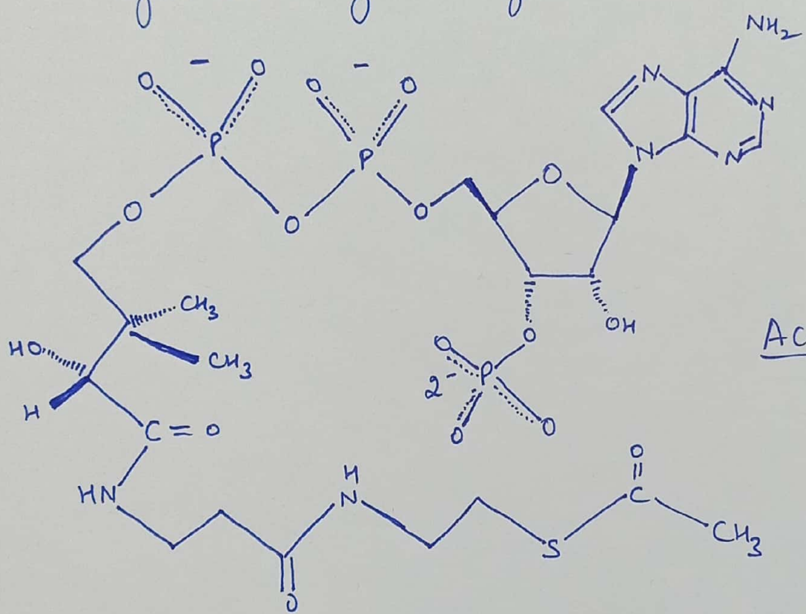
Source:- Lubert Stryer, Lehninger

B.Sc. Zoology IV Semester

Biochemistry of Metabolic Processes. 11:00 AM Tuesday (17th March 2020)

THE CITRIC ACID CYCLE.

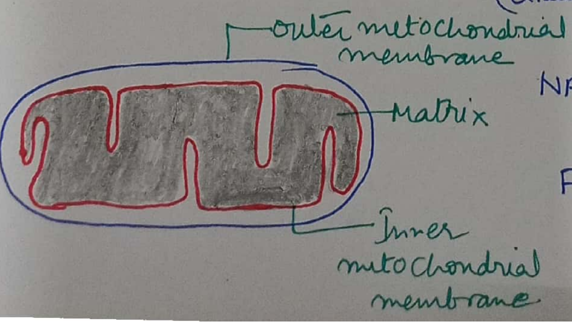
Most of the ATP generated in metabolism is provided by the aerobic processing of Glucose. This process starts with the complete oxidation of glucose derivatives to CO_2. This oxidation takes place in a series of reactions called the citric acid cycle; also known as Tricarboxylic acid cycle or the Krebs cycle. The citric acid cycle is the final common pathway for the oxidation of fuel molecules - Carbohydrates, fatty acids and amino acids. Most fuel molecules enter the cycle as Acetyl coenzyme A.

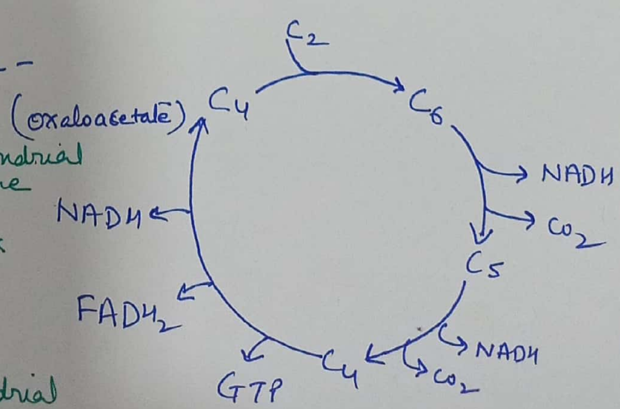


Acetyl coenzyme A

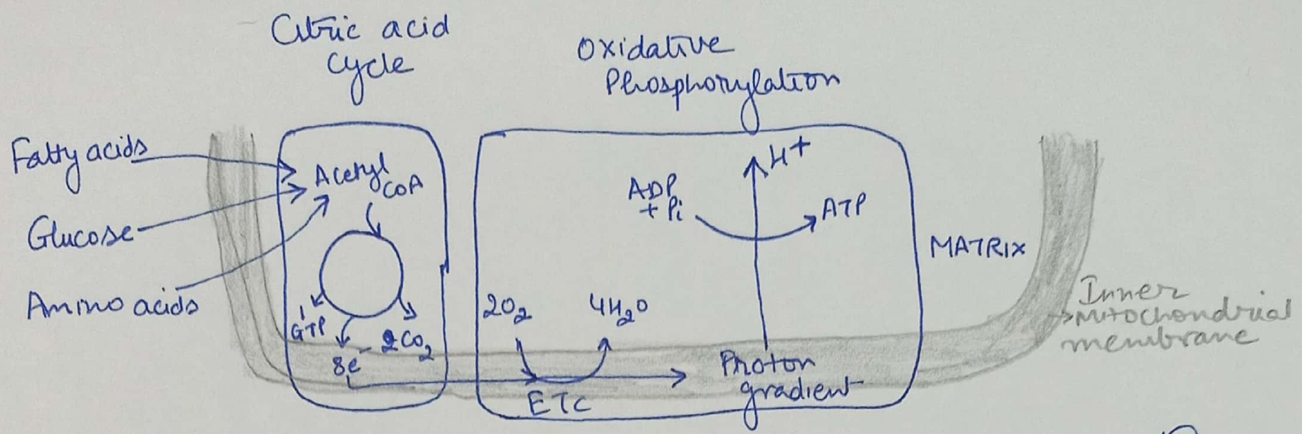
Under aerobic conditions, the pyruvate generated from glucose is oxidatively decarboxylated to form acetyl CoA. In eukaryotes, the reactions of the citric acid cycle takes place inside mitochondria.

Overview of citric acid cycle -





Cellular Respiration



The citric acid cycle harvests high-energy electrons from fuel carbon.

The citric acid cycle is the central metabolic hub of the cell. It is the gateway to the anaerobic metabolism of any molecule that can be transformed into an acetyl group or a component of citric acid cycle. The cycle is also an important source of precursors for the building blocks of many other molecules such as amino acids, nucleotide bases, and porphyrin (organic component of heme). Fuel molecules are carbon compounds that are capable of being oxidised — of losing electrons. The citric acid cycle includes a series of oxidation-reduction reactions that result in the oxidation of an acetyl group to two molecules of CO_2. This oxidation generates high-energy electrons that will be used to power the synthesis of ATP.

Pyruvate dehydrogenase links Glycolysis to the Citric acid cycle.

Under aerobic conditions, the pyruvate is transported into mitochondria by a specific carrier protein embedded in the mitochondrial membrane. In the mitochondrial matrix, pyruvate is oxidatively decarboxylated by the pyruvate dehydrogenase complex to form acetyl CoA.

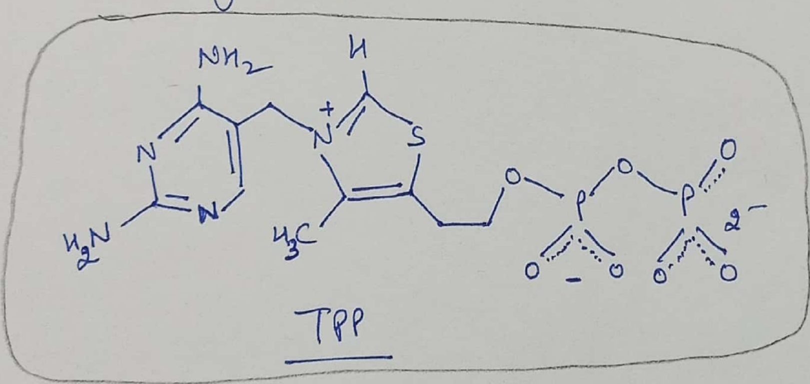
$$\text{Pyruvate} + \text{CoA} + NAD^+ \longrightarrow \text{acetyl CoA} + CO_2 + NADH + H^+$$

This irreversible reaction is the link between Glycolysis and the citric acid cycle. The pyruvate dehydrogenase complex produces CO_2 and captures high-transfer-potential electrons in the form of NADH. Thus, the pyruvate dehydrogenase reaction has many of the key features of the reaction of the citric acid cycle itself.

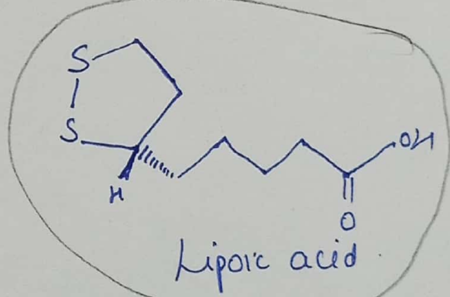
The pyruvate dehydrogenase complex is a large, highly integrated complex of three distinct enzymes. Pyruvate dehydrogenase complex is a membrane of a family of homologous complexes that include the Citric acid Cycle enzyme α-ketoglutarate dehydrogenase complex.

Mechanism: The synthesis of Acetyl Coenzyme A from Pyruvate requires three enzymes and five Coenzymes.

The mechanism of pyruvate dehydrogenase reaction is wonderfully complex, ~~more so than~~ The reaction requires the participation of the three enzymes of pyruvate dehydrogenase complex and five Coenzymes. The Coenzyme Thiamine pyrophosphate (TPP), Lipoic acid, and FAD serves as catalytic cofactor and CoA and NAD^+ are stoichiometric cofactors.

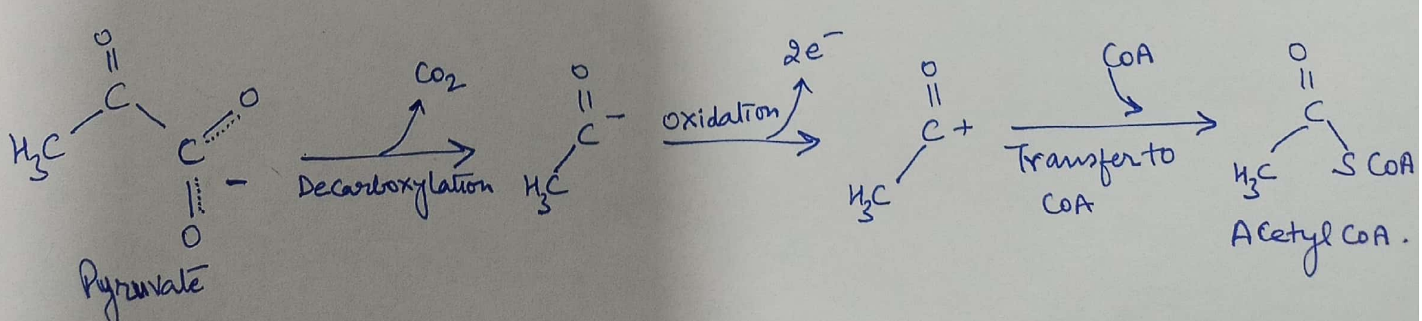


TPP



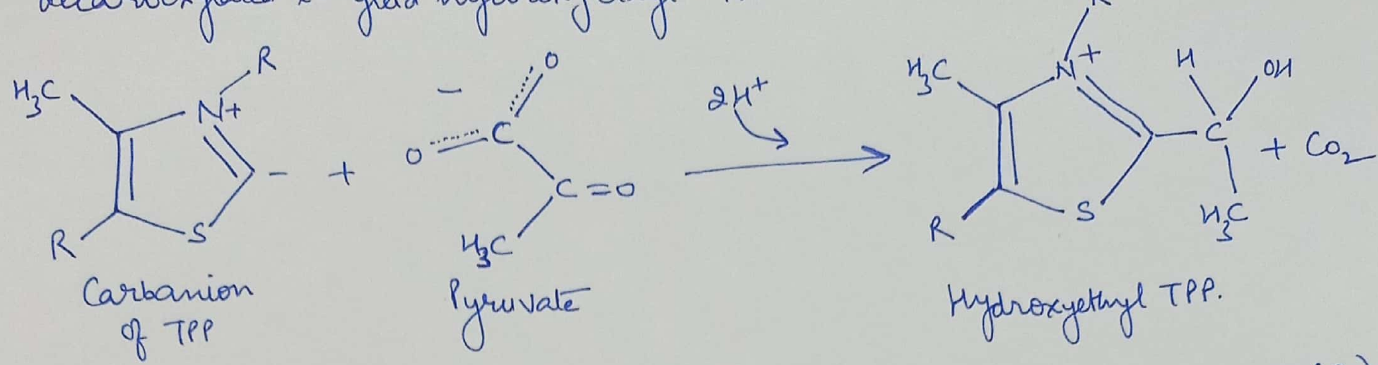
Lipoic acid

The Conversion of pyruvate into acetyl CoA consists of three steps:- decarboxylation, oxidation and transfer of the resultant acetyl group to CoA.



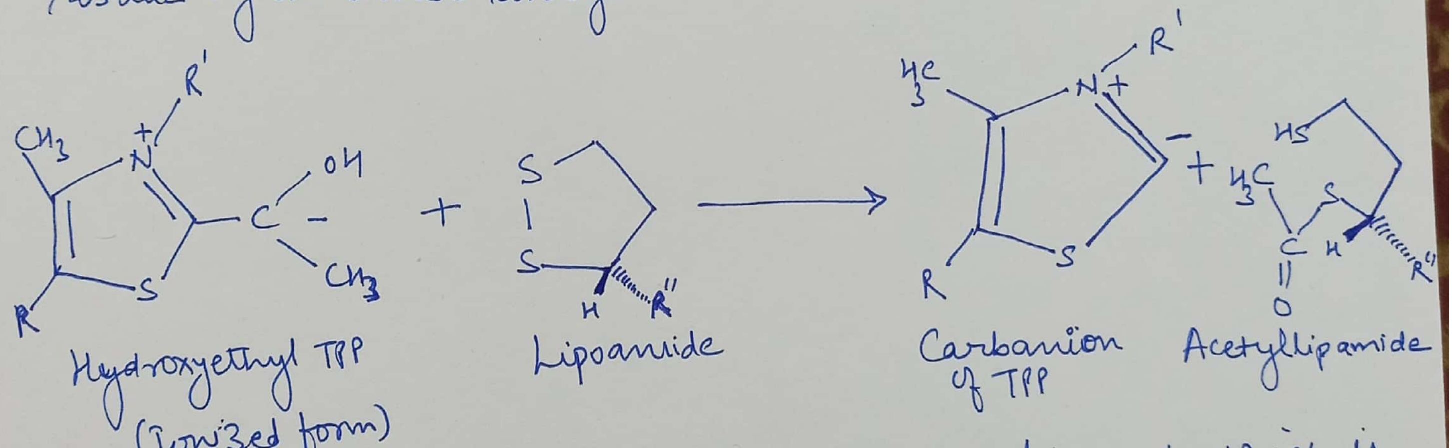
These steps must be coupled to preserve the free energy derived from the decarboxylation step to drive the formation of NADH and acetyl CoA.

1. Decarboxylation – Pyruvate combines with TPP and is then decarboxylated to yield hydroxyethyl-TPP.



This reaction is catalysed by the pyruvate dehydrogenase component (E_1) of the multienzyme complex. TPP is the prosthetic group of the Pyruvate dehydrogenase component.

2. Oxidation – The hydroxyethyl group attached to TPP is oxidized to form an acetyl group while being simultaneously transferred to lipoamide, a derivative of lipoic acid that is linked to the side chain of a lysin residue by an amide linkage.



The oxidation in this reaction is the disulfide group of lipoamide, which is reduced to its disulfhydryl form. This reaction, also catalyzed by the Pyruvate dehydrogenase component E1 yields acetyllipoamide.

3. Formation of Acetyl CoA. – The acetyl group is transferred from ~~acetyllipoamide~~ acetyllipoamide to CoA to form acetyl CoA.