**Conversion of PEP to glucose**

This pathway is opposite of glycolysis. However,

One step in glycolytic pathway where PFK-1 is involved is irreversible so during gluconeogenesis enzyme fructose 1,6 bisphosphatase acts without using ATP and converts fructose-1,6-bisphosphate to fructose-6-phosphate. Fructose-1,6-bisphosphatase is an allosterically regulated enzyme. Citrate stimulates bisphosphatase activity, but fructose-2,6-bisphosphate is a potent allosteric inhibitor. AMP also inhibits the bisphosphatase.

Another step where glucose converted into glucose-6-phosphate during glycolysis is catalyzed by hexokinase and requires ATP. This reaction is also irreversible. During gluconeogenesis conversion of glucose-6-phosphate to glucose requires glucose-6-phosphatase and no ATP is required. This enzyme is present in the membranes of the endoplasmic reticulum of liver and kidney cells, but is absent in muscle and brain. For this reason, gluconeogenesis is not carried out in muscle and brain.

*Energetics of gluconeogenetic pathway*

$$2\ \text{Pyruvate} + 2\text{NADH} + 4\text{ATP} + 2\text{GTP} + 6\text{H}_2\text{O} \longrightarrow \text{Glucose} + 2\text{NAD}^+ + 2\text{GDP} + 4\text{ADP}$$

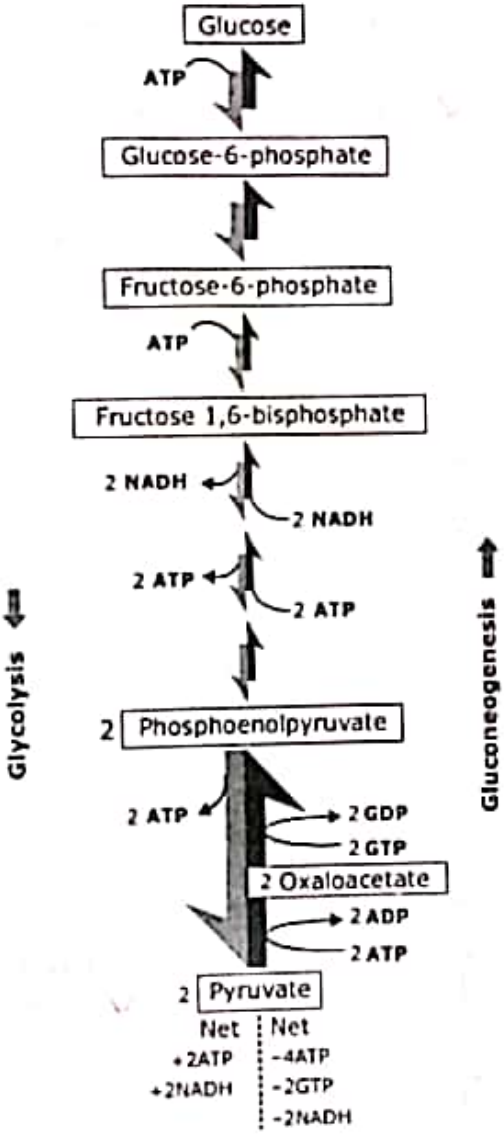



**Figure 2.41 :** Reactions of glycolysis and gluconeogenesis.

**Glucose alanine cycle**

Pyruvate formed during glycolysis in muscle can undergo transamination with glutamate to yield alanine. The alanine is transported to the liver. In the liver, alanine transaminates with α-ketoglutarate to yield glutamate and pyruvate. The pyruvate is used to produce glucose by the gluconeogenetic pathway.

Pyruvate + Glutamate ⟶ Alanine + α-Ketoglutarate

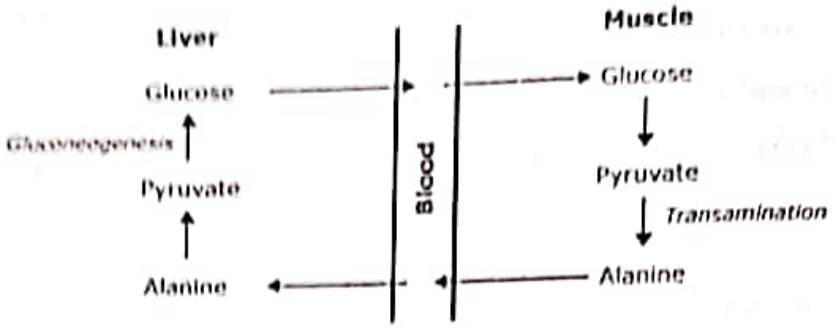



**Figure 2.42 :** Glucose-alanine cycle.

**Regulation of gluconeogenesis**

Most of the reactions of gluconeogenesis take place in the cytosol, which is also the site of glycolysis. So if metabolic control were not exerted over these (gluconeogenesis and glycolysis) reactions, glycolytic degradation of glucose and the gluconeogenetic synthesis of glucose could operate simultaneously with no net benefit to the cell and with considerable consumption of ATP. Hence glycolysis and gluconeogenesis is regulated in such a way, so that glycolysis is inhibited when gluconeogensis is active, and vice versa. Gluconeogenesis is regulated by allosteric and substrate level control mechanism. The site of regulation along with activators and inhibitors are described in the following diagram.

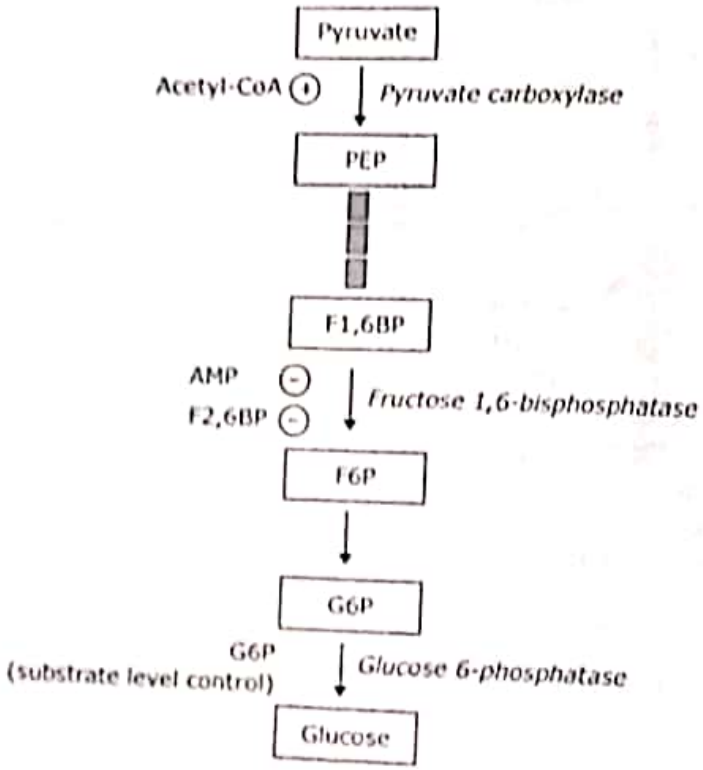



**Figure : 2.43**
Regulation of gluconeogenesis.
Activators are indicated by plus signs and inhibitors by minus sign.

OAA — Oxaloacetic acid
PEP — Phosphoenol pyruvate
F1,6BP — Fructose 1,6-bisphosphate
F2,6BP — Fructose 2,6-bisphosphate
F6P — Fructose 6-phosphate
G6P — Glucose 6-phosphate

## 2.6.3 Fatty acid oxidation

### β-oxidation

Most fatty acids are degraded by the sequential removal of two-carbon fragments from the carboxyl end of fatty acids. During this process, referred to as *β-oxidation*, acetyl-CoA is formed as the bond between the α- and β-carbon atoms are broken. β-oxidation is so named because the β-carbon of fatty acids is oxidized. β-oxidation occurs primarily within mitochondria.

### Fatty acid activation and transport across the mitochondrial membrane

Before β-oxidation begins, each fatty acid is activated in a reaction with ATP and CoA. Fatty acids undergo for ATP dependent acylation reaction to form fatty acyl-CoA. This activation process is catalyzed by acyl-CoA synthetase (also called acyl CoA ligase or acyl CoA thiokinase) in the cytosol.

$$\text{Fatty acid} + \text{CoA} + \text{ATP} \rightleftharpoons \text{Fatty acyl-CoA} + \text{AMP} + PP_i$$

Although fatty acids are activated for oxidation in the cytosol, they are oxidized in the mitochondrion. A long chain fatty acyl-CoA cannot directly cross the inner mitochondrial membrane. Because the mitochondrial inner membrane is impermeable to most acyl-CoA molecules, a special carrier called *carnitine* (β-hydroxy γ-trimethyl ammonium butyrate) is used to transport acyl groups into the mitochondrion (as shown in figure). Carnitine-mediated transfer of fatty acyl-CoA into the mitochondrial matrix is accomplished through the following mechanism.

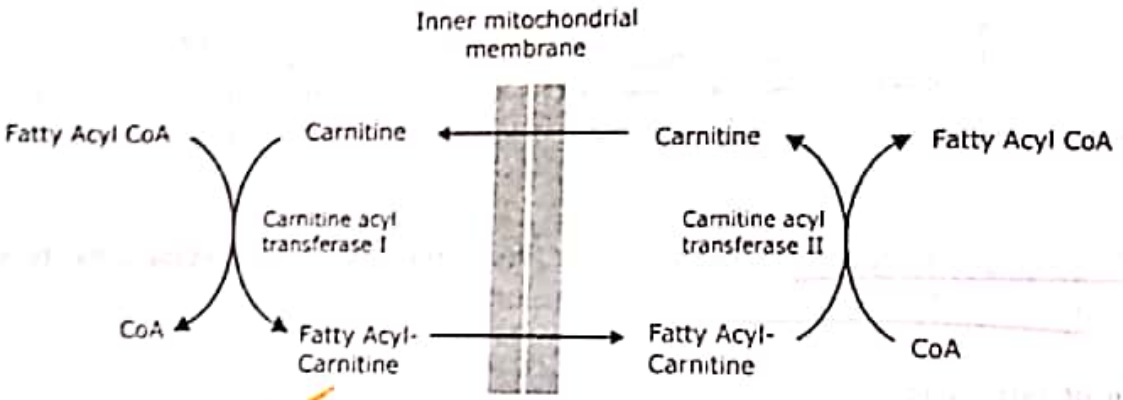


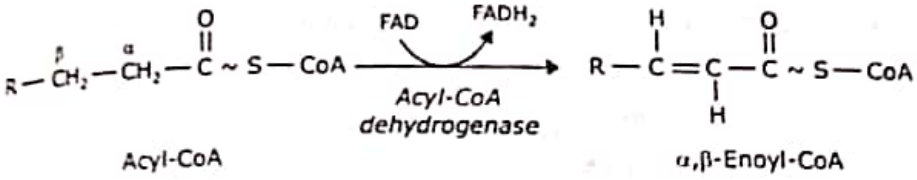

**Figure 2.54 :** Transport of fatty acids into the mitochondria.

1. Each fatty acyl-CoA molecule is converted to a fatty acyl carnitine derivative by *carnitine acyl transferase I*, located on the outer side of the inner mitochondrial membrane.
2. A carrier protein (carnitine : acyl carnitine translocase) within the mitochondrial inner membrane transfers fatty acyl carnitine into the mitochondrial matrix.
3. Fatty acyl-CoA is regenerated by *carnitine acyl transferase II*, located on the matrix side of inner mitochondrial membrane.
4. Carnitine is transported back into the intermembrane space by the carrier protein. It then reacts with another fatty acyl-CoA.

## β-oxidation of saturated fatty acids (e.g., palmitic acid)

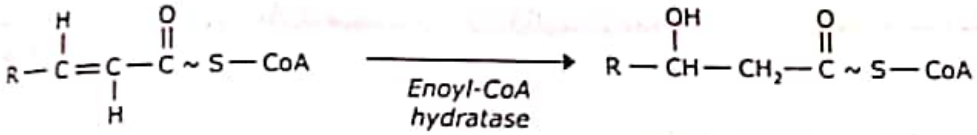
Once inside the mitochondrial matrix, fatty acyl-CoA is oxidized with oxidation of the β-carbon and long-chain fatty acyl-CoA are subjected to a repeated four-step process, which removes two carbons from the chain successively until the last two-carbon fragment is obtained. A summary of the reactions of the β-oxidation of palmitic acid is shown below.

### Oxidation



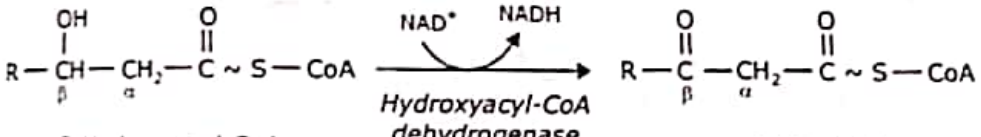

Acyl-CoA → α,β-Enoyl-CoA

### Hydrolysis



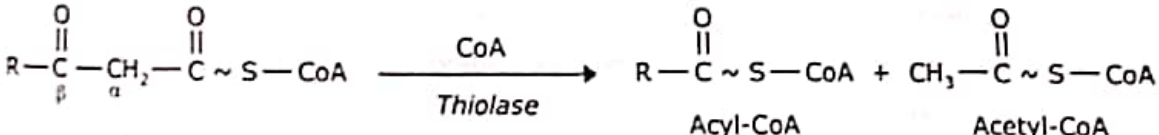

α,β-Enoyl-CoA → 3-Hydroxyacyl-CoA

### Oxidation




3-Hydroxyacyl-CoA → β-Ketoacyl-CoA

### Thiolysis




β-Ketoacyl-CoA → Acyl-CoA + Acetyl-CoA

This series of four reactions has yielded a fatty acyl-CoA that has been shortened by two carbons, and one molecule of acetyl-CoA. The shortened fatty acyl-CoA can now go through another β-oxidation cycle. Repetition of this cycle with palmitic acid with an even number of carbons eventually yields 8 molecules of acetyl-CoA.

**Stoichiometry of β-oxidation**

β-Oxidation of palmitate (16 carbons)

Palmitoyl CoA + 7 CoA + 7 FAD + 7 $NAD^+$ + 7 $H_2O$ ⟶ 8 acetyl-CoA + 7 $FADH_2$ + 7 NADH

Acetyl-CoA is catabolized via TCA cycle, and $FADH_2$ and NADH transfer electrons to the electron transport chain. Thus we can easily compute the metabolic energy yield fatty acid oxidation in terms of moles of ATP synthesized.

| *Reaction* | *ATP yield* | *ATP consumed* |
|---|---|---|
| Activation of palmitate to palmitoyl-CoA | | -2 |
| Oxidation of 8 acetyl-CoA | 8 × 10 = 80 | |
| Oxidation of 7 $FADH_2$ | 7 × 1.5 = 10.5 | |
| Oxidation of 7 NADH | 7 × 2.5 = 17.5 | |
| Net : Palmitate → 16 $CO_2$ + 130 $H_2O$ | 106 | |

These calculations assume that mitochondrial oxidative phosphorylation produces 1.5 ATP per $FADH_2$ oxidized and 2.5 ATP per NADH oxidized.

**Oxidation of fatty acids**