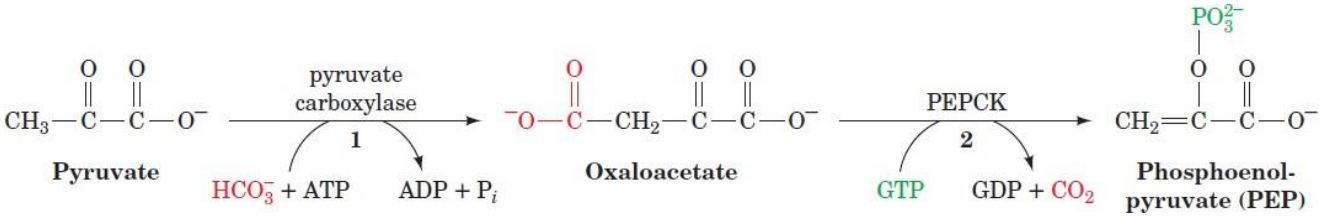
- ➢ It rescues lactate for further use (gluconeogenesis)
- ➢ It counteracts lactic acidosis.

- It is of less importance in starvation but important in more normal situations especially in certain cells such as matured RBC, medulla, retina which are lacking mitochondria and virtually anaerobic. It does not consume any energy

**Pyruvate to Phosphoenolpyruvate**




Endergonic & requires free energy input. This is accomplished by first converting the pyruvate to oxaloacetate, a "high-energy" intermediate. $CO_2$ is added to pyruvate by pyruvate carboxylase enzyme. $CO_2$ that was added to pyruvate to form OAA is released in the reaction catalyzed by phosphoenolpyruvate carboxykinase (PEPCK) to form PEP, Exergonic decarboxylation OAA provides the free energy necessary for PEP synthesis. GTP provides a source of energy & phosphate groupof PEP.




### Fructose 1, 6-Bis P to Fructose 6-P

This step is irreversible hydrolysis of fructose 1,6- bisphosphate to fructose 6-phosphate and Pi.

**Fructose 1,6-bisphosphatase (FBPase-1)** Mg 2+dependent enzyme catalyzes this exergonic hydrolysis.

It is present in liver, kidney, and skeletal muscle, but is probably absent from heart and smooth muscle.

It is an allosteric enzyme that participates in the regulationof gluconeogenesis.

### Glucose 6-P to Glucose

This final step in the generation of glucose does not take placein the cytosol.

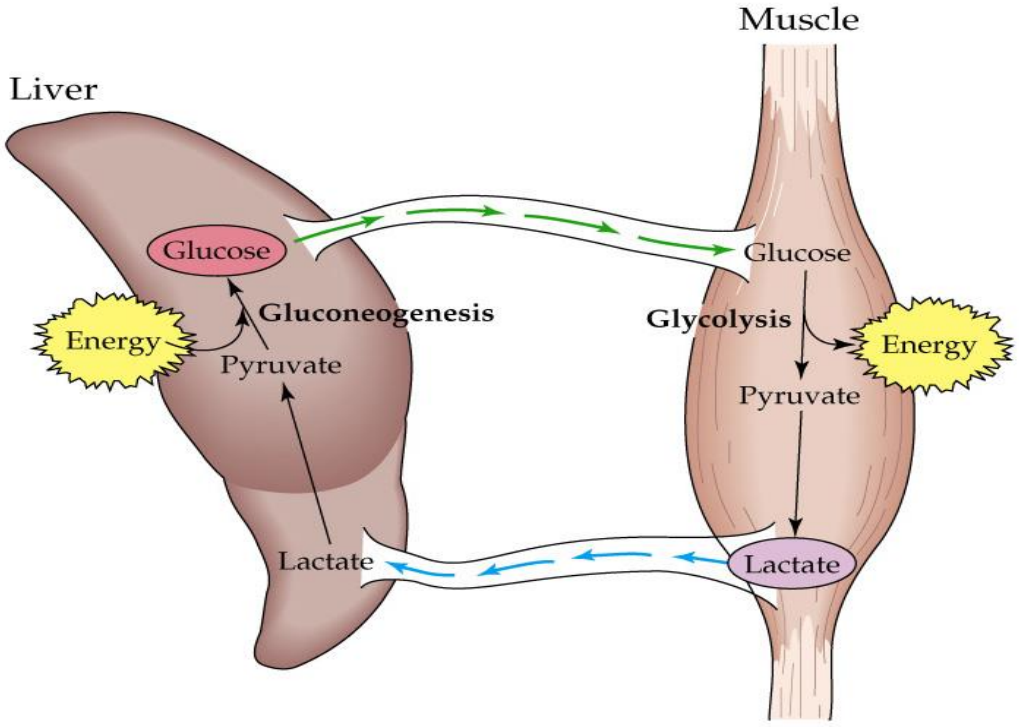
Glucose 6-P is transported into the lumen of the endoplasmic reticulum, where it is hydrolyzed to glucose by **glucose 6- phosphatase**, which is bound to the membrane at the luminal side.

This *compartmentalisation* can only be seen in glucose producing cells like hepatocytes, renal cells and epithelial cellsof small intestine

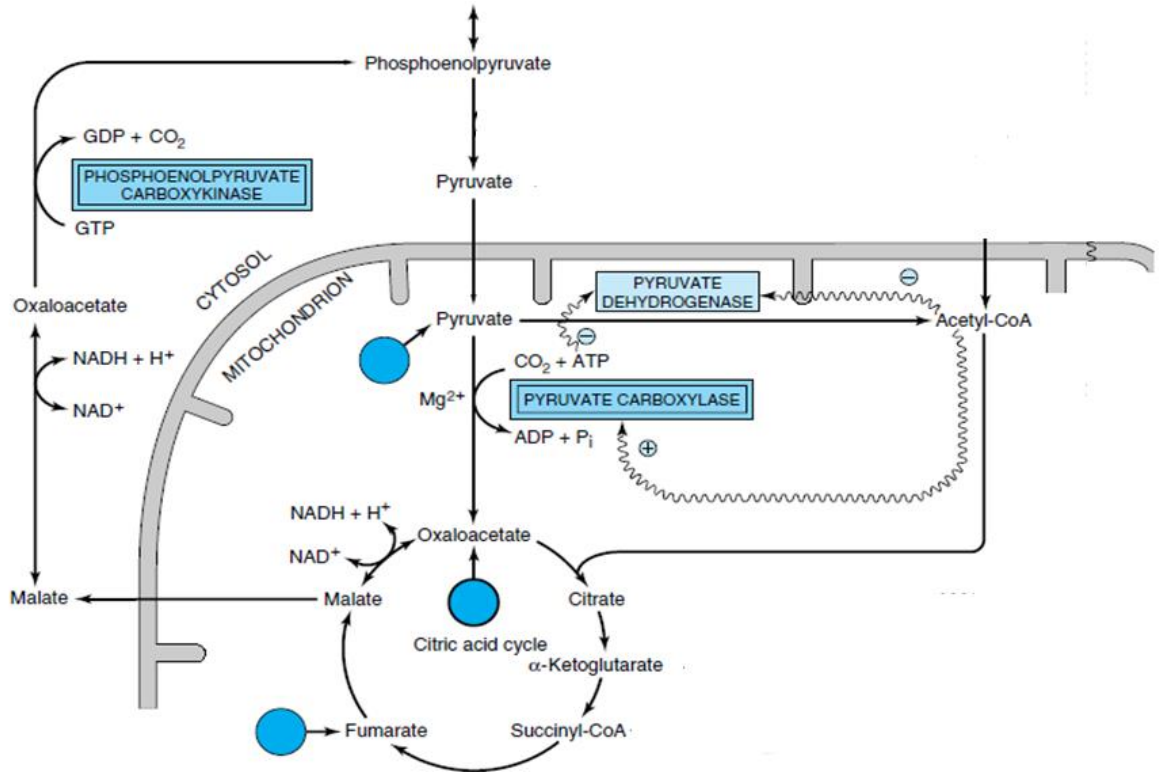
An associated $Ca^{2+}$binding stabilizing protein is essential for phosphatase activity.

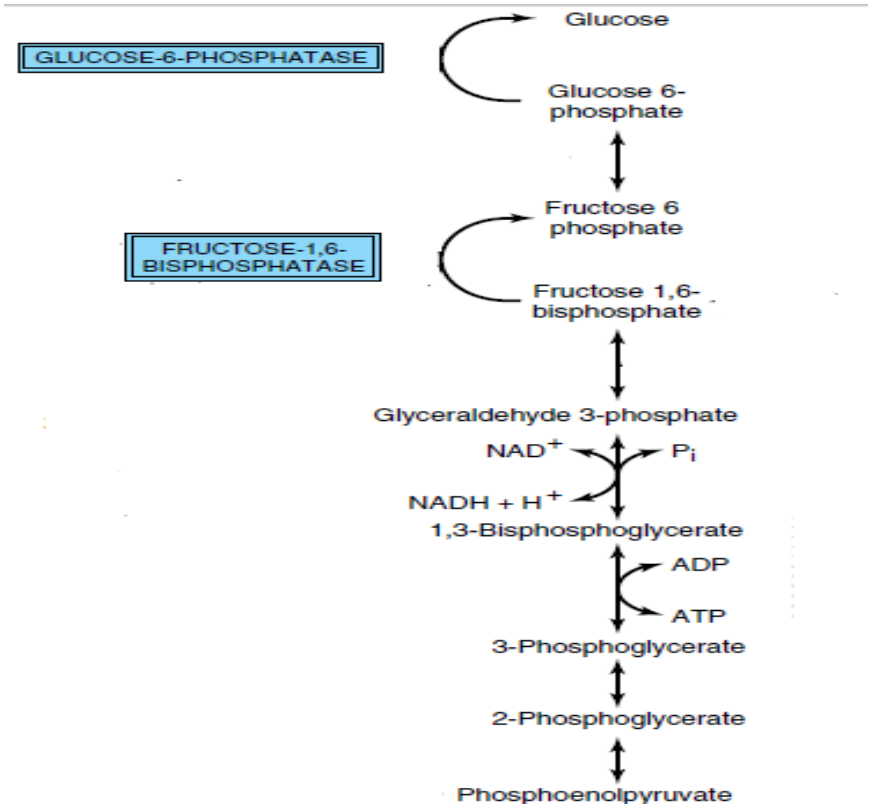
Glucose and Pi are then shuttled back to the cytosol by a pairof transporters.

***Lactate to Glucose***



***Lactate to Glucose***






**Energy requirement**

- 2 pyruvate gives 2 oxaloacetate = 2 ATP
- 2 oxaloacetate gives 2 phosphoenol pyruvate

  (2GTP) = 2 ATP
- 2x3 phospho glycerate gives
- 2 x 1,3 bis phospho glycerate = 2 ATP
- Total 6 ATP utilised

**Glycerol to Glucose**

- This happens in starvation where fat becomes the primary fuel.
- In the absence of external food the fat that is stored in adipose tissue is mobilized to get free fatty acids and it provides glycerol too.

**Adipose tissue**

↓ Lipolysis by hormone dependent LPL

**Glycerol**

↓ Glycerol kinase

**Glycerol – 3 phosphate**

↓ Glyceraldehyde 3 po4 dehydrogenase

**Dihydroxy acetone po4**

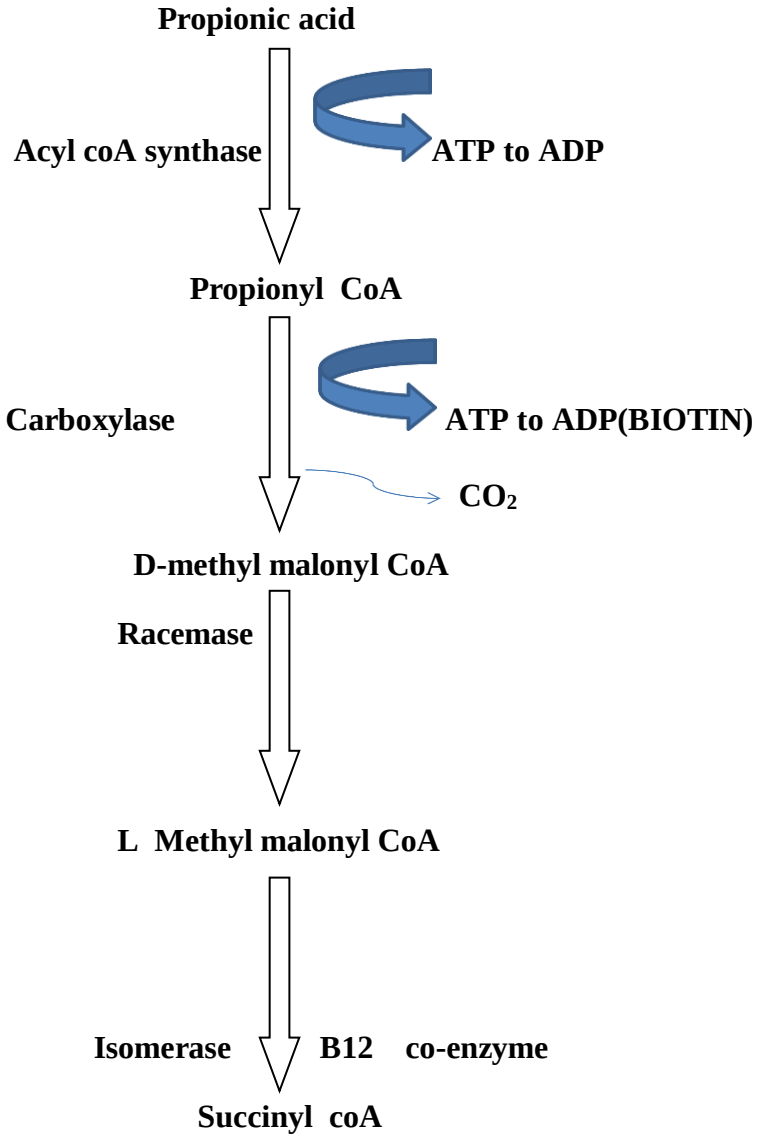
↓ Triose isomerase

**Glyceraldehyde 3 - po4**

↓ Reversal of glycolysis

**Gluconeogenesis**

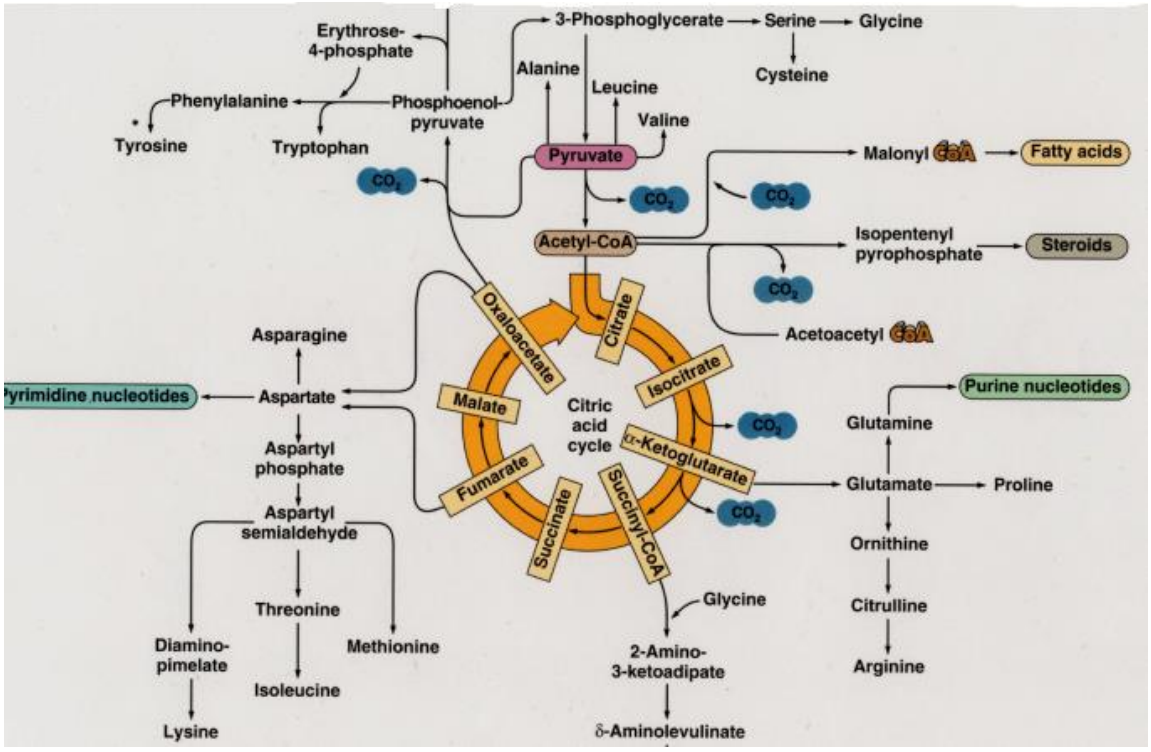
# PROPIONIC ACID TO GLUCOSE



# GLUCOGENIC AMINO ACIDS

| | |
|---|---|
| **Pyruvate** | **Succinyl-CoA** |
| Alanine | Isoleucine* |
| Cysteine | Methionine |
| Glycine | Threonine |
| Serine | Valine |
| Threonine | **Fumarate** |
| Tryptophan* | Phenylalanine* |
| **α-Ketoglutarate** | Tyrosine* |
| Arginine | **Oxaloacetate** |
| Glutamate | Asparagine |
| Glutamine | Aspartate |
| Histidine | |
| Proline | |

**Glucogenic aminoacids are derived from the intermediates of TCA cycle.**




Most of the amino acids are converted to alanine and this is the one present in highest concentration in circulation about 4-5 hours after intake of food.

**Glucose-Alanine cycle (Cahill cycle)**

- Alanine synthesized in muscle and transported to liver, transaminated to pyruvate and is converted to glucose.
- This glucose may again enter the glycolytic pathway to form pyruvate, which inturn can be transaminated to alanine.

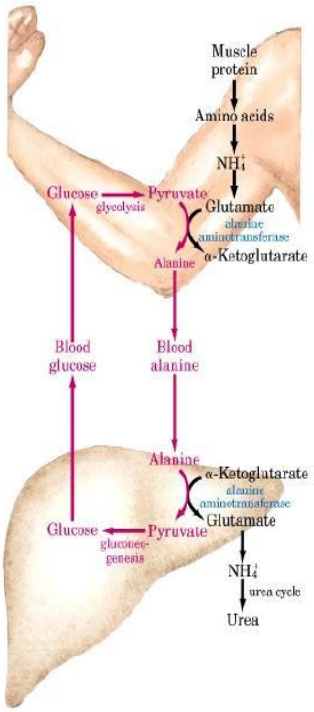
**Muscle protein-------- alanine-------- pyruvate---- glucose**

- It occurs in
    1. Starvation
    2. Uncontrolled diabetes
- In starvation after the exhaustion of glycogen reserves, the main source of pyruvate comes from the breakdown of muscle proteins.
- Catabolism is favored by corticosteroids & the hydrolysis of proteins yields the 20 different amino acid.

Among total amino acids 30 % is in the form of alanine.

Glycogenic amino acids forms intermediates of citric acid cycle to enter gluconeogenesis.

Glucose-Alanine
Cylcle (alanine cycle)



## KEY ENZYMES IN GLYCOLYSIS AND GLUCONEOGENESIS

| *Glycolysis* | *Gluconeogenesis* |
|---|---|
| Hexokinase | Glucose 6-phosphatase |
| Phosphofructokinase | Fructose 1,6-bisphosphatase |
| Pyruvate kinase | Pyruvate carboxylase<br>Phosphoenolpyruvate carboxykinase |