

Energy Metabolism

What is metabolism?

Catabolic reactions:

Complex molecules → Simple molecules + Energy

Anabolic reactions:

Simple molecules + Energy (in cell) → Complex molecules

Glycolysis is derived from the Greek words (glycose-sweet or sugar; lysis-dissolution).

It is a universal pathway in the living cells. The complete pathway of glycolysis was elucidated in 1940. This pathway is often referred to as Embden-Meyerhoff pathway (E.M. pathway) in honour of the two biochemists who made a major contribution to the knowledge of glycolysis.

Glycolysis is defined as the sequence of reactions converting glucose (or glycogen) to pyruvate or lactate, with the production of ATP.

REACTIONS OF GLYCOLYSIS

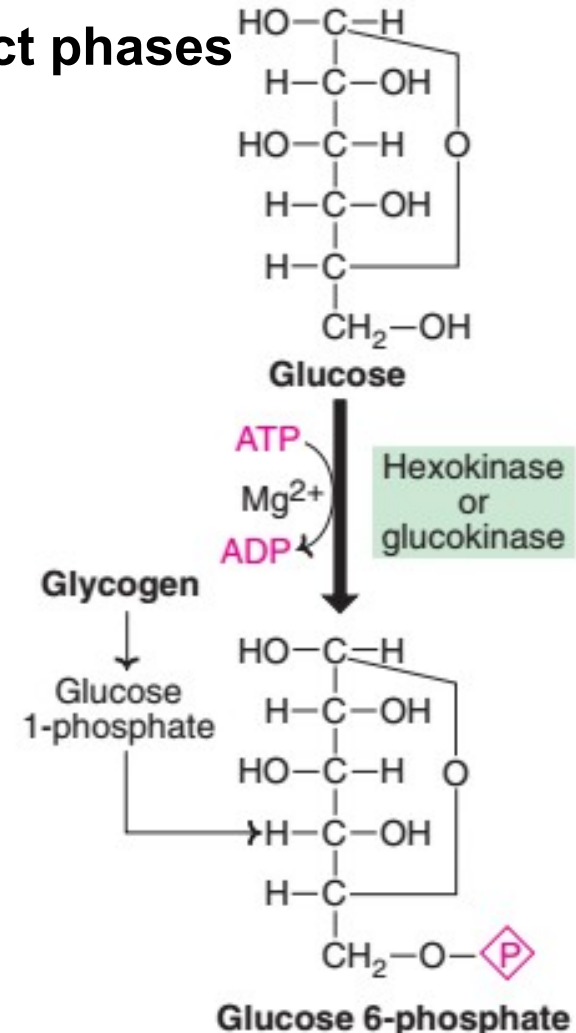
The pathway can be divided into three distinct phases

- A. Energy investment phase
- B. Splitting phase
- C. Energy generation phase

A. Energy investment phase

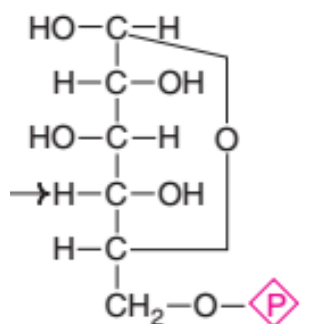
1. Glucose is phosphorylated to **glucose 6-phosphate** by **hexokinase**.

This is an irreversible reaction, dependent on ATP and Mg²⁺.



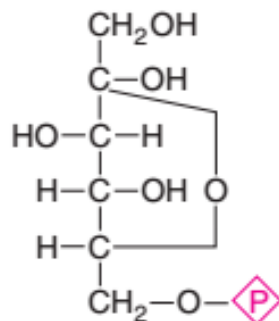
2. **Glucose 6-phosphate** undergoes isomerization to give fructose **6-phosphate** in the presence of the enzyme **phosphohexose isomerase** and Mg^{2+} .

3. **Fructose 6-phosphate** is phosphorylated to fructose **1,6-bisphosphate** by **phosphofructokinase (PFK)**. This is an irreversible and a regulatory step in glycolysis.

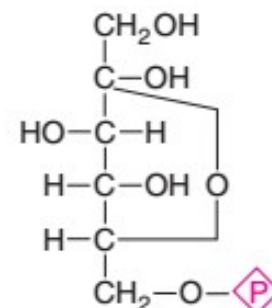


Glucose 6-phosphate

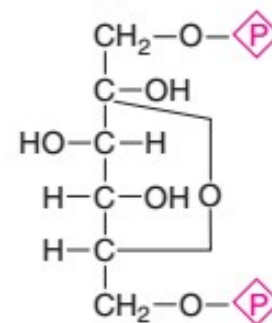
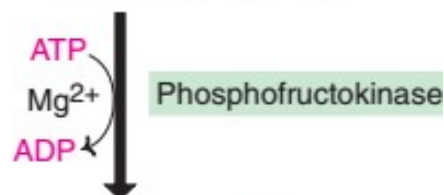
Phosphohexose isomerase



Fructose 6-phosphate



Fructose 6-phosphate

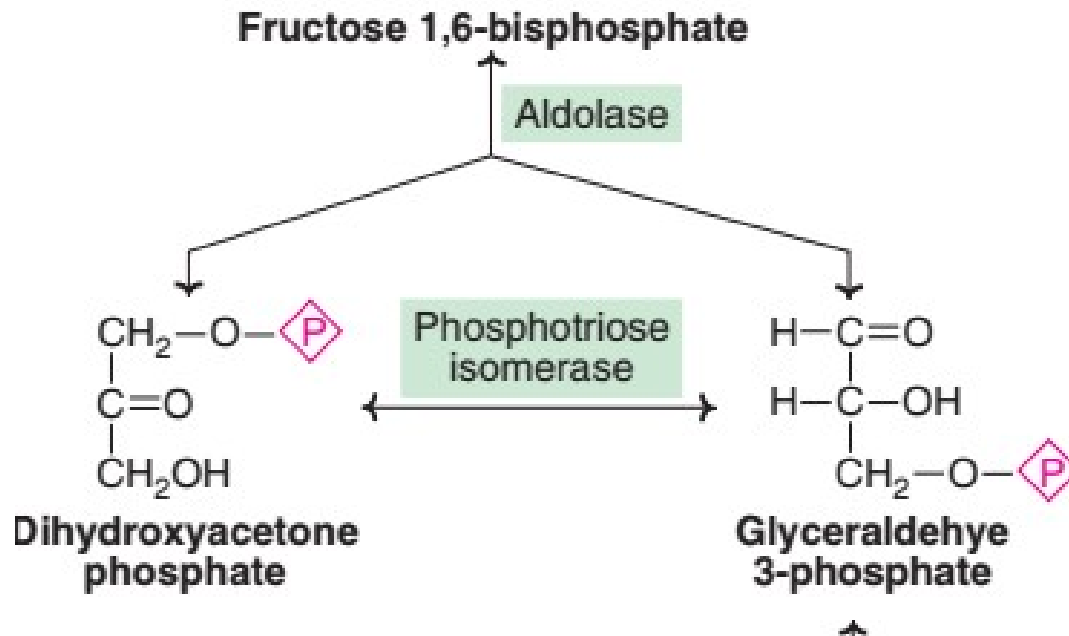


Fructose 1,6-bisphosphate

B. Splitting phase

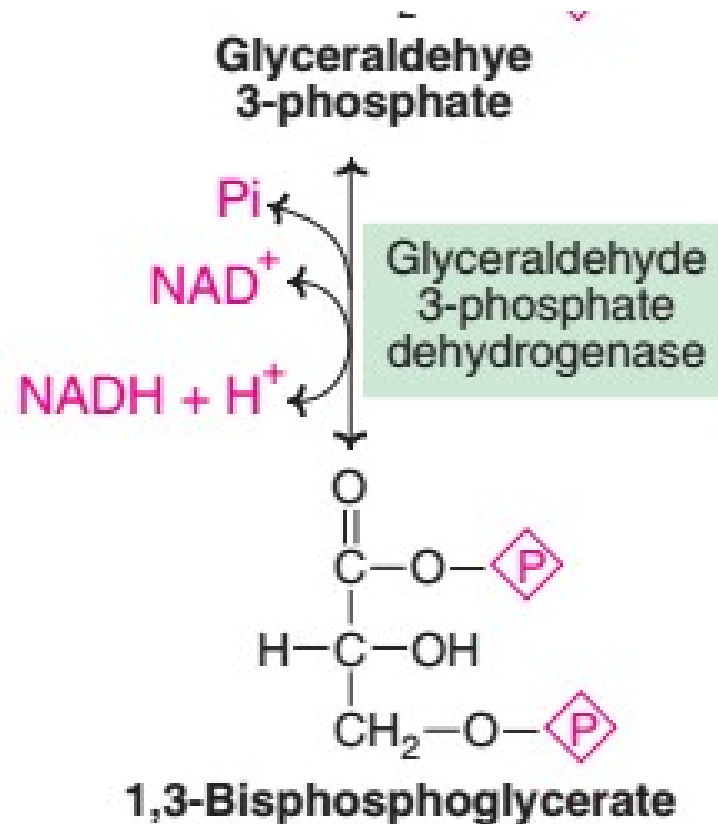
4. The six carbon **fructose 1,6-bisphosphate** is split (hence the name glycolysis) to two three-carbon compounds, **glyceraldehyde 3-phosphate** and **dihydroxyacetone** phosphate by the enzyme **aldolase** (fructose 1,6- bisphosphate aldolase).

5. The enzyme **phosphotriose isomerase** catalyses the reversible interconversion of **glyceraldehyde 3-phosphate** and **dihydroxyacetone phosphate**. Thus, two molecules of glyceraldehyde 3-phosphate are obtained from one molecule of glucose.



C. Energy generation phase

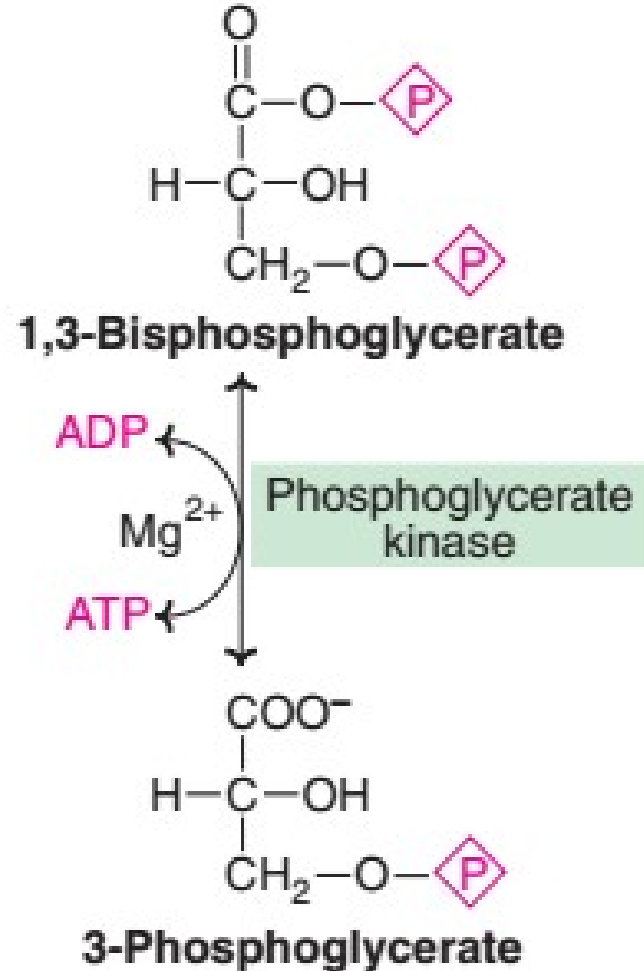
6. **Glyceraldehyde 3-phosphate dehydrogenase** converts **glyceraldehyde 3-phosphate** to 1,3-bisphosphoglycerate. This step is important as it is involved in the formation of $\text{NADH} + \text{H}^+$ and a high energy compound 1,3-bisphosphoglycerate.



7. The enzyme phosphoglycerate kinase acts on **1,3-bisphosphoglycerate**

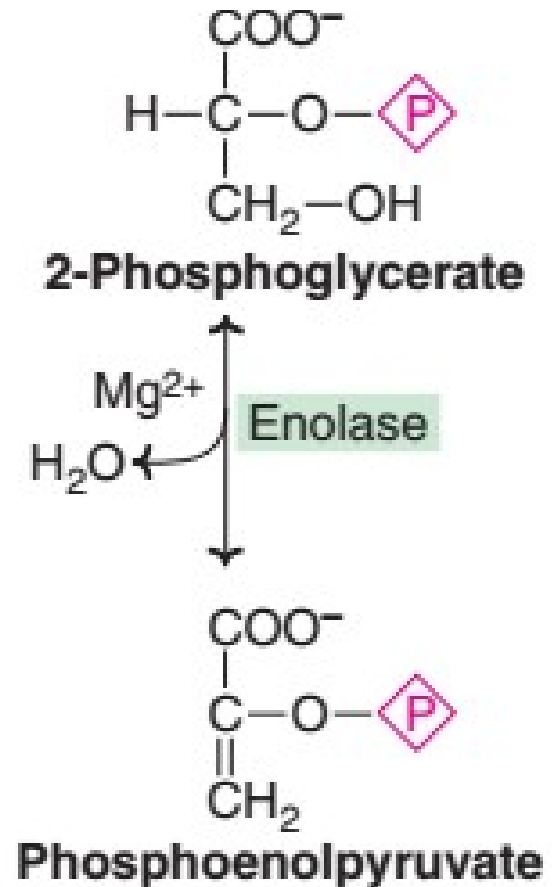
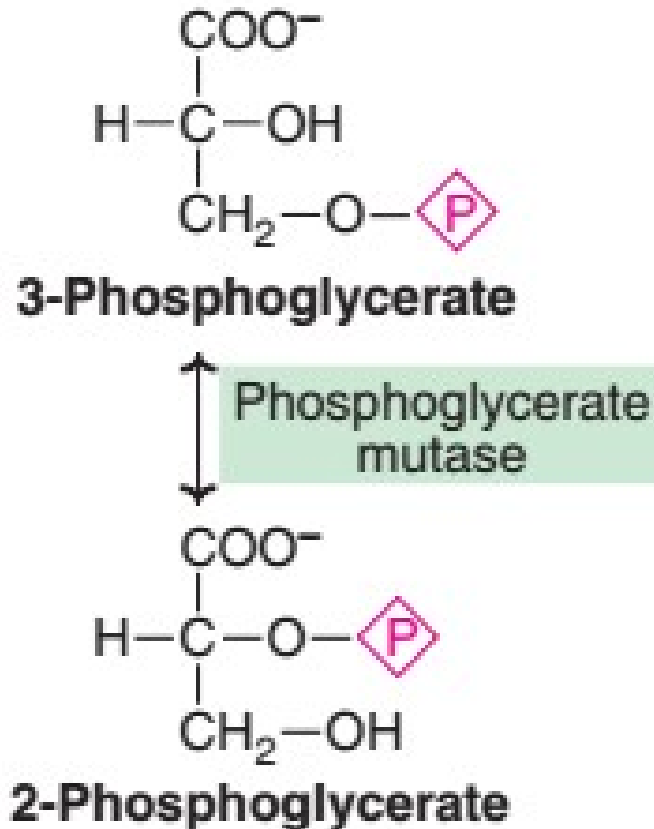
resulting in the synthesis of ATP and formation of **3-phosphoglycerate**.

This step is a good example of substrate level phosphorylation, since ATP is synthesized from the substrate without the involvement of electron transport chain. Phosphoglycerate kinase reaction is reversible.

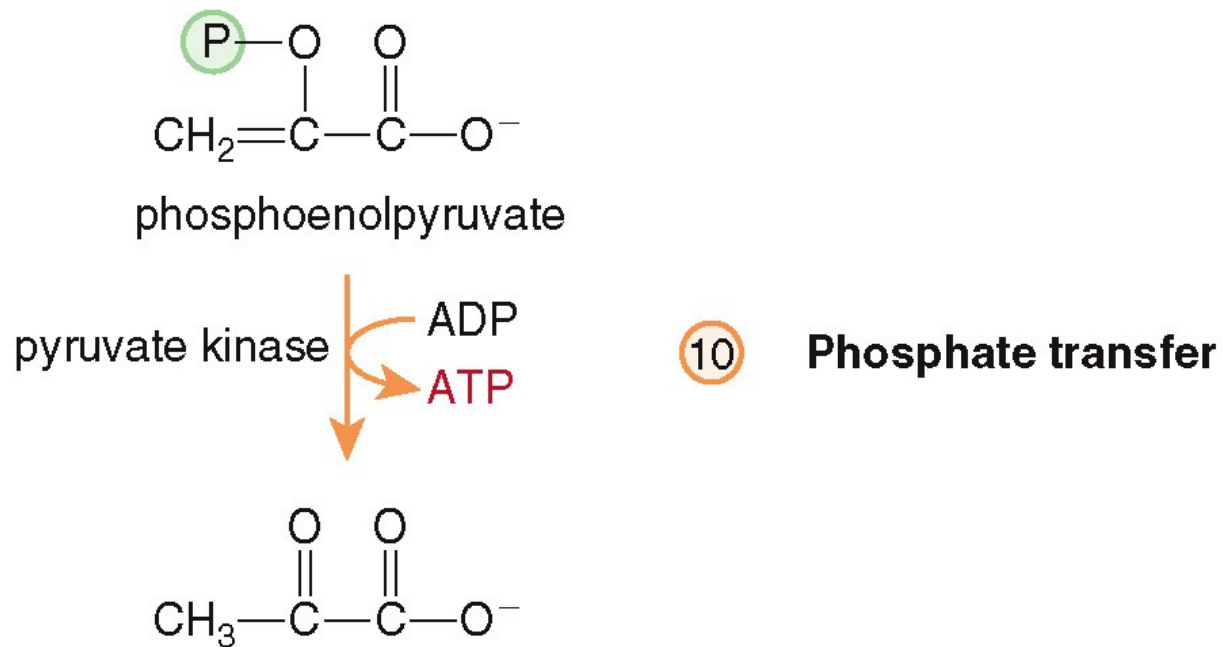


8. **3-Phosphoglycerate** is converted to **2-phosphoglycerate** by **phosphoglycerate mutase**. This is an isomerization reaction.

9. The high energy compound **phosphoenol pyruvate** is generated from **2-phosphoglycerate** by the enzyme **enolase**. This enzyme requires Mg^{2+} .



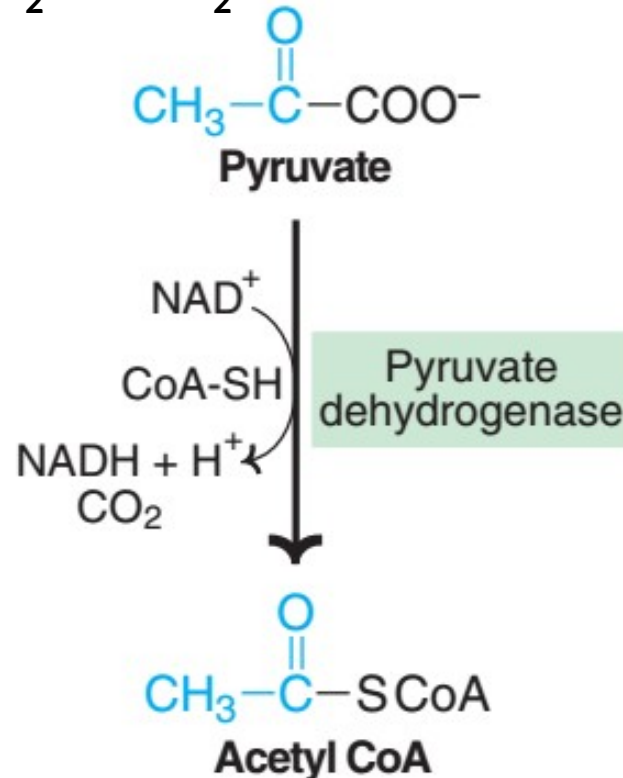
10. The enzyme **pyruvate kinase** catalyses the transfer of high energy phosphate from **phosphoenolpyruvate** to ADP, leading to the formation of ATP. This step also is a substrate level phosphorylation. This reaction is irreversible.

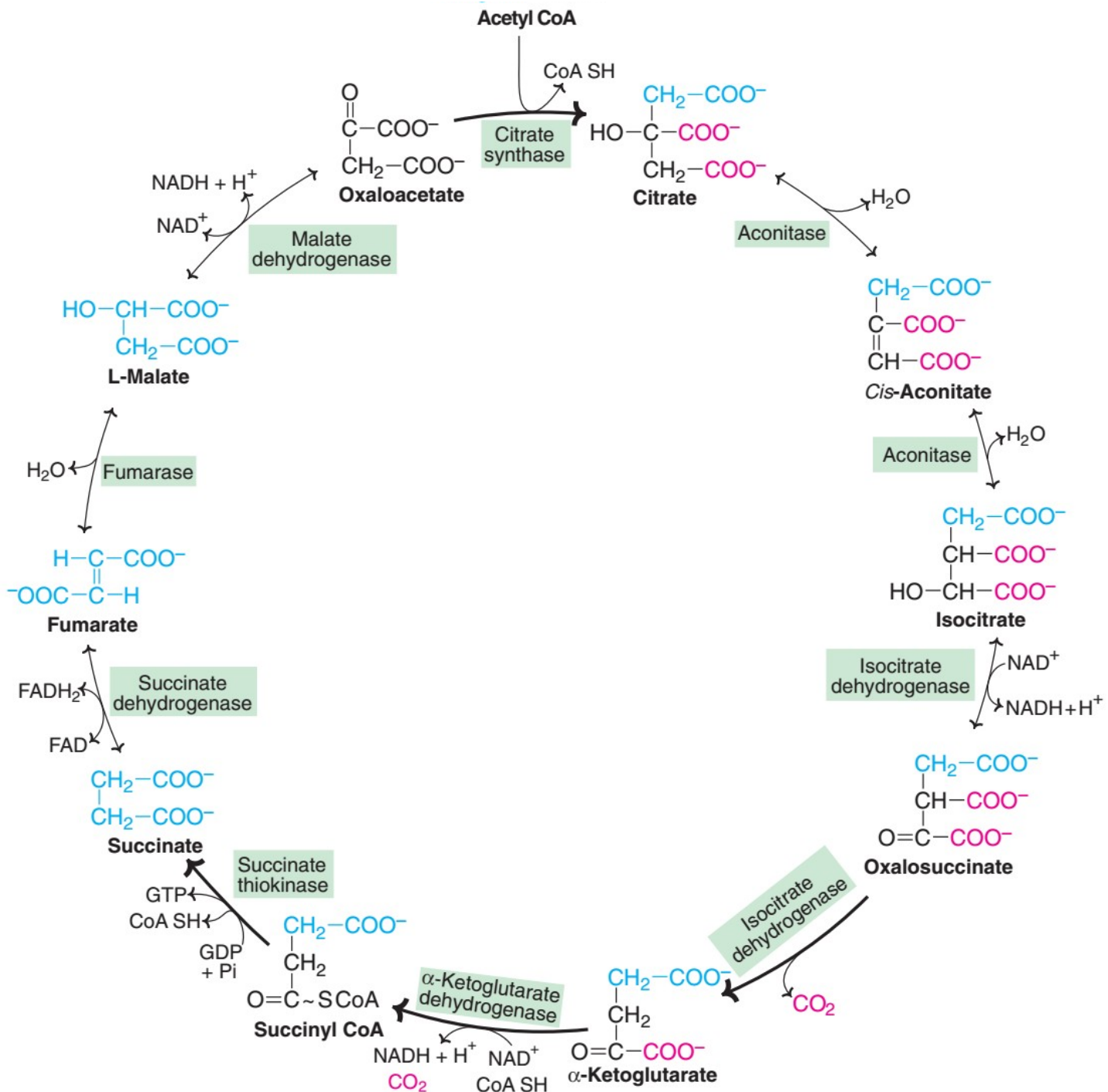


<i>Pathway</i>	<i>Enzyme (method of ATP synthesis)</i>	<i>Number of ATP synthesized</i>
Glycolysis	Glyceraldehyde 3-phosphate dehydrogenase (2 NADH, ETC, oxidative phosphorylation)	6(5)
	Phosphoglycerate kinase (substrate level phosphorylation)	2
	Pyruvate kinase (substrate level phosphorylation)	2
	Two ATP are consumed in the reactions catalysed by hexokinase and phosphofructokinase	-2
	<i>Net ATP synthesis in glycolysis in aerobic condition</i>	8(7)
	Pyruvate dehydrogenase (2 NADH, ETC, oxidative phosphorylation)	6(5)
Citric acid cycle	Isocitrate dehydrogenase (2 NADH, ETC, oxidative phosphorylation)	6(5)
	α -Ketoglutarate dehydrogenase	6(5)
	Succinate thiokinase (substrate level phosphorylation)	2
	Succinate dehydrogenase (2 FADH ₂ , ETC, oxidative phosphorylation)	4(3)
	Malate dehydrogenase (2 NADH, ETC, oxidative phosphorylation)	6(5)
	<i>Total ATP per mole of glucose under aerobic condition</i>	38(32)

Krebs Cycle

The citric acid cycle (Krebs cycle or tricarboxylic acid—TCA cycle) is the most important metabolic pathway for the energy supply to the body. About 65-70% of the ATP is synthesized in Krebs cycle. Citric acid cycle essentially involves the oxidation of acetyl CoA to CO_2 and H_2O .





Formation of citrate: Krebs cycle proper starts with the condensation of acetyl CoA and oxaloacetate, catalysed by the enzyme citrate synthase.

Citrate is isomerized to isocitrate by the enzyme aconitase. This is achieved in a two stage reaction of dehydration followed by hydration through the formation of an intermediate—cis-aconitate.

Formation of α -ketoglutarate :The enzyme isocitrate dehydrogenase catalyses the conversion (oxidative decarboxylation) of isocitrate to oxalosuccinate and then to α -ketoglutarate. The formation of NADH and the liberation of CO_2 occur at this stage.

Conversion of α -ketoglutarate to succinyl CoA occurs through oxidative decarboxylation, catalyzed by D-ketoglutarate dehydrogenase complex.

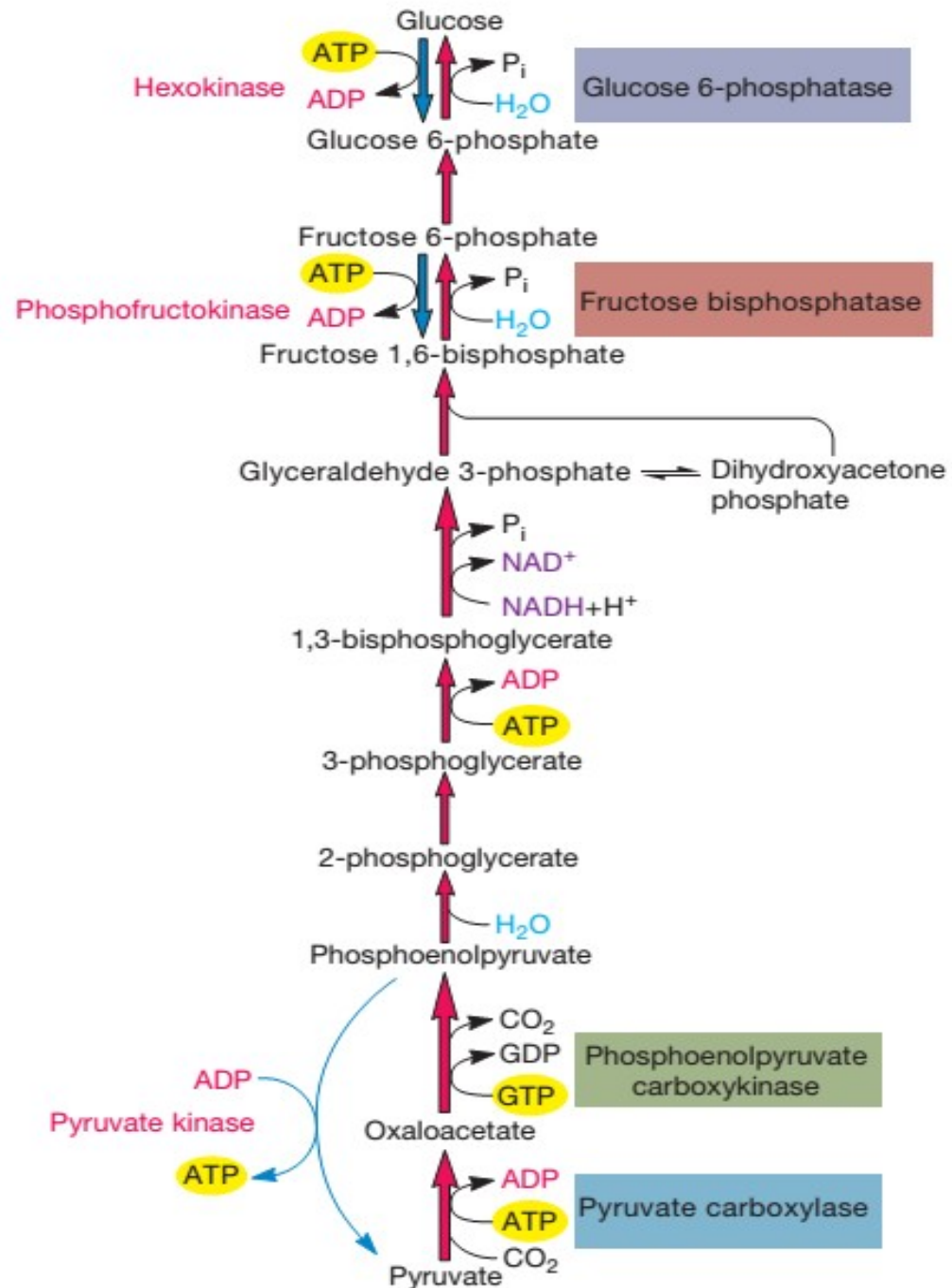
Formation of succinate: Succinyl CoA is converted to succinate by succinate thiokinase. This reaction is coupled with the phosphorylation of GDP to GTP.

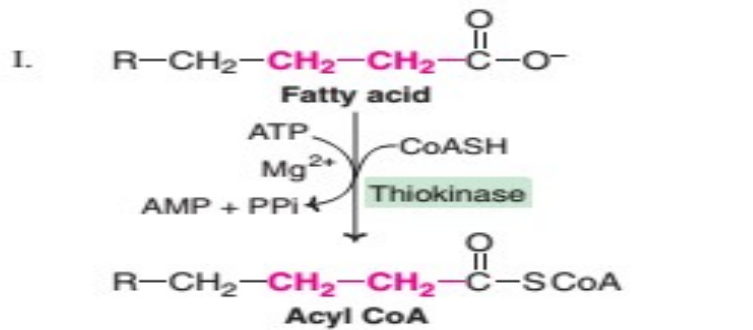
Conversion of succinate to fumarate : Succinate is oxidized by succinate dehydrogenase to fumarate. This reaction results in the production of FADH_2 and not NADH.

Formation of malate :The enzyme fumarase catalyses the conversion of fumarate to malate with the addition of H_2O .

Conversion of malate to oxaloacetate : Malate is then oxidized to oxaloacetate by malate dehydrogenase. The third and final synthesis of NADH occurs at this stage.

Gluconeogenesis closely resembles the reversed pathway of glycolysis, although it is not the complete reversal of glycolysis. The seven reactions are common for both glycolysis and gluconeogenesis.

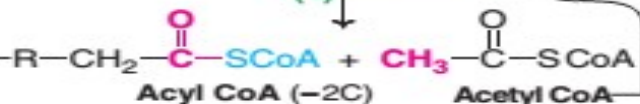
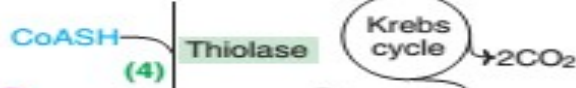
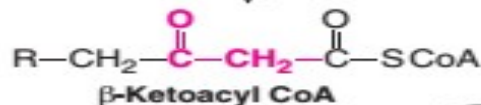
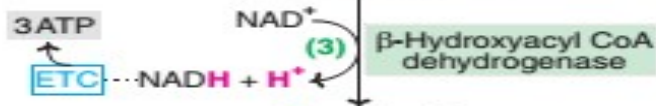
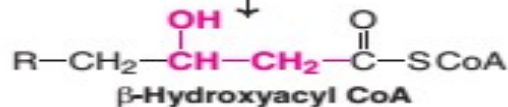
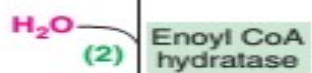
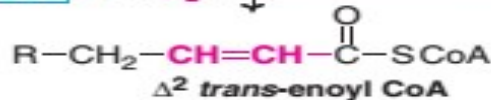
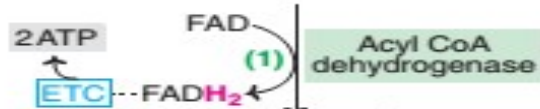
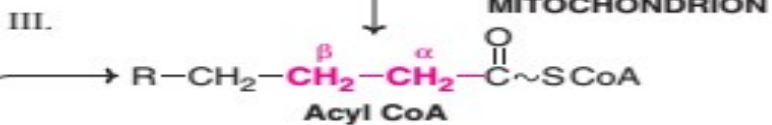




CYTOSOL

II. Carnitine transport system

MITOCHONDRION



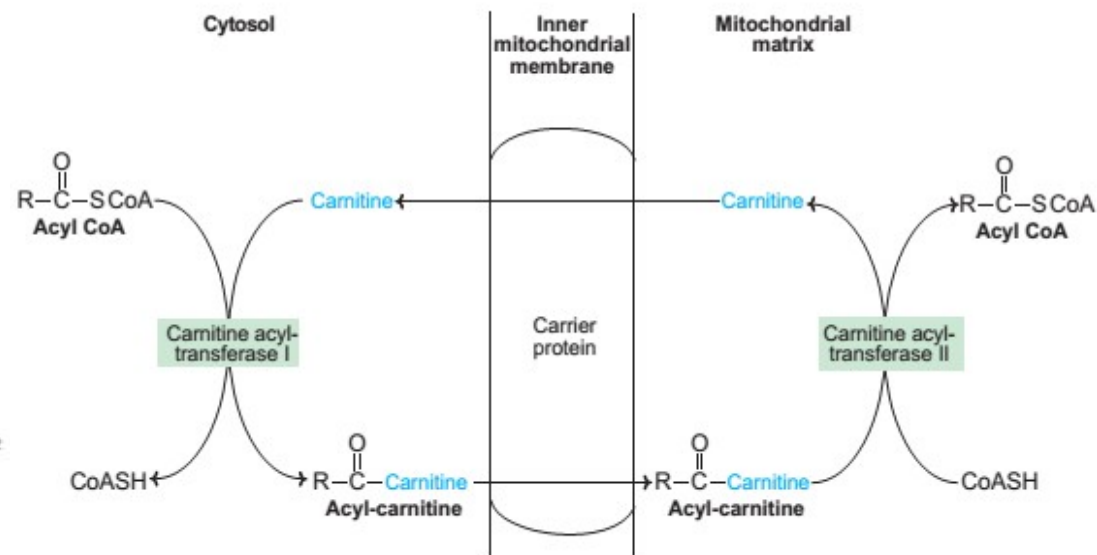
The inner mitochondrial membrane is impermeable to fatty acids. A specialized **carnitine carrier system (carnitine shuttle)** operates to transport activated fatty acids from cytosol to the mitochondria. This occurs in four steps (**Fig.14.6**).

1. Acyl group of acyl CoA is transferred to **carnitine** (β -hydroxy γ -trimethyl aminobutyrate), catalysed by carnitine acyltransferase I (present on the outer surface of inner mitochondrial membrane).

2. The acyl-carnitine is transported across the membrane to mitochondrial matrix by a specific carrier protein.

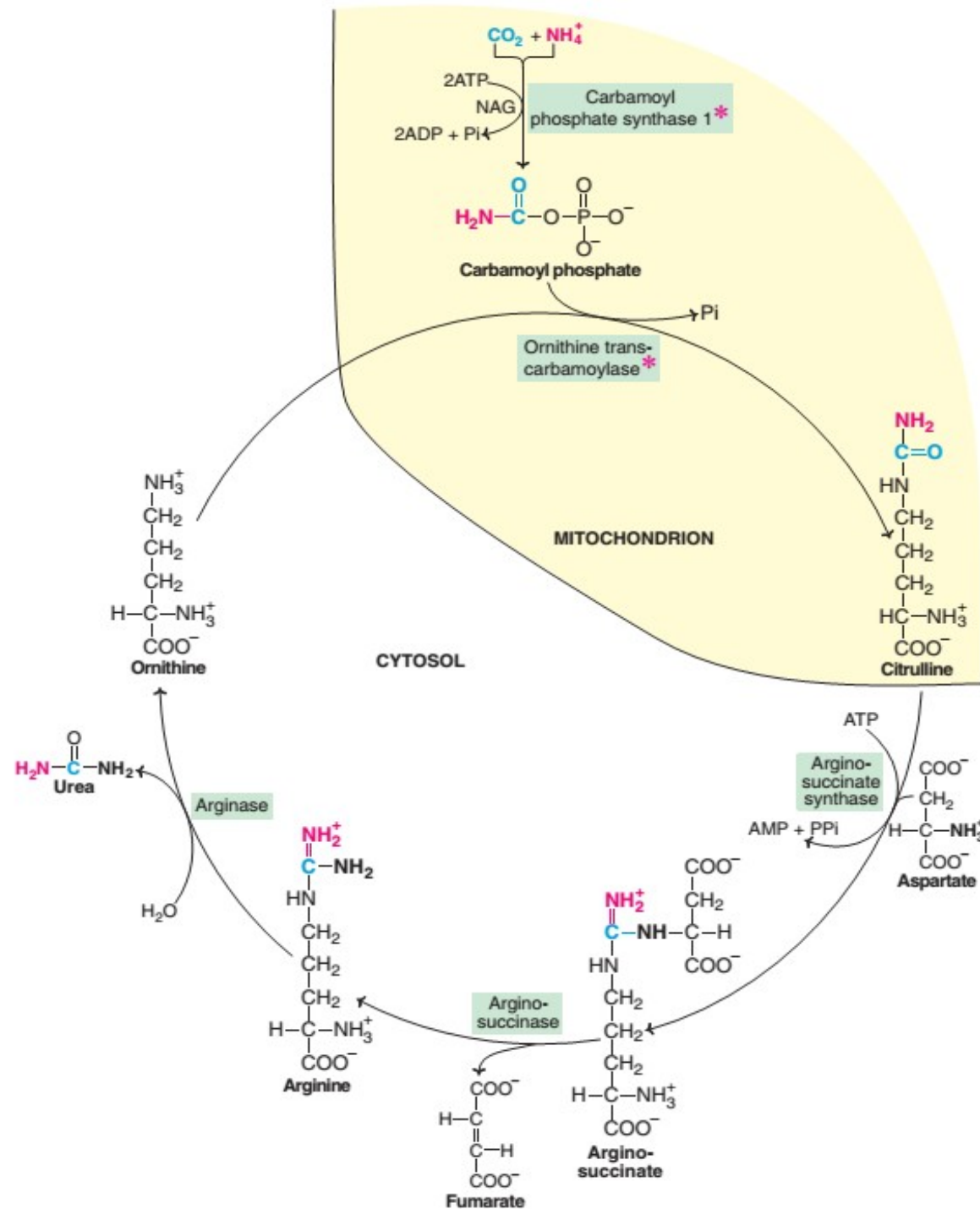
3. Carnitine acyl transferase II (found on the inner surface of inner mitochondrial membrane) converts acyl-carnitine to acyl CoA.

4. The carnitine released returns to cytosol for reuse.



- 1.Oxidation:** Acyl CoA undergoes dehydrogenation by an FAD-dependent flavoenzyme, acyl CoA dehydrogenase. A double bond is formed between α and β carbons (i.e., 2 and 3 carbons).
- 2.Hydration:** Enoyl CoA hydratase brings about the hydration of the double bond to form β -hydroxyacyl CoA.
- 3.Oxidation:** β -Hydroxyacyl CoA dehydrogenase catalyses the second oxidation and generates NADH. The product formed is β -ketoacyl CoA.
- 4.Cleavage:** The final reaction in β -oxidation is the liberation of a 2 carbon fragment, acetyl CoA from acyl CoA. This occurs by a thiolytic cleavage catalysed by β -ketoacyl CoA thiolase(or simply thiolase).

The new acyl CoA, containing two carbons less than the original, reenters the β -oxidation cycle. The process continues till the fatty acid is completely oxidized.



Urea is the end product of protein metabolism (amino acid metabolism). The nitrogen of amino acids, converted to ammonia, is toxic to the body. It is converted to urea and detoxified. Urea is synthesized in liver and transported to kidneys for excretion in urine.

Synthesis of carbamoyl phosphate: Carbamoyl phosphate synthase I (CPS I) of mitochondria catalyses the condensation of NH_4^+ ions with CO_2 to form carbamoyl phosphate. This step consumes two ATP and is irreversible.

Formation of citrulline: Citrulline is synthesized from carbamoyl phosphate and ornithine by ornithine transcarbamoylase. Ornithine is regenerated and used in urea cycle.

Synthesis of arginosuccinate: Arginosuccinate synthase condenses citrulline with aspartate to produce arginosuccinate. The second amino group of urea is incorporated in this reaction. This step requires ATP which is cleaved to AMP and pyrophosphate (PPi).

Cleavage of arginosuccinate: Arginosuccinase cleaves arginosuccinate to give arginine and fumarate. Arginine is the immediate precursor for urea.

Formation of urea: Arginase cleaves arginine to yield urea and ornithine. Ornithine enters mitochondria for its reuse in the urea cycle.