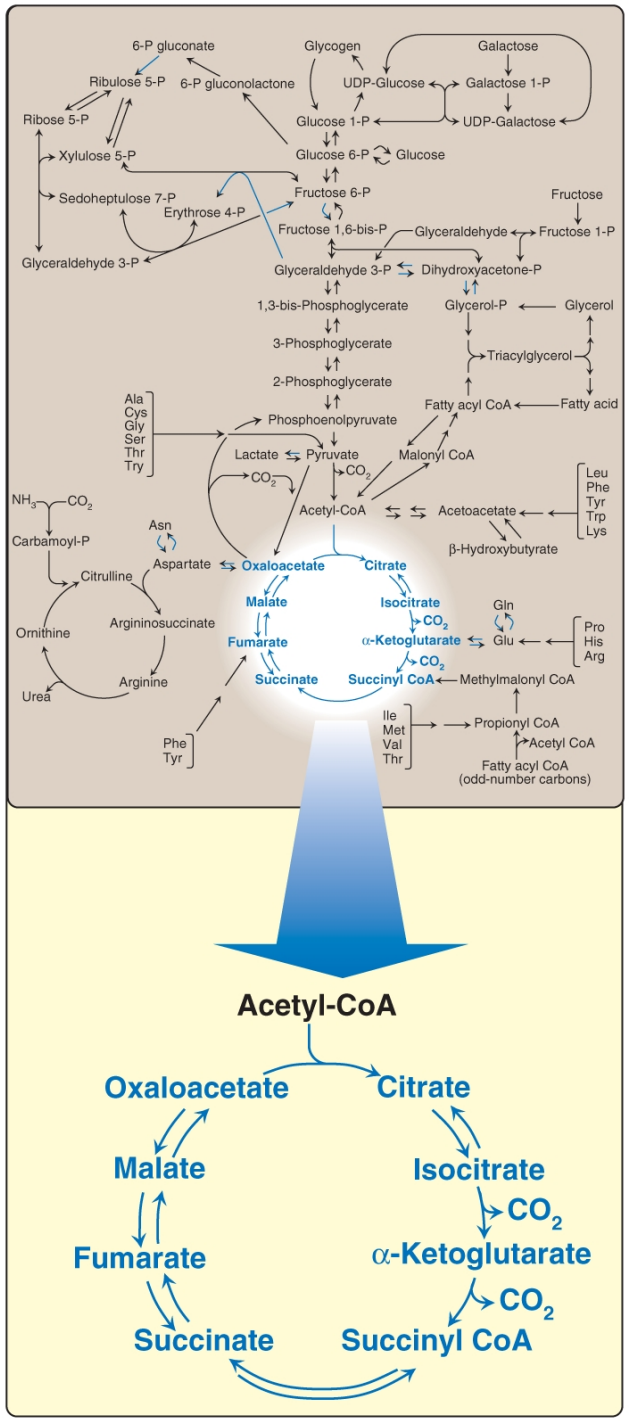


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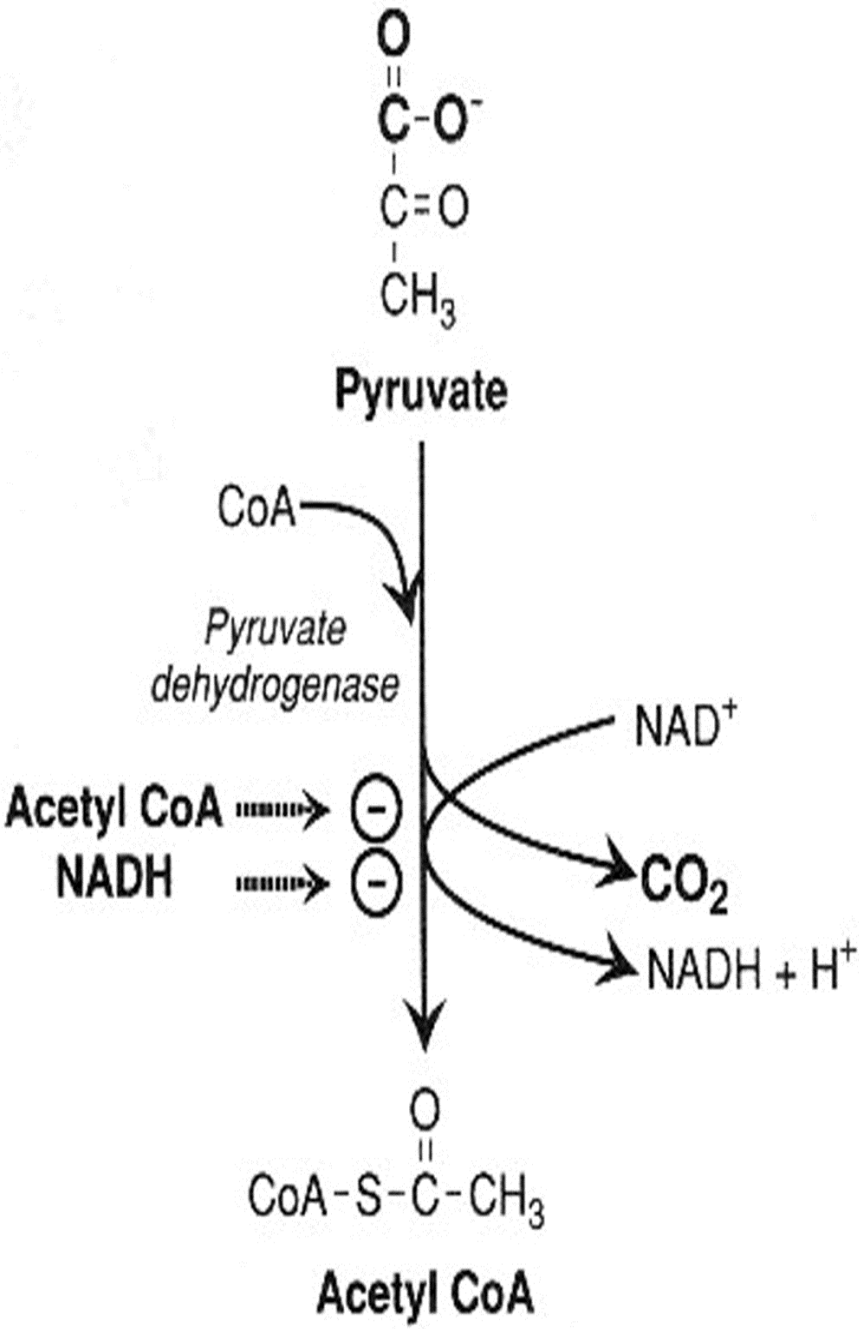
# Citric Acid Cycle

**The central role is the oxidation of acetyl CoA to $CO_2$ and $H_2O$. It accounts for 2/3 of all the oxygen consumption and ATP production. It occurs in the mitochondria.**

**After glycolysis pyruvate needs to be converted to acetyl CoA so that it could be oxidized through the citric acid cycle. This oxidative decarboxylation of pyruvate is performed by the pyruvate dehydrogenase complex.**




The oxidation of pyruvate to form Acetyl CoA and $CO_2$ and NADH is carried out by an enzyme complex which contains three (3) different enzymatic activities and requires 5 different cofactors. This reaction takes place in the mitochondria. This reaction is irreversible. This explains why glucose can not be formed from acetyl CoA in gluconeogenesis. This reaction is the major source of acetyl CoA for the cycle.

**Sources**

Carbohydrate - Pyruvate
Fatty Acids
Protein - Amino Acids

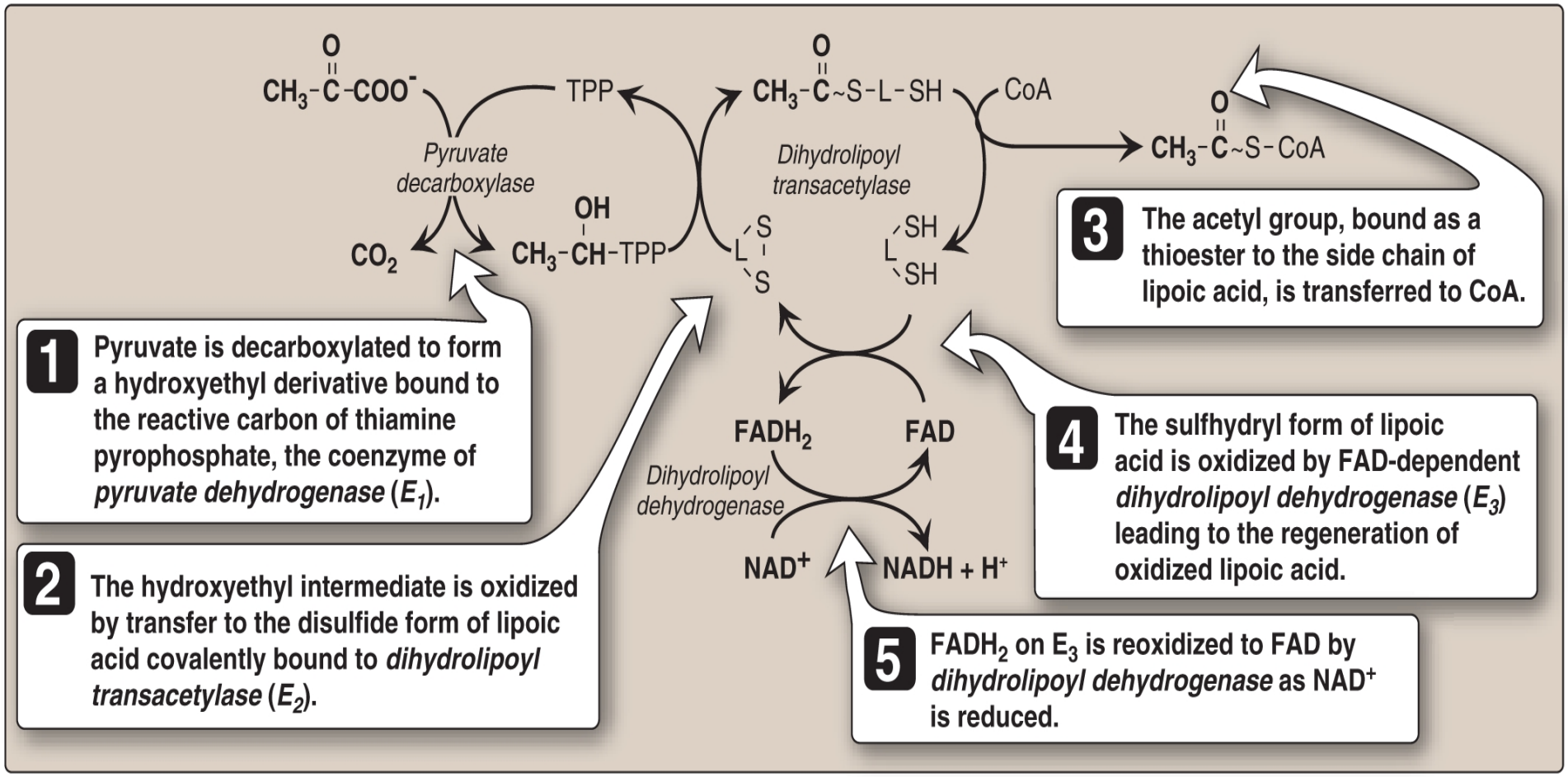
# Acetyl CoA

**Fates**

Tricarboxylic Acid Cycle -Oxidation
Fatty Acid and Sterol Biosynthesis
Ketone Body Production

Like pyruvate, acetyl CoA is a key metabolic intermediate which interacts with carbohydrate, fatty acid and amino acid metabolism.

# Pyruvate metabolism
# The pyruvate dehydrogenase complex (PDH)

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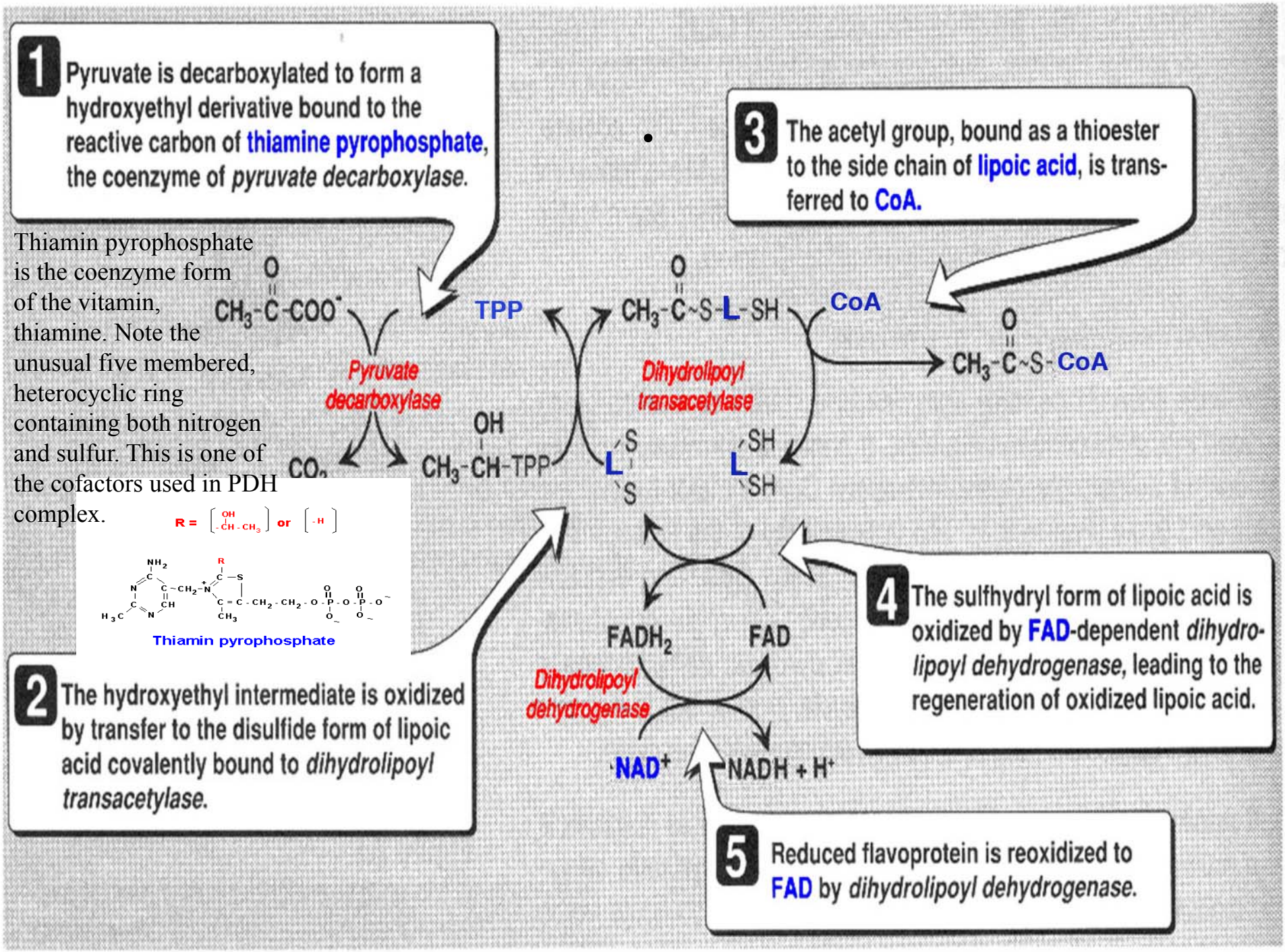
Deficiencies of TPP can cause serious CNS problems. Brain cells are unable to produce sufficient ATP (via TCA) if the PDH complex is inactive. Wernicle-Korsakoff, encephalopathy-psychosis syndrome TPP deficiency, with alcohol abuse.

Thiamin pyrophosphate is the coenzyme form of the vitamin, thiamine. Note the unusual five membered, heterocyclic ring containing both nitrogen and sulfur. This is one of the cofactors used in PDH complex.



# The Pyruvate Dehydrogenase Reaction

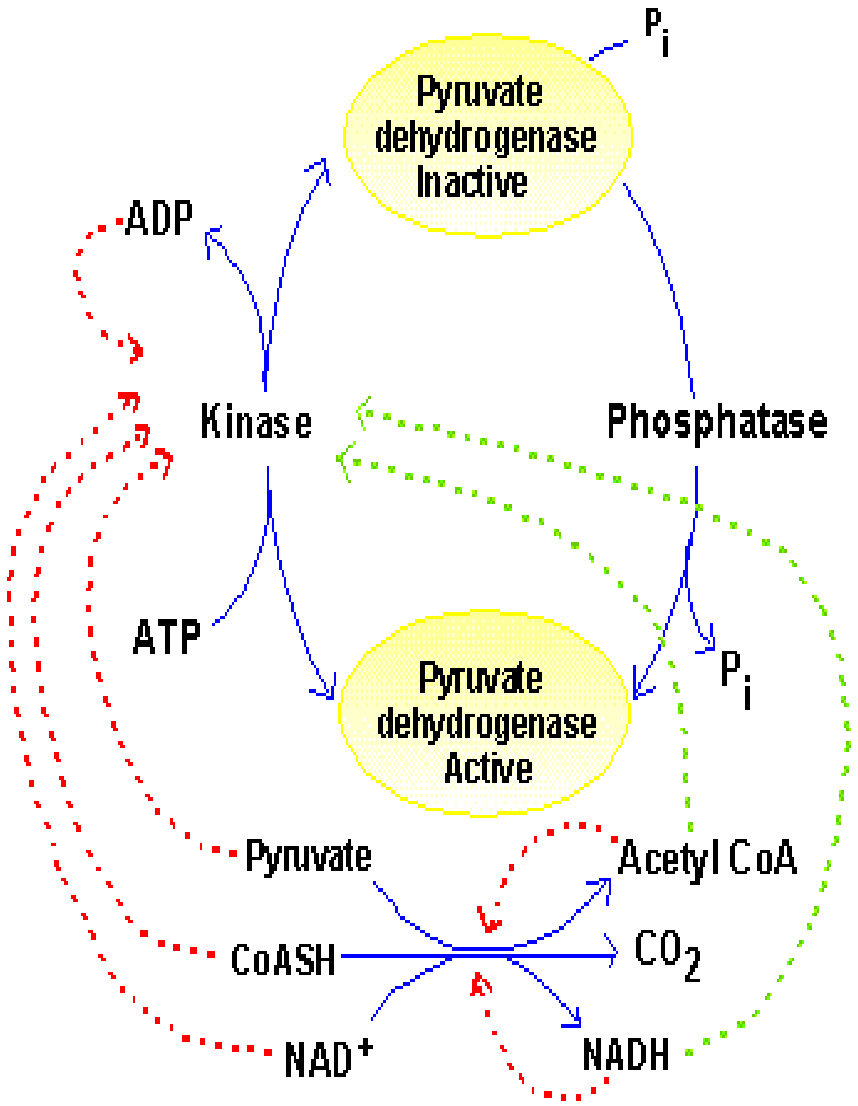

## This is an irreversible reaction

This reaction is catalyzed by a multifunctional enzyme complex which requires 5 different coenzymes or cofactors and catalyzes three discrete reactions.

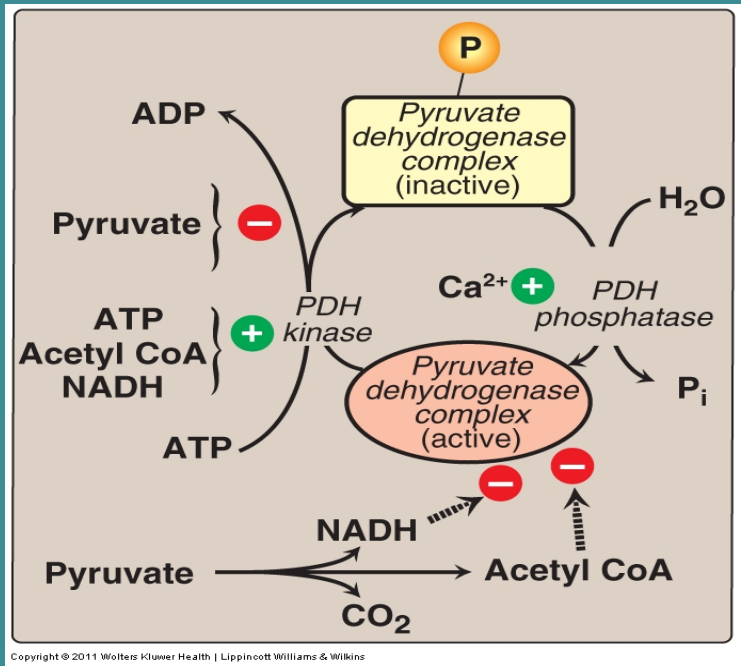
1. pyruvate dehydrogenase
2. dihydrolipoyl transacetylase
3. dihydrolipoyl dehydrogenase

Pyruvate dehydrogenase complex (mitochondrion)

A covalent intermediate is formed with the release of CO2 and ultimately the two remaining carbons are transferred to CoASH to form acetyl CoA and regenerate the enzyme. This is a highly regulated enzyme. The 5 cofactors or coenzymes involved are NADH, Thiamin pyrophosphate, lipoic acid, FAD and CoASH. This is a key enzyme in metabolism and on EXAMS.




The pyruvate dehydrogenase complex is subject to complex control by means of phospho. and dephosphorylation. The primary control is on the PDH kinase enzyme which inactivates the complex. Note that several required cofactors and one of the products, acetyl CoA, are effectors of this system.



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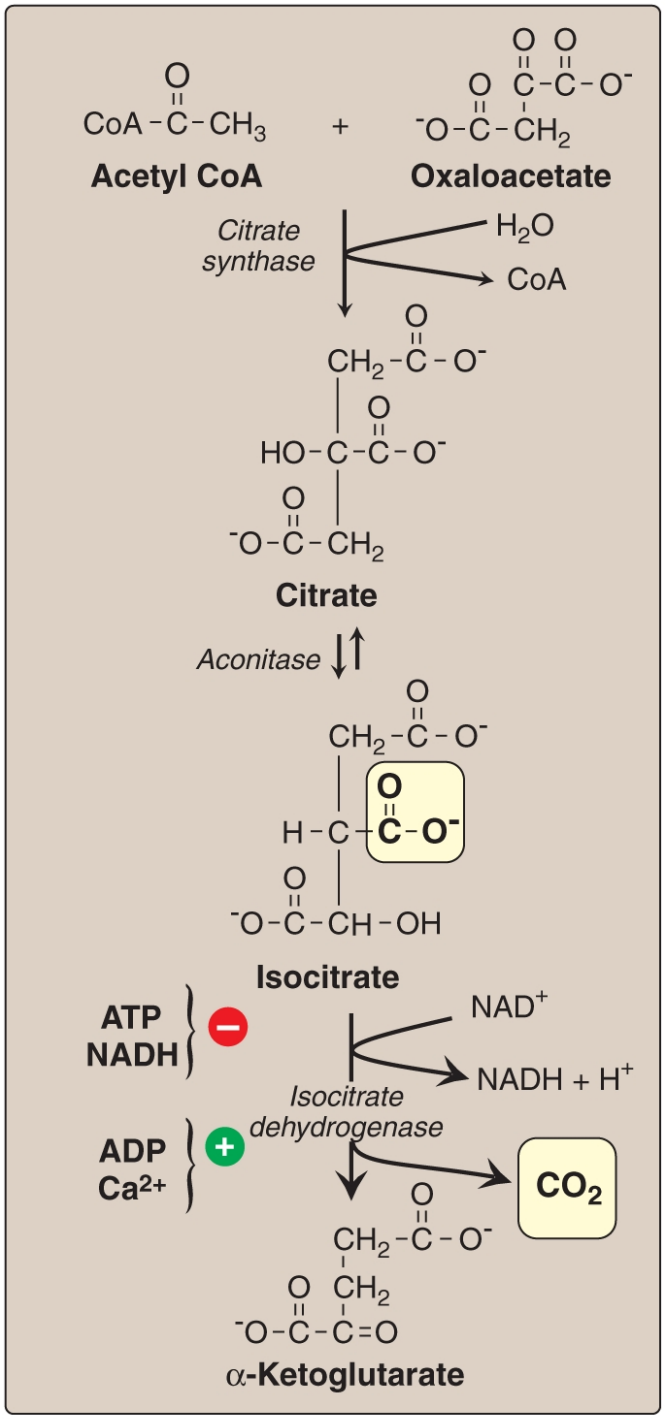


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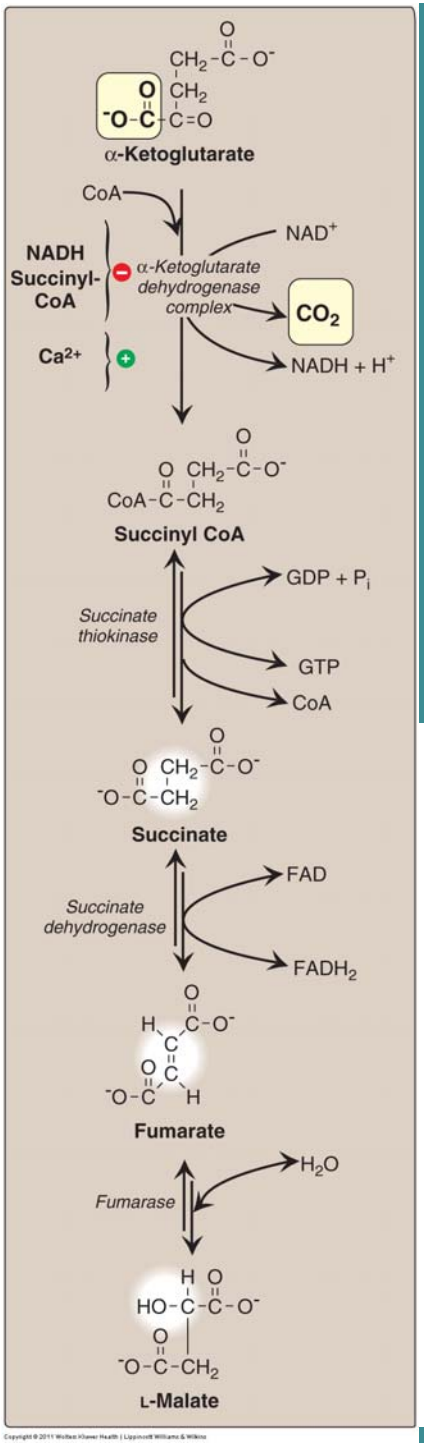
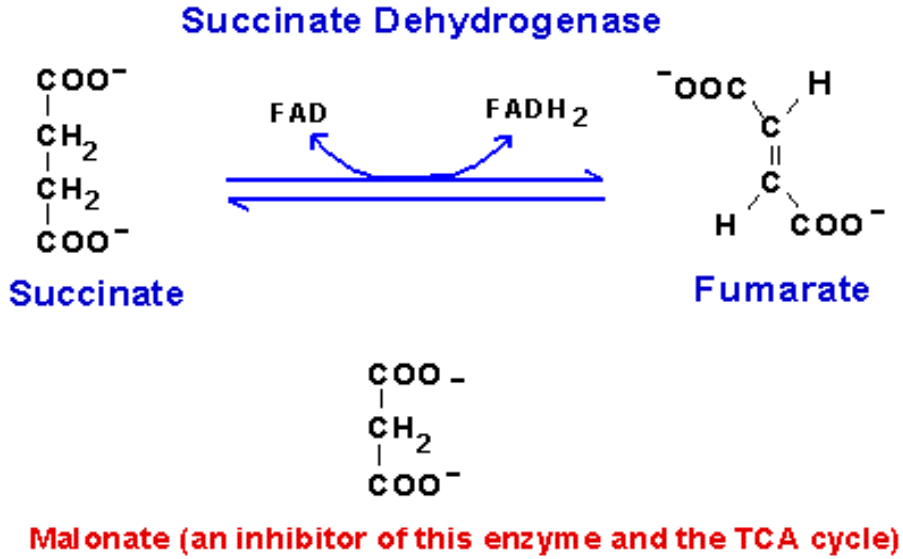
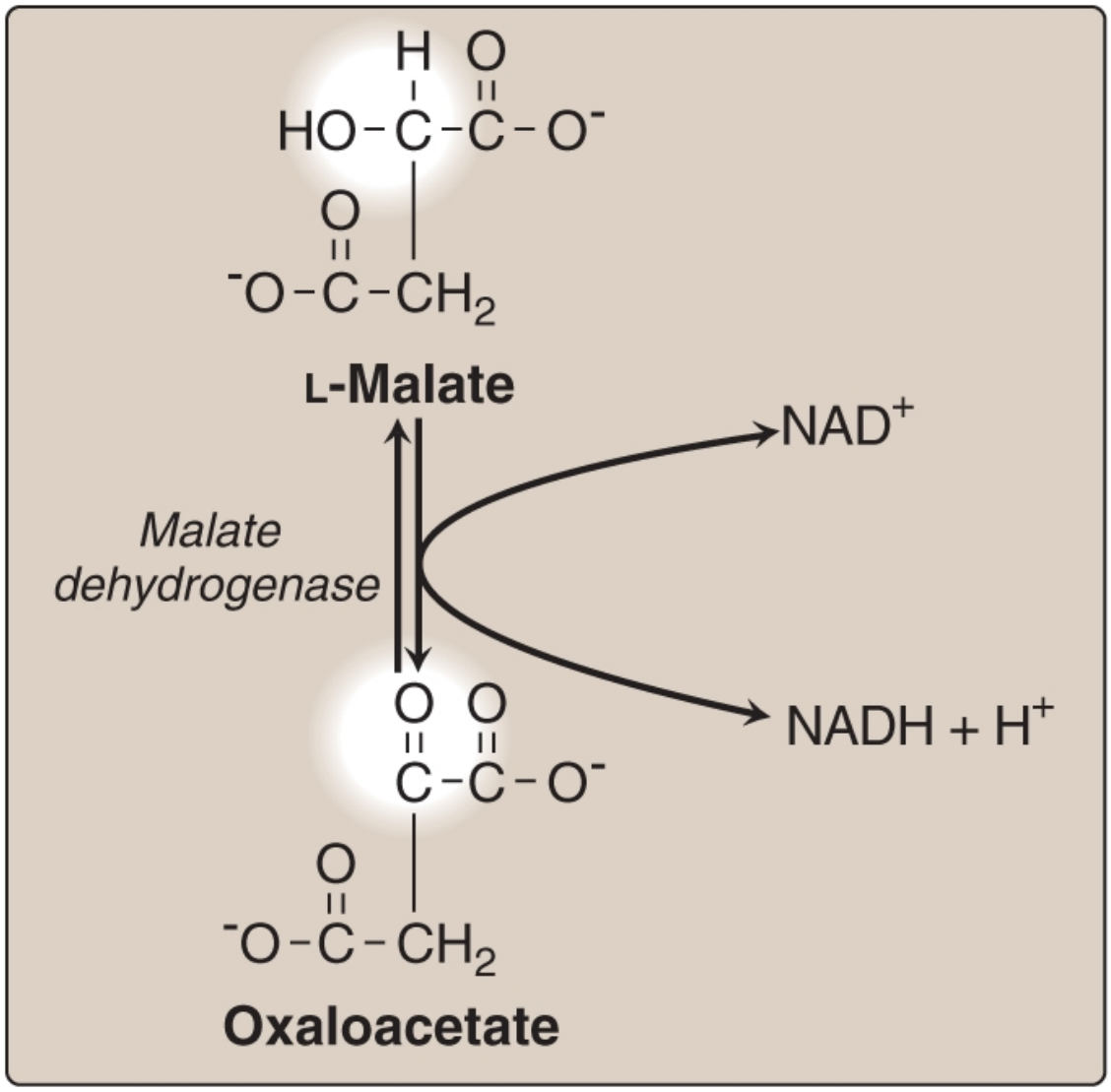
The citric acid or TCA cycle is one of the core pathways in metabolism. It begins with the condensation of oxaloacetate and acetyl CoA to form the tricarboxylic acid, citric acid (citrate) after which the cycle is named. The reaction is catalyzed by citrate synthase. Citrate provides Acetyl CoA for fatty acid synthesis. Citrate (-) PFK-1. The second discrete step in the tricarboxylic acid cycle is the conversion of citrate to isocitrate. cis-aconitrate has been shown to be an enzyme bound intermediate in this conversion. The reaction is catalyzed by the enzyme Aconitase. The third step in the tricarboxylic acid cycle is the conversion of isocitrate to α-ketoglutarate with the loss of $CO_2$ and the production of an NADH. Oxalosuccinate has been identified as an intermediate in this conversion. The reaction is catalyzed by Isocitrate Dehydrogenase. Notice that it is the second irreversible reaction of the cycle. It is one of the rate limiting steps of the cycle.




α-ketoglutarate is next converted to succinyl CoA again with the loss of the second production of $CO_2$ and NADH. This reaction requires CoASH and is similar in mechanism to the pyruvate dehydrogenase reaction. This step in the cycle is catalyzed by αKetoglutarate Dehydrogenase complex. Coenzymes required lipoic acid, tiamine pyrophosphate, FAD,NAD, and CoASH. (-) ATP, GTP, NADH & succinyl CoA. Not reg. by phosphor Cleavage of succinyl CoA yields a substrate level phosphorylation (GTP) and CoA. Oxidation of succinate to fumarate yields




FADH2. Hydration of fumarate to malate.

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Malate is oxidized to Oxaloacetate by malate dehydrogenase. This produces the third and final NADH of the cycle.

| Energy producing reaction | Number of ATP produced |
|---|---|
| 3 NADH $\longrightarrow$ 3 $NAD^+$ | 9 |
| $FADH_2 \longrightarrow FAD$ | 2 |
| $GDP + P_i \longrightarrow GTP$ | 1 |
| | 12 ATP/acetyl CoA oxidized |

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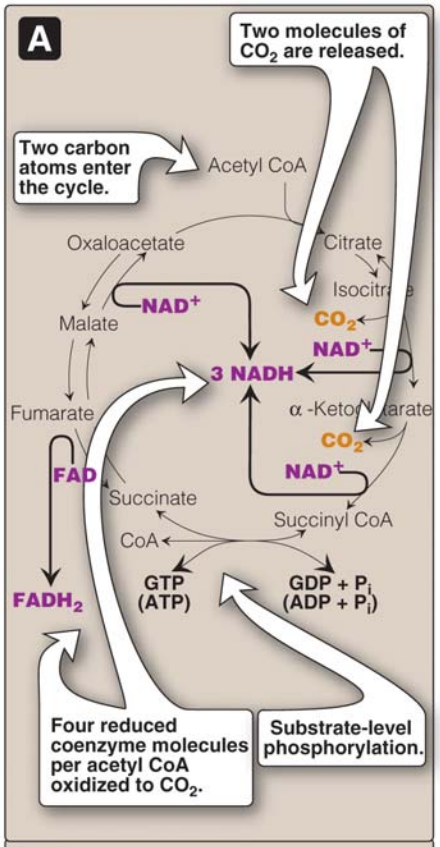
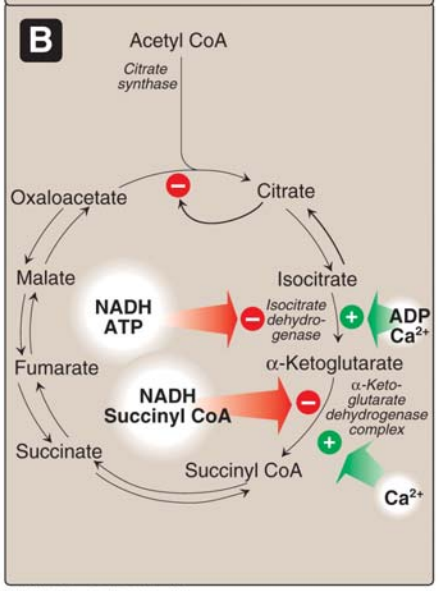
Summary of reactions. Two carbon atoms enter the cycle as Acetyl CoA and leave as $CO_2$. No net consumption or production of oxaloacetate or other intermediates. Four pairs of electrons are transferred during one turn (3 NAD to NADH) (1 FAD to $FADH_2$). NADH = 3ATP, $FADH_2$= 2ATP

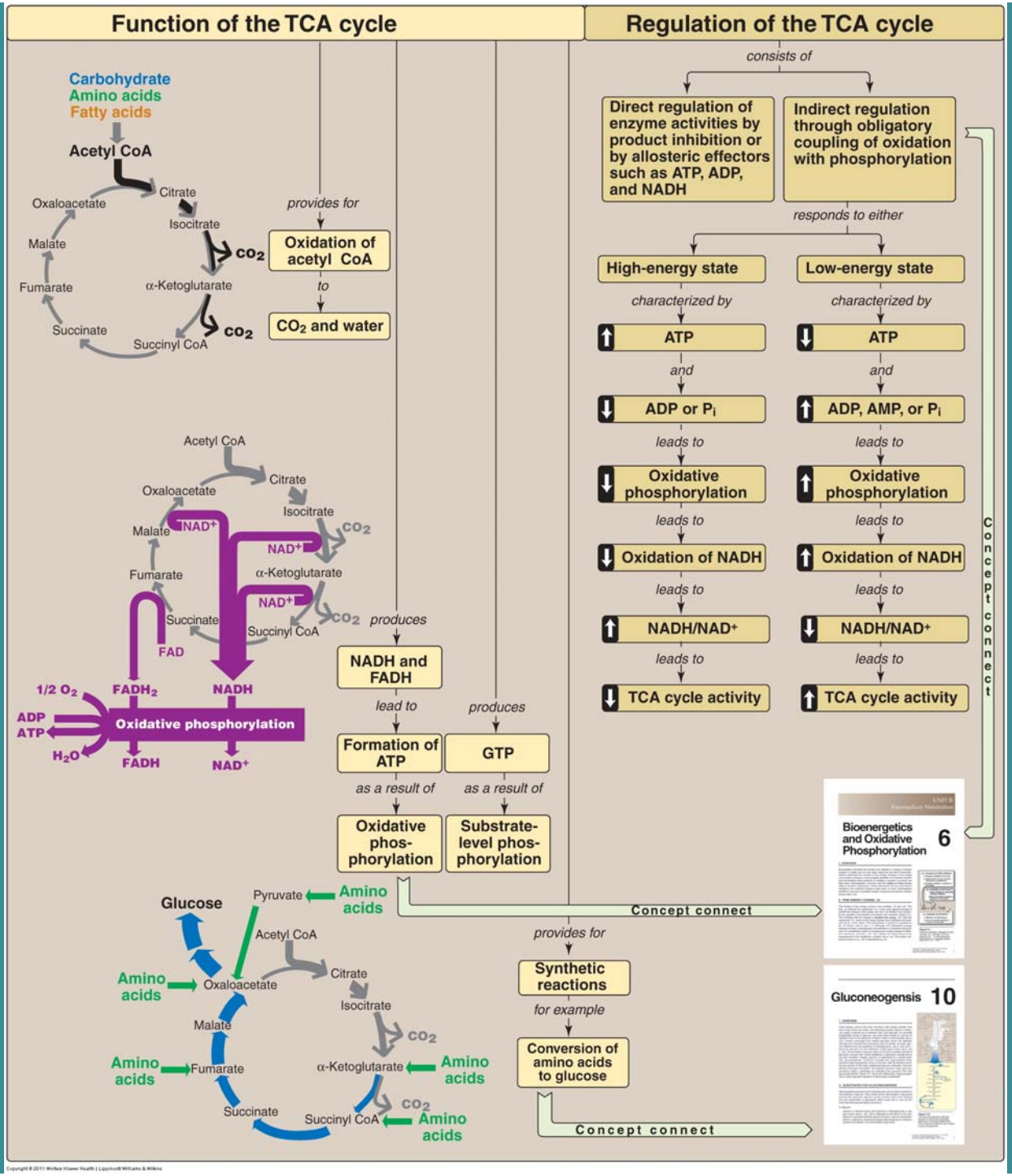



The acetyl CoA produced by the pyruvate dehydrogenase reaction or derived from fatty acid degradation or amino acid degradation can feed its two carbons into the Tricarboxylic acid cycle, resulting in the release of $2CO_2$, the generation of a GTP and reduced coenzymes which can supply electrons to the mitochondrial electron c transport. Inducers and inhibitors of enzymes in the cycle are illustrated.

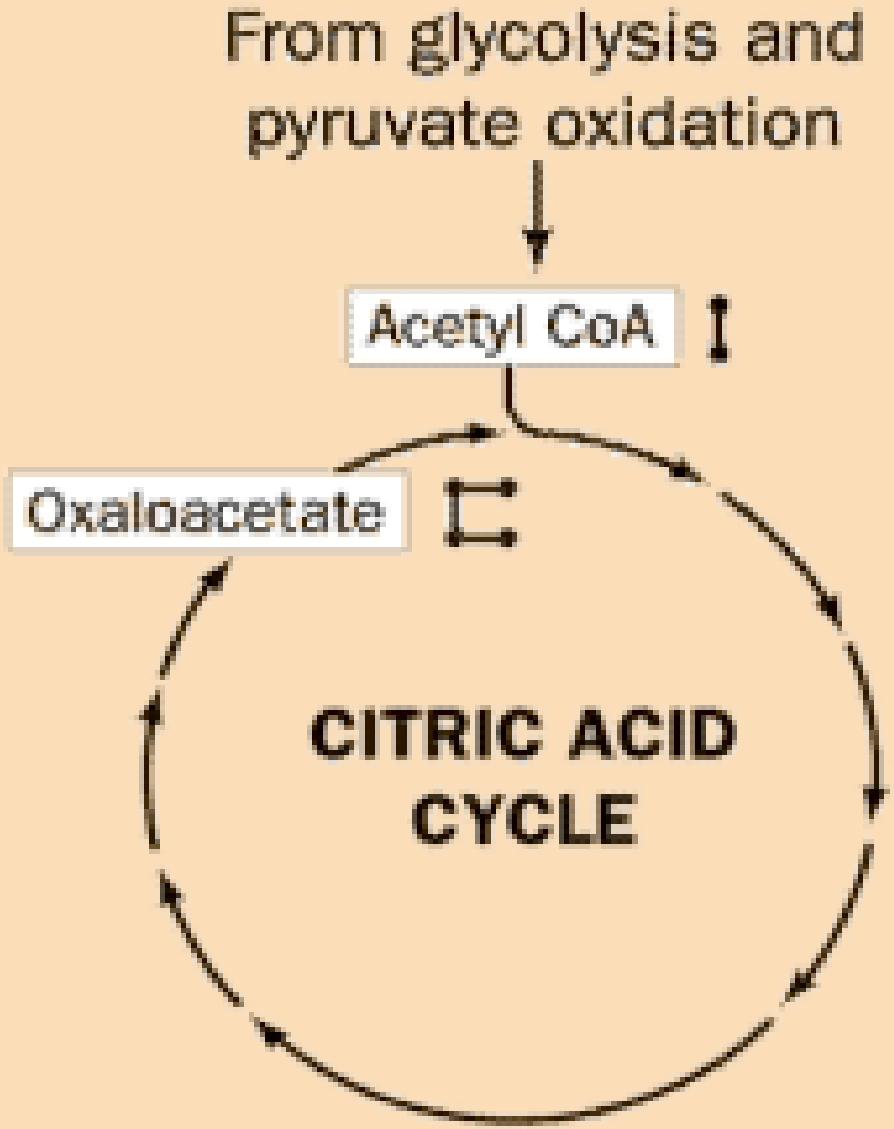
Regulation of the TCA cycle (8 rxs)

A. Activation and inhibition of enzymes: the cycle is regulated by several enzymes (highly – $\Delta G$, citrate synthase, isocitrate dehydrogenase, ketoglutarate dehydrogenase complex. B. Effects by the availability of ADP : high ADP accelerates rxs that use ADP. ATP increases until production equal consumption. Low ADP decreases oxidative phosphorylation due to lack of acceptor. Oxidation and phosphorylation are coupled, therefore, NAD and FAD are depleted because NADH and FADH are accumulated.


Function of the TCA cycle
Regulation of the TCA cycle
Carbohydrate
Amino acids
Fatty acids
Acetyl CoA
Citrate
Isocitrate
α-Ketoglutarate
Succinyl CoA
Succinate
Fumarate
Malate
Oxaloacetate
$CO_2$
provides for
Oxidation of acetyl CoA
to
$CO_2$ and water
NAD+
FAD
$FADH_2$
NADH
1/2 $O_2$
ADP
ATP
$H_2O$
FADH
Oxidative phosphorylation
produces
NADH and FADH
lead to
Formation of ATP
as a result of
Oxidative phos-phorylation
produces
GTP
as a result of
Substrate-level phos-phorylation
Glucose
Pyruvate
Amino acids
Concept connect
provides for
Synthetic reactions
for example
Conversion of amino acids to glucose
Concept connect
consists of
Direct regulation of enzyme activities by product inhibition or by allosteric effectors such as ATP, ADP, and NADH
Indirect regulation through obligatory coupling of oxidation with phosphorylation
responds to either
High-energy state
Low-energy state
characterized by
ATP
and
ADP or $P_i$
ADP, AMP, or $P_i$
leads to
Oxidative phosphorylation
Oxidation of NADH
NADH/NAD+
TCA cycle activity
Concept connect
Bioenergetics and Oxidative Phosphorylation 6
Gluconeogensis 10

# Veamos la animación

# Summary TCA cycle



# Veamos la animación

# First reactions of the TCA cycle

# Veamos la animación

# Middle reactions of the TCA cycle

# Veamos la animación

# Final three reactions of TCA cycle