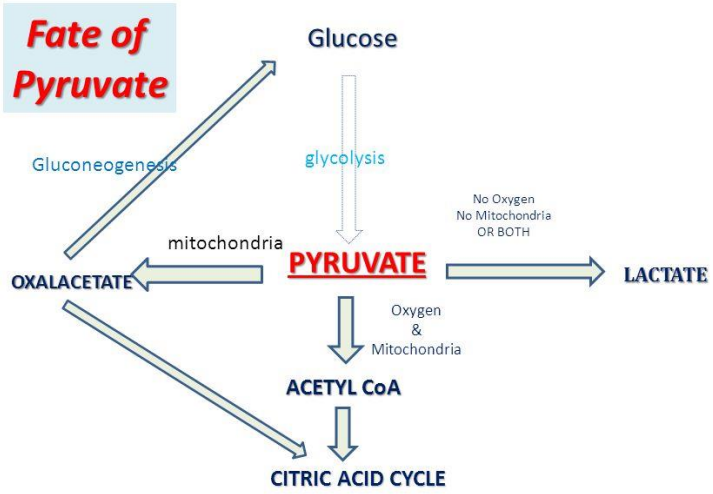
THE CITRIC ACID CYCLE
(KREBS CYCLE)
TCA (tricarboxylic acid cycle)

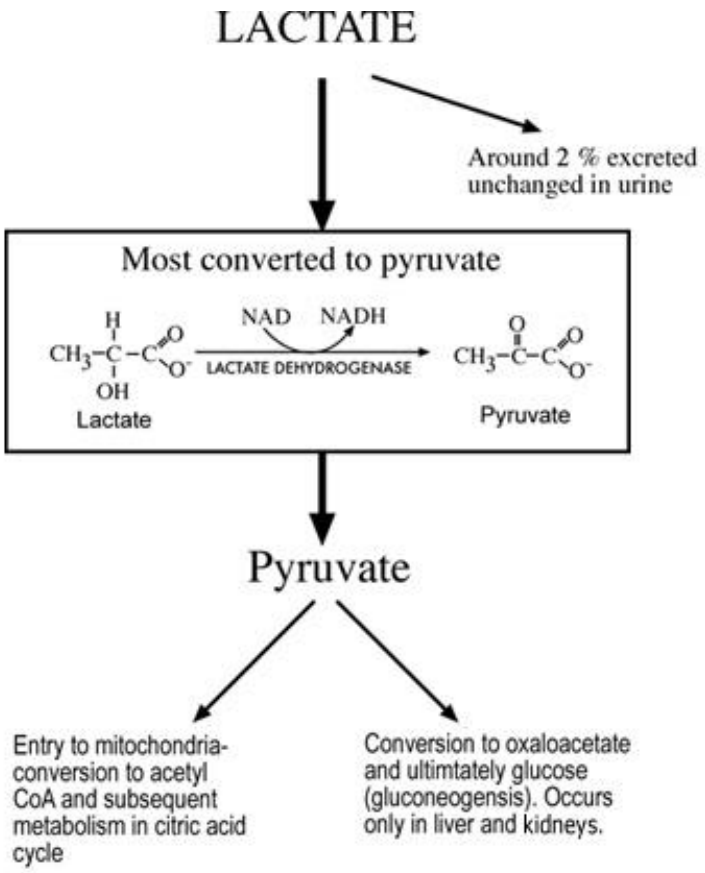
THE OXIDATION OF PYRUVATE TO ACETYL CoA

LEARNING OBJECTIVES:

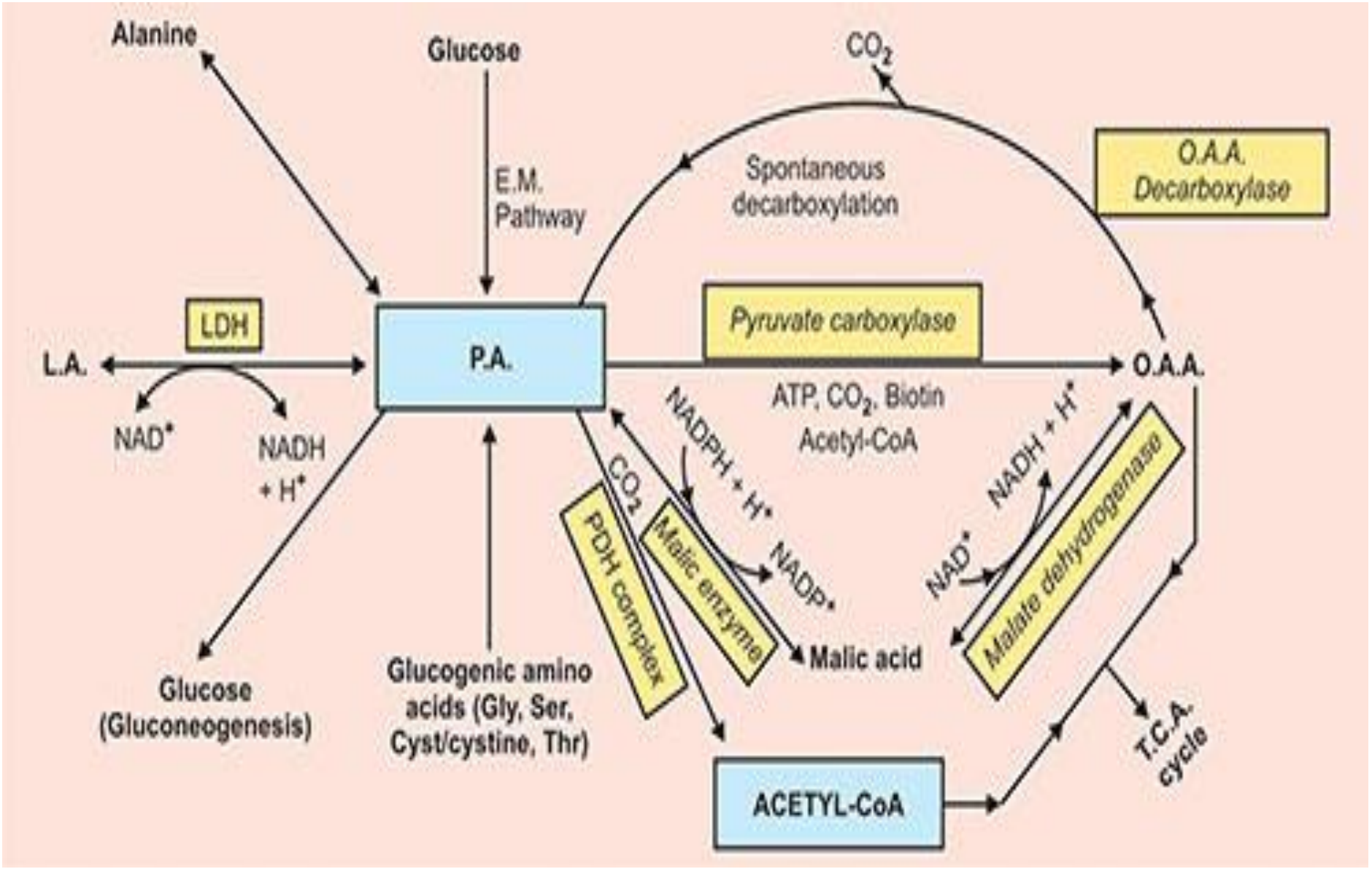
- Describe the oxidation of pyruvate

1. What is PDH complex.
2. What are the enzymes, co-enzymes and regulatory enzymes of PDH complex.
3. Effect of deficiency of pyruvate dehydrogenase
4. Reactions and ATPS generated in TCA cycle.
5. Role of vitamins in TCA cycle


Fate of Pyruvate
Glucose
Gluconeogenesis
glycolysis
No Oxygen
No Mitochondria
OR BOTH
mitochondria
OXALACETATE
PYRUVATE
LACTATE
Oxygen
&
Mitochondria
ACETYL CoA
CITRIC ACID CYCLE

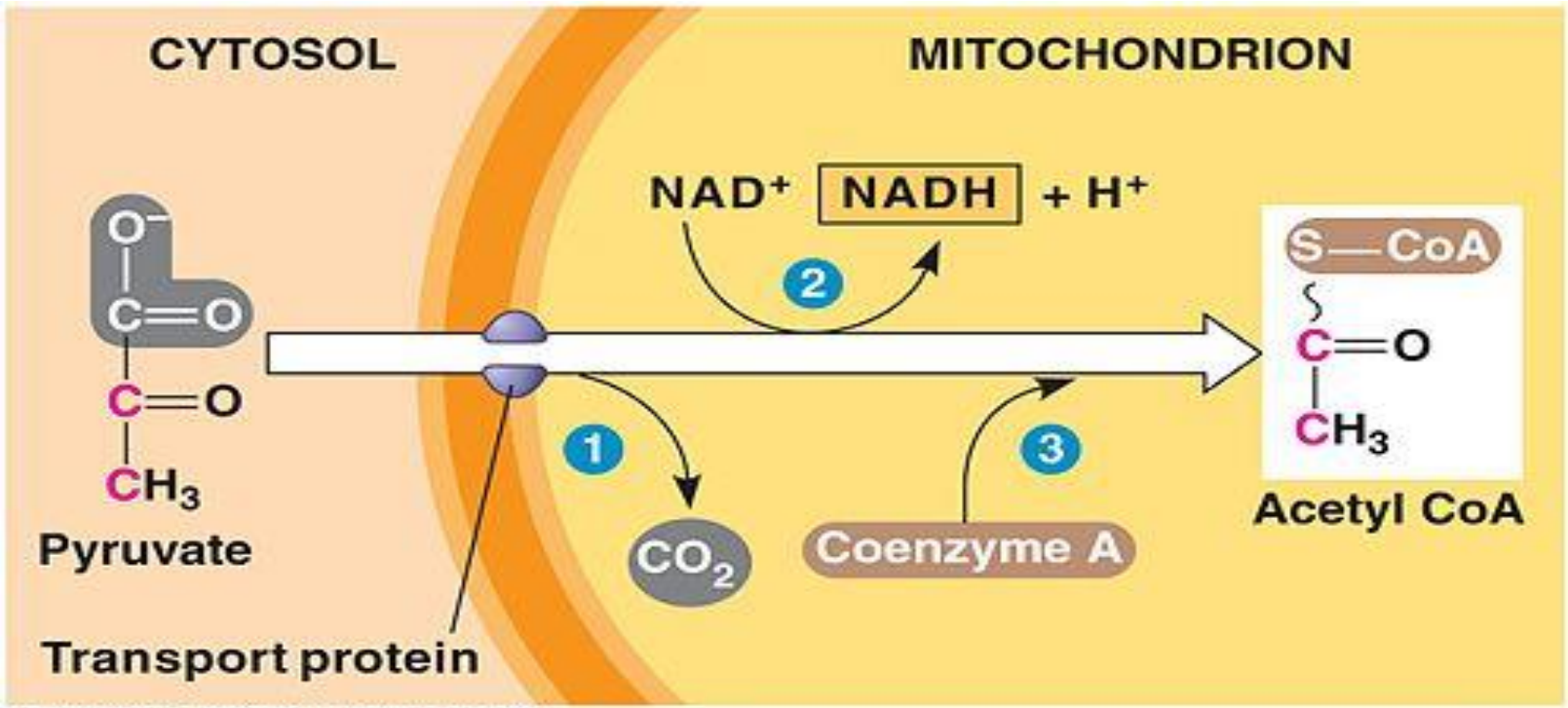

LACTATE
Around 2 % excreted unchanged in urine
Most converted to pyruvate
NAD
NADH
LACTATE DEHYDROGENASE
Lactate
Pyruvate
Pyruvate
Entry to mitochondria- conversion to acetyl CoA and subsequent metabolism in citric acid cycle
Conversion to oxaloacetate and ultimtately glucose (gluconeogensis). Occurs only in liver and kidneys.

Formation and fate of pyruvate



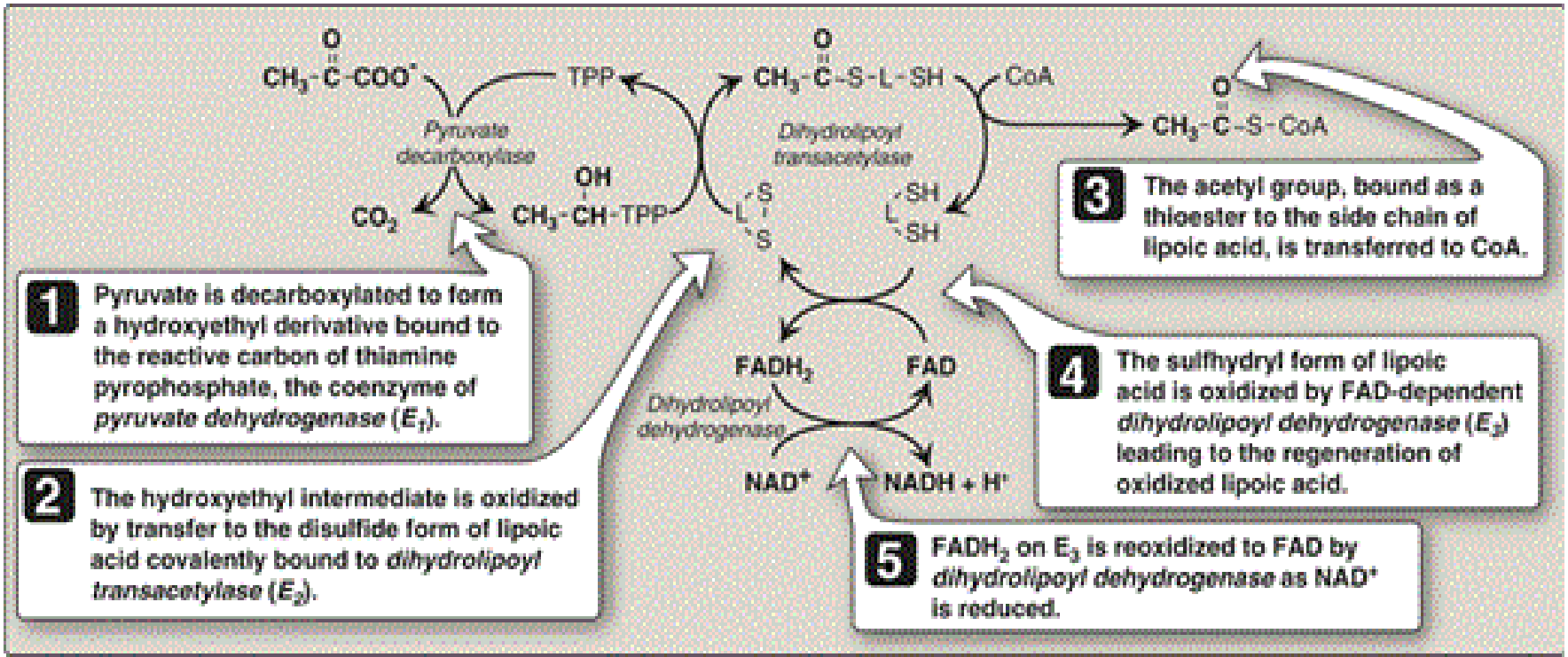
OXIDATION OF PYRUVATE TO ACETYL CoA

- Pyruvate after formation in cytosol is transported to mitochondrion_____
- ***proton symporter***



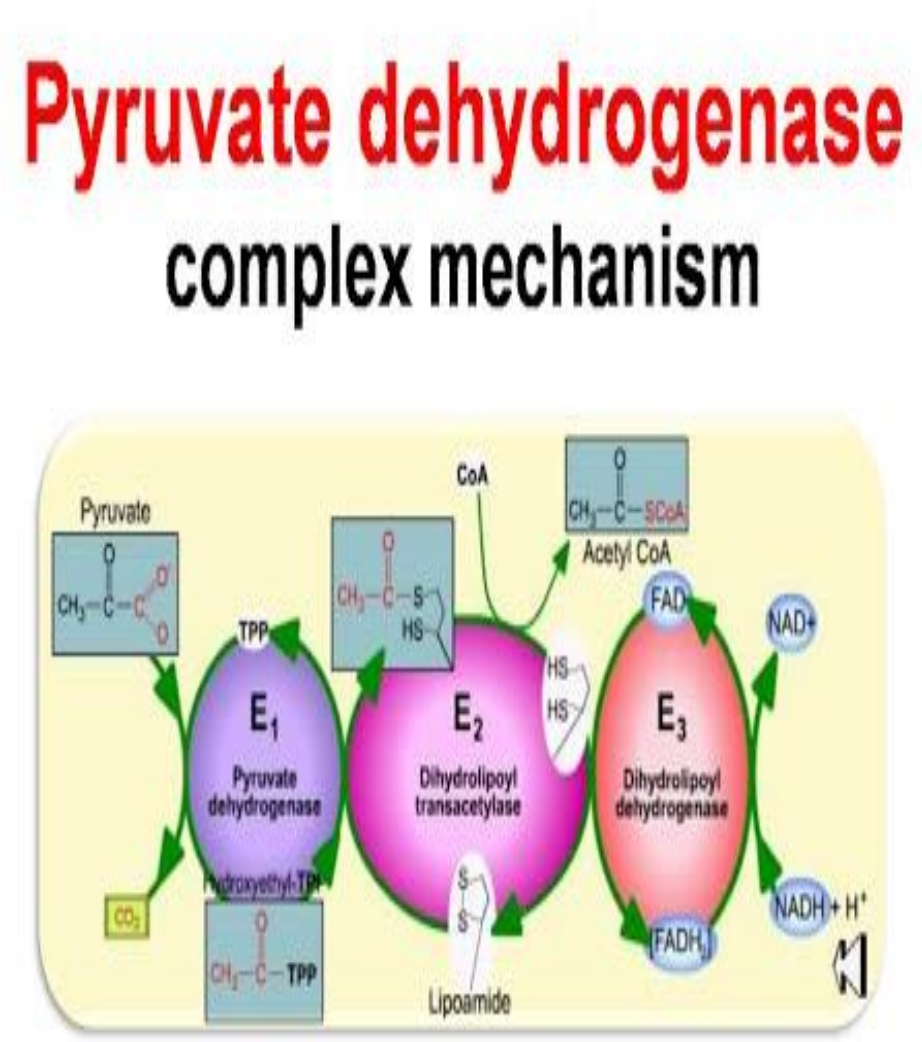
OXIDATION OF PYRUVATE TO ACETYL CoA

- Inside mitochondrial matrix , pyruvate is converted to acetyl COA by PDH complex.
- ***PDH complex is a multi enzyme complex.***



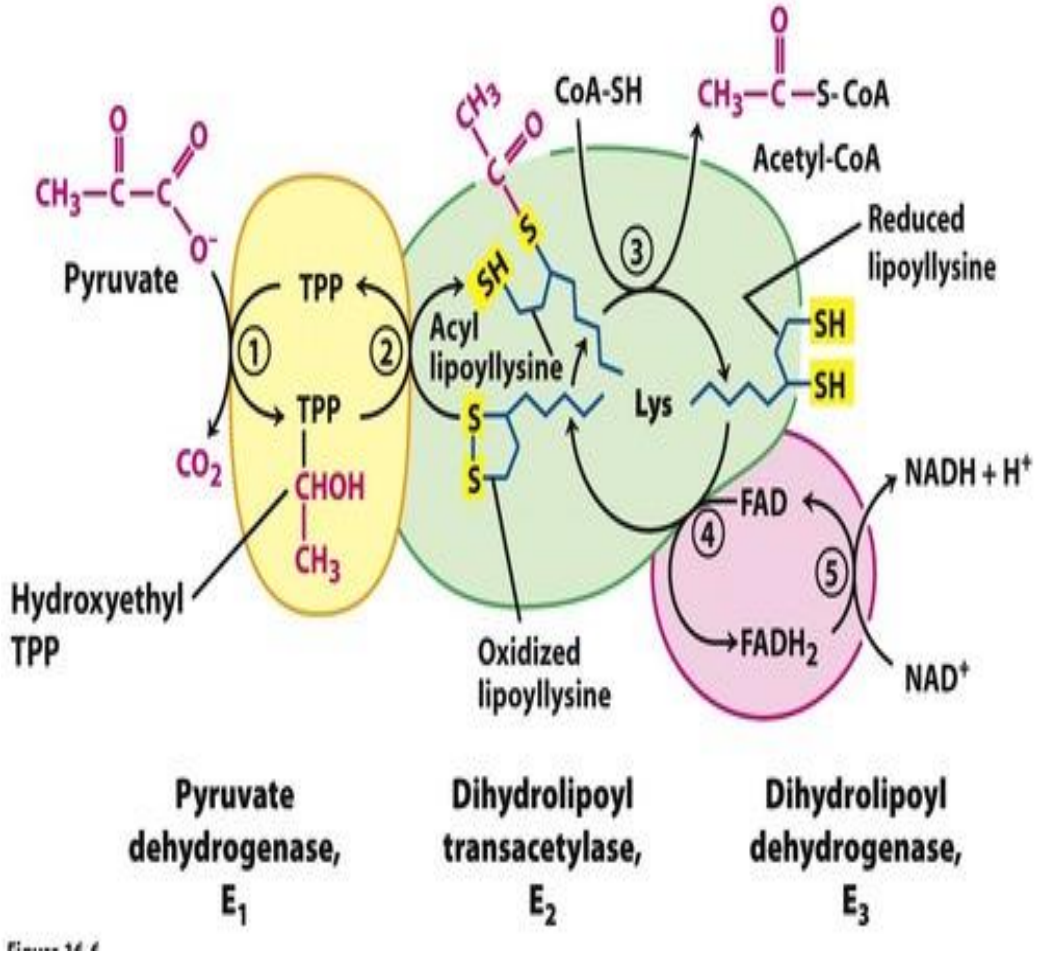
Pyruvate dehydrogenase complex

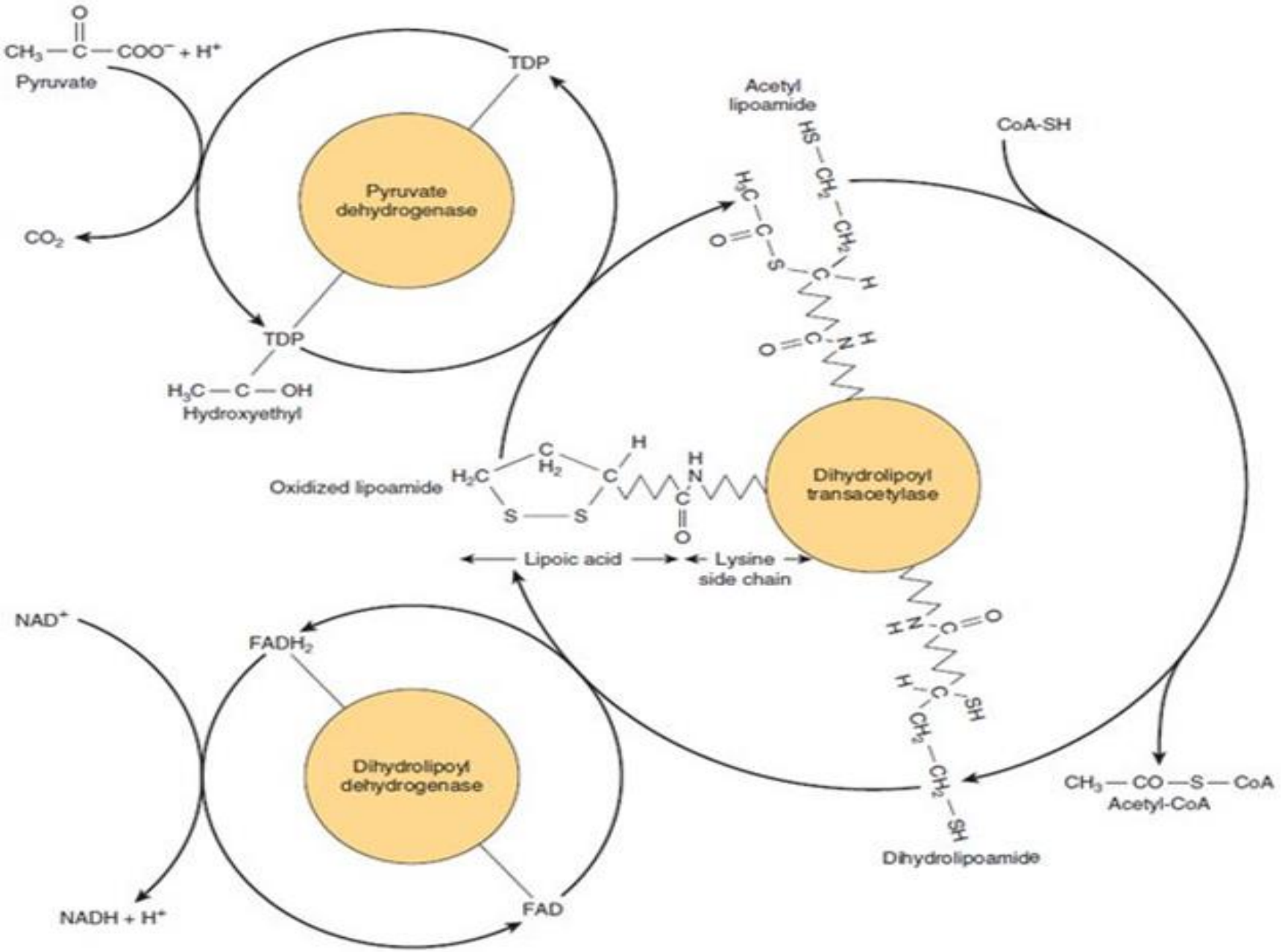
- It comprises of 3 enzymes
- ***Pyruvate dehydrogenase – E1***
- ***Dihydrolipoyl transacetylase – E2***
- ***Dihydrolipoyl dehydrogenase – E3***



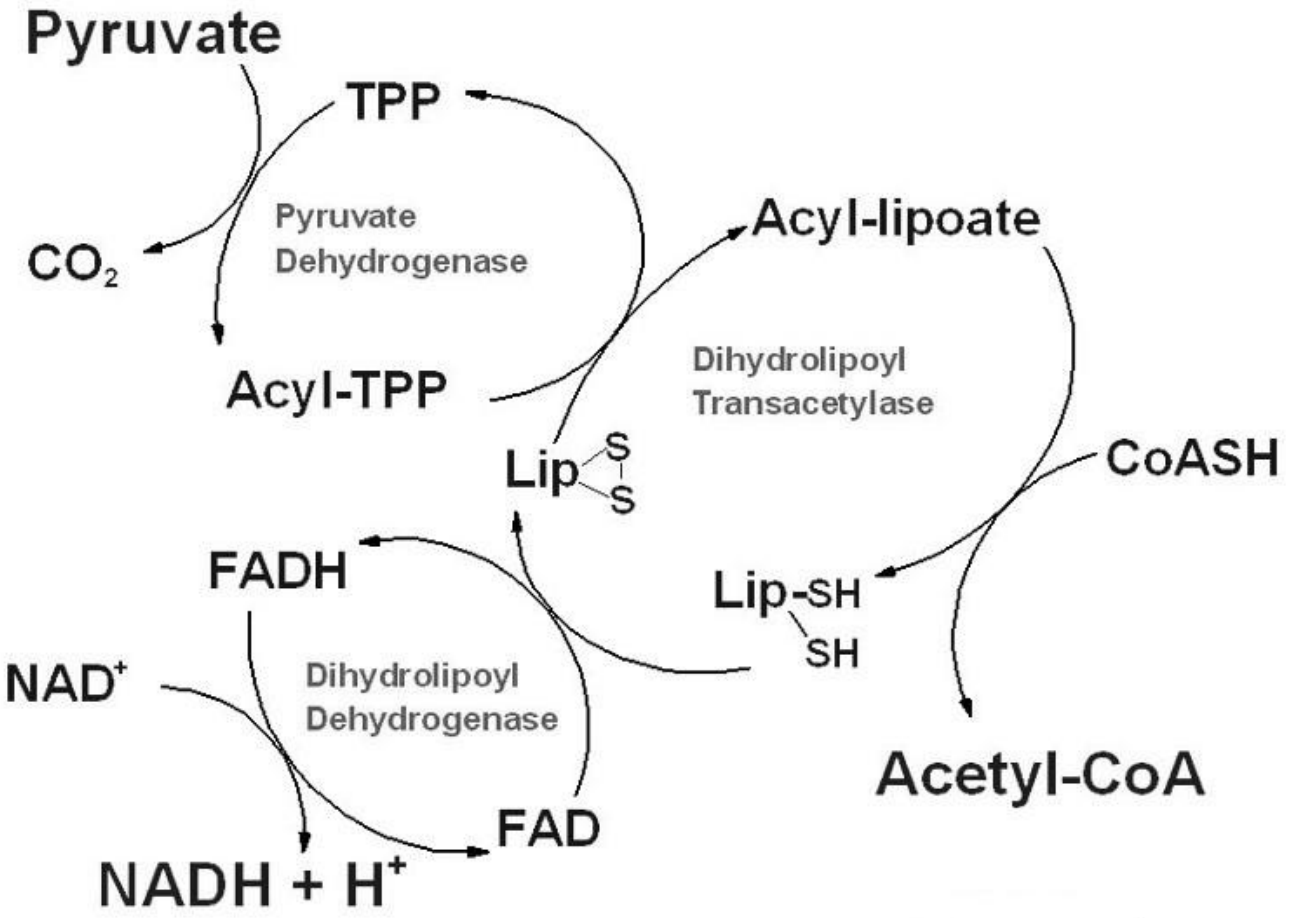
Coenzymes of pyruvate dehydrogenase complex

- The five co-enzymes involved are
- ***E1 _____ TPP***
- ***E2 _____ lipoate coenzyme A***
- ***E3 _____ FAD NAD***
- The complex also contains two tightly bound ***REGULATORY*** enzymes
- ***Pyruvate dehydrogenase kinase***
- ***Pyruvate dehydrogenase phosphatase***



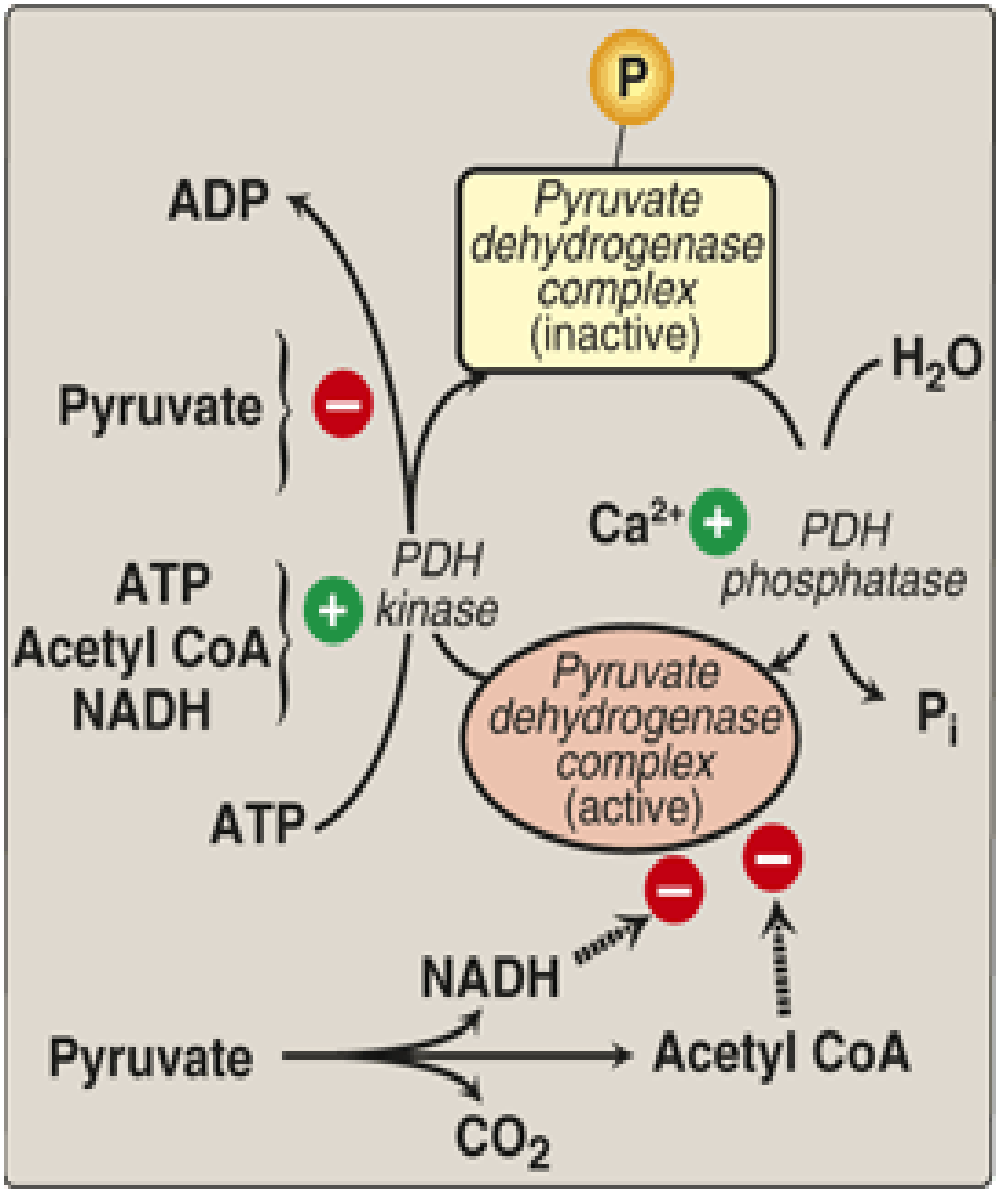

Pyruvate
TDP
Pyruvate dehydrogenase
CO_2
TDP
Hydroxyethyl
Acetyl lipoamide
CoA-SH
Oxidized lipoamide
Dihydrolipoyl transacetylase
Lipoic acid
Lysine side chain
NAD^+
$FADH_2$
Dihydrolipoyl dehydrogenase
$NADH + H^+$
FAD
Dihydrolipoamide
Acetyl-CoA

OXIDATION OF PYRUVATE TO ACETYL CoA



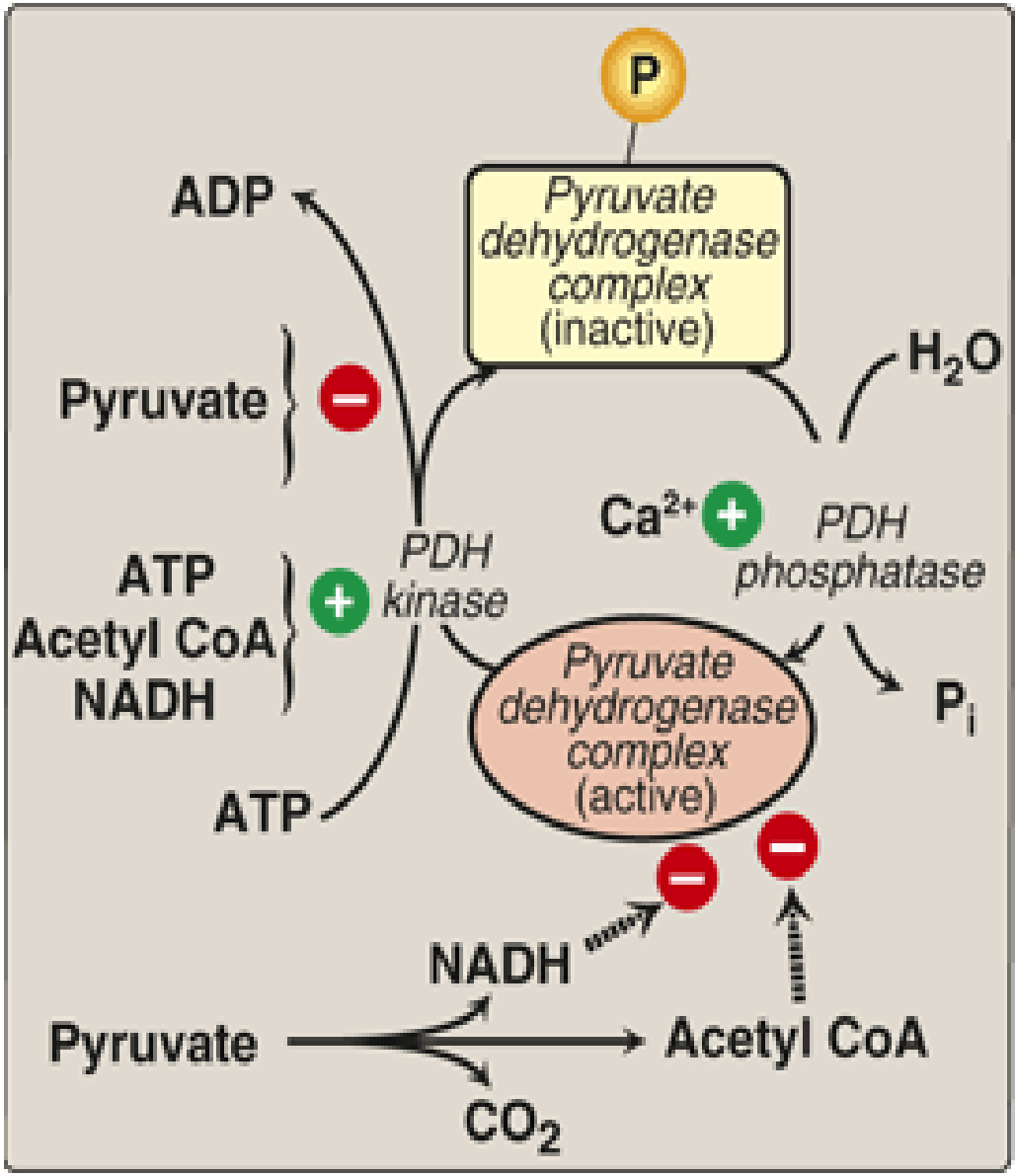
REGULATION OF PDH complex:

- PDH KINASE
- PDH PHOSPHATASE
- PDH kinase phosphorylates PDH complex and makes it inactive.
- PDH kinase itself is allosterically activated by ATP,ACETYL COA and NADH.
- Therefore in the presence of high energy signals PDH complex is turned off.



REGULATION OF PDH COMPLEX:

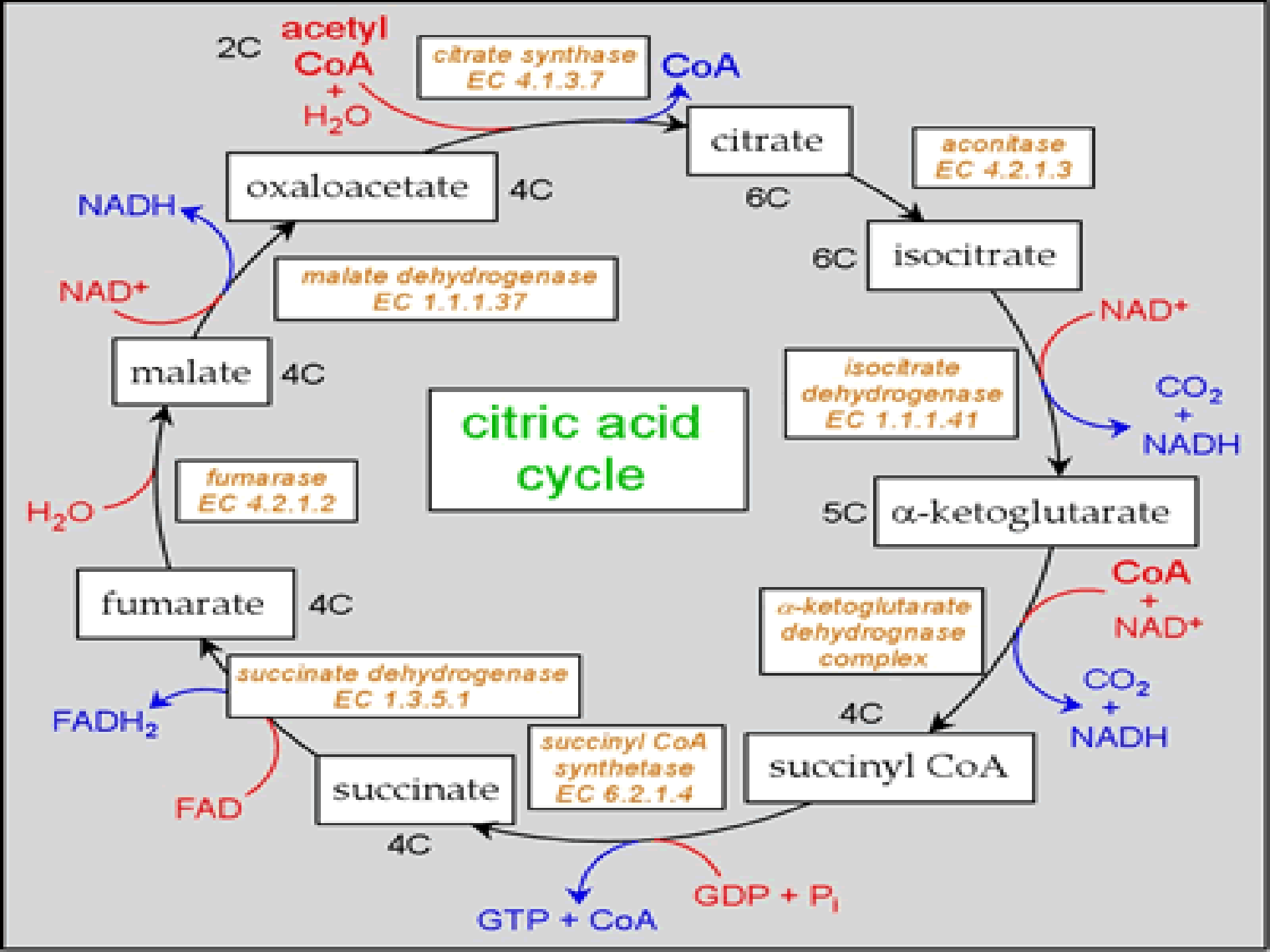
- Pyruvate is the potent inhibitor of PDH kinase.
- Elevated pyruvate concentration,E1 will be maximally active.
- Calcium is a potent activator of PDH phosphatase, stimulating E1 activity.



DEFICIENCY OF PYRUVATE DEHYDROGENASE

- Deficiency in **E1 --- congenital lactic acidosis**

- Inability to convert pyruvate to acetyl CoA
- Pyruvate is shunted to lactate by lactate dehydrogenase.
- Brain reliant on TCA for most of its energy
- Neuro degeneration
- Muscle spasticity
- In neonates --- early death


citric acid cycle
2C
acetyl CoA + H_2O
citrate synthase EC 4.1.3.7
CoA
citrate
6C
aconitase EC 4.2.1.3
isocitrate
6C
NAD+
isocitrate dehydrogenase EC 1.1.1.41
CO_2 + NADH
α-ketoglutarate
5C
CoA + NAD+
α-ketoglutarate dehydrognase complex
CO_2 + NADH
succinyl CoA
4C
succinyl CoA synthetase EC 6.2.1.4
GDP + P_i
GTP + CoA
succinate
4C
FAD
succinate dehydrogenase EC 1.3.5.1
$FADH_2$
fumarate
4C
fumarase EC 4.2.1.2
H_2O
malate
4C
malate dehydrogenase EC 1.1.1.37
NAD+
NADH
oxaloacetate
4C

THE CITRIC ACID CYCLE

- The Citric acid cycle also known as ***Kreb's cycle*** or ***Tricarboxylic acid cycle*** is the
- ***final common pathway*** for the oxidation of
- Carbohydrates
- Lipids
- Proteins, because ……

- glucose,fatty acids and most amino acids are metabolized to acetyl CoA or intermediates of the cycle.

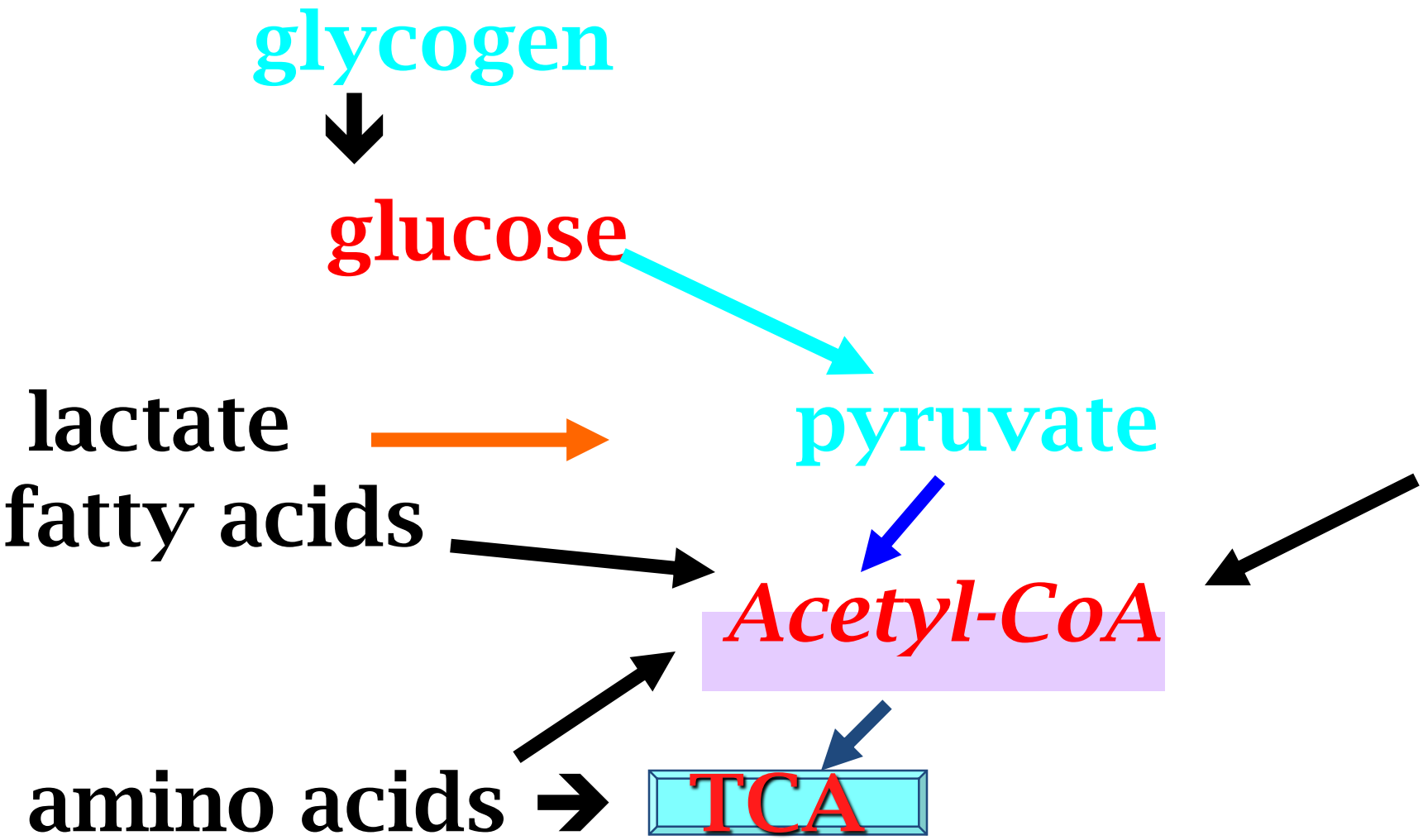
- Their carbon skeleton converted to CO2

- Majority of the ***energy*** required for production of ***ATP*** is provided by this oxidation

Biomedical importance of citric acid cycle

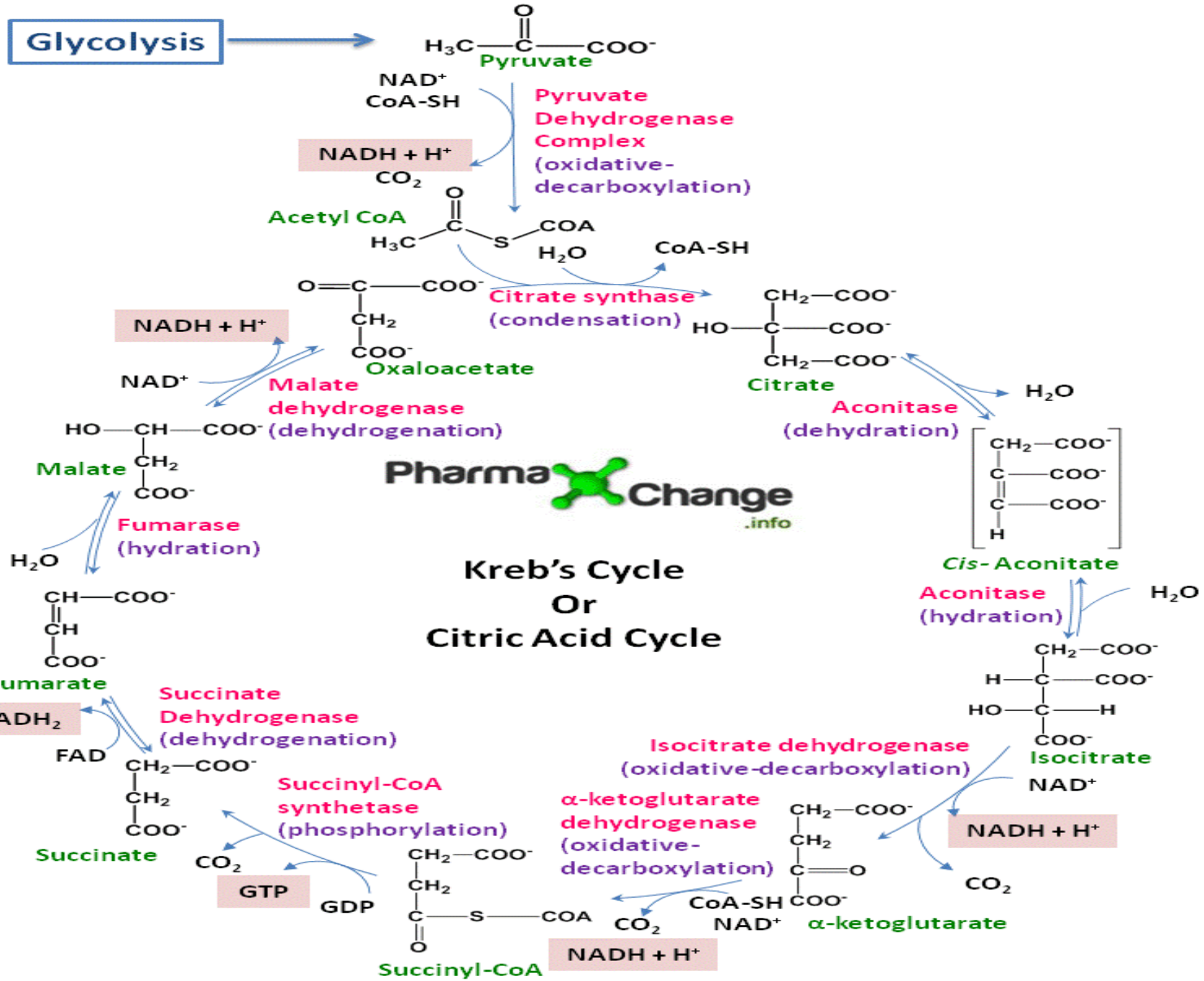
- Citric acid cycle essentially involves the oxidation of acetyl CoA to CO_2 and H_2O.
- About 65%-70% of the ATP is synthesized in citric acid cycle.
- This cycle utilizes about 2/3rd of oxygen consumed by the body.

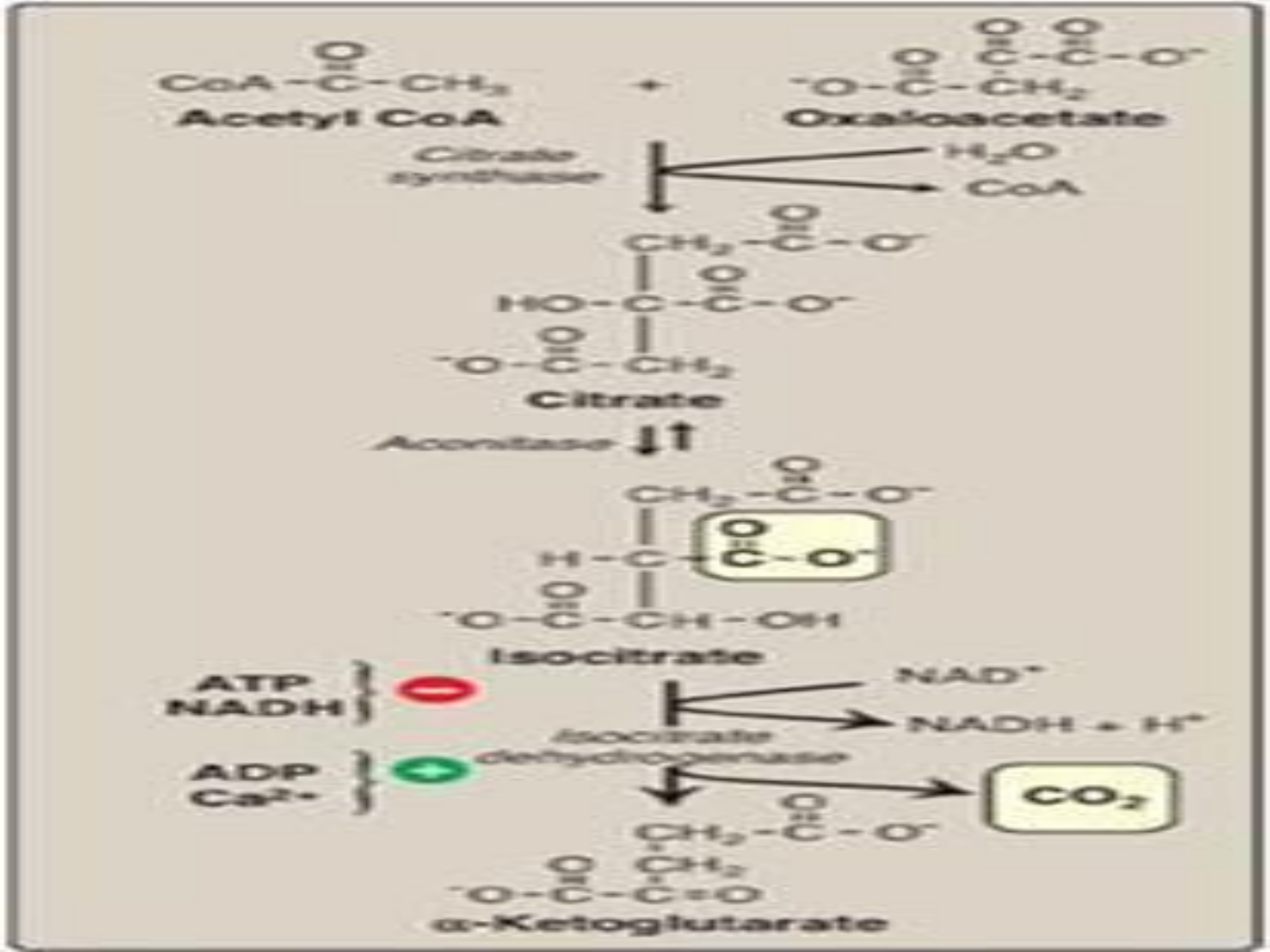
pathways yielding **Acetyl CoA**
for the TCA cycle



- TCA has central role in
- Gluconeogenesis
- Lipogenesis
- Interconversion of amino acids

- TCA is an aerobic pathway
- The TCA occurs entirely in the mitochondria
- It is in close proximity to the reactions of electron transport chain _____ oxidizes the reduced co-enzymes of TCA.


Glycolysis
Pyruvate
NAD+
CoA-SH
Pyruvate Dehydrogenase Complex (oxidative-decarboxylation)
NADH + H+
CO2
Acetyl CoA
COA
H2O
CoA-SH
Citrate synthase (condensation)
Oxaloacetate
NADH + H+
NAD+
Malate dehydrogenase (dehydrogenation)
Malate
Citrate
Aconitase (dehydration)
H2O
Fumarase (hydration)
H2O
Cis-Aconitate
Aconitase (hydration)
H2O
Fumarate
Succinate Dehydrogenase (dehydrogenation)
FADH2
FAD
Isocitrate dehydrogenase (oxidative-decarboxylation)
Isocitrate
NAD+
NADH + H+
CO2
α-ketoglutarate dehydrogenase (oxidative-decarboxylation)
Succinyl-CoA synthetase (phosphorylation)
Succinate
CO2
GTP
GDP
CoA-SH
NAD+
α-ketoglutarate
CO2
Succinyl-CoA
NADH + H+
PharmaXChange.info
Kreb's Cycle
Or
Citric Acid Cycle


Acetyl CoA
Oxaloacetate
Citrate synthase
H_2O
CoA
Citrate
Aconitase
Isocitrate
ATP
NADH
ADP
Ca^{2+}
NAD^+
$NADH + H^+$
Isocitrate dehydrogenase
CO_2
α-Ketoglutarate

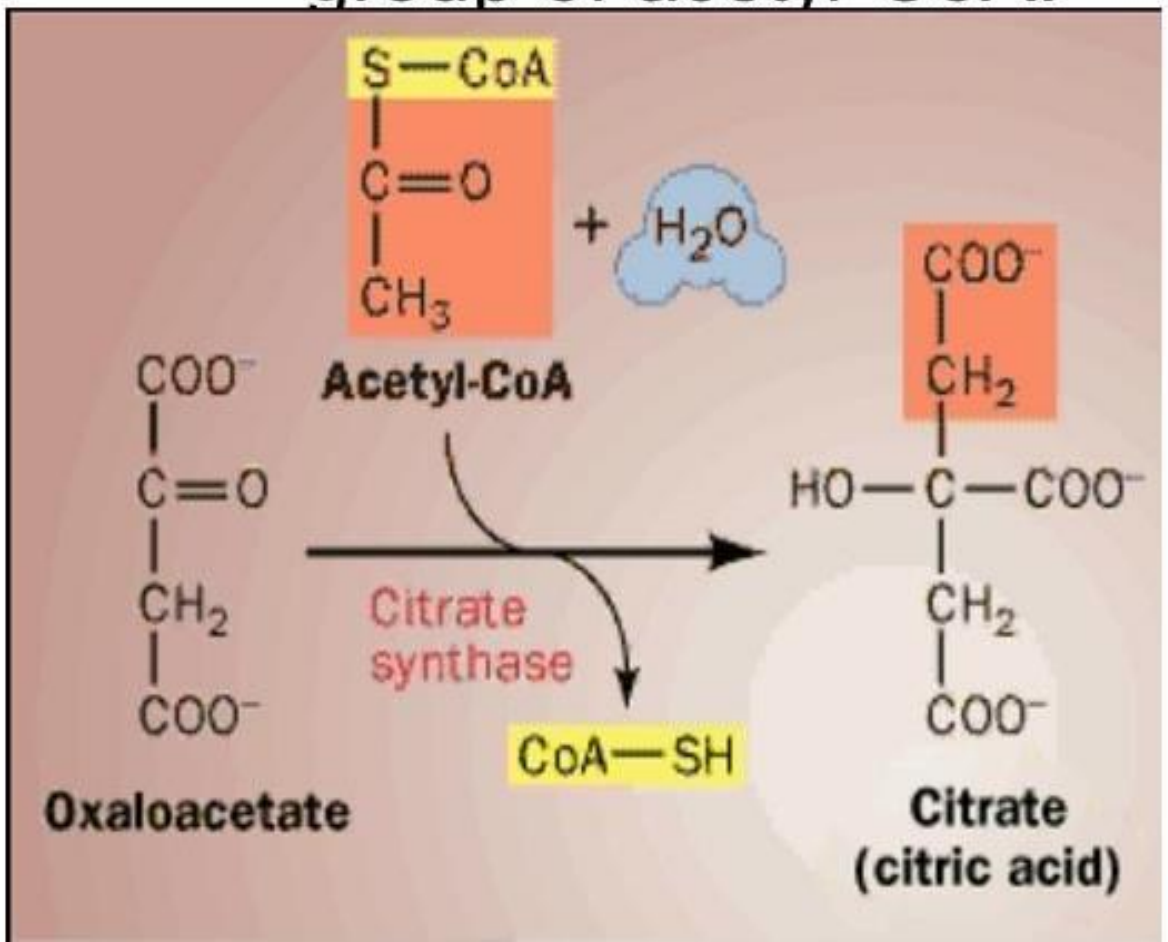
1- Condensing acetyl-CoA with oxaloacetate

- Condensation of a four-carbon unit, oxaloacetate, and a two-carbon unit, the acetyl group of acetyl CoA.

Enzyme = citrate synthase

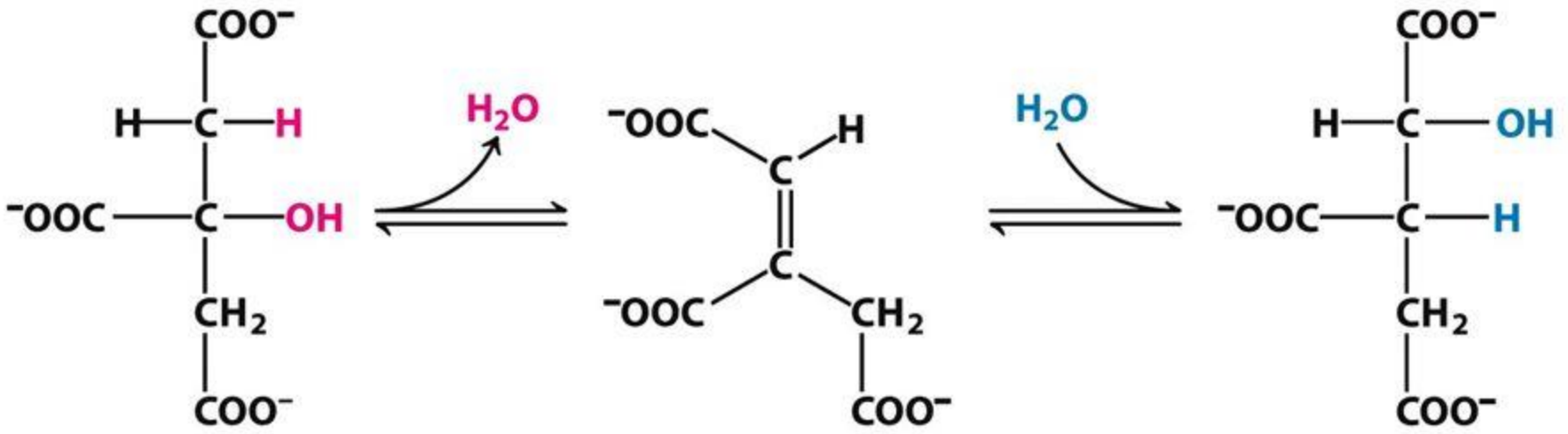
committed step in TCA cycle

◆ highly exergonic bond of acetyl CoA



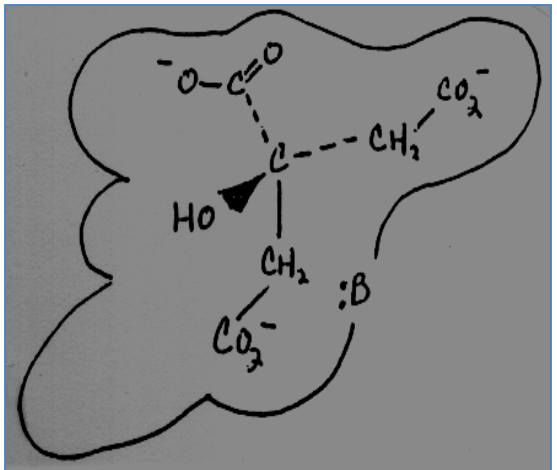
Citrate to Isocitrate Conversion via Aconitase

Hydroxyl shift for subsequent oxidative decarboxylation

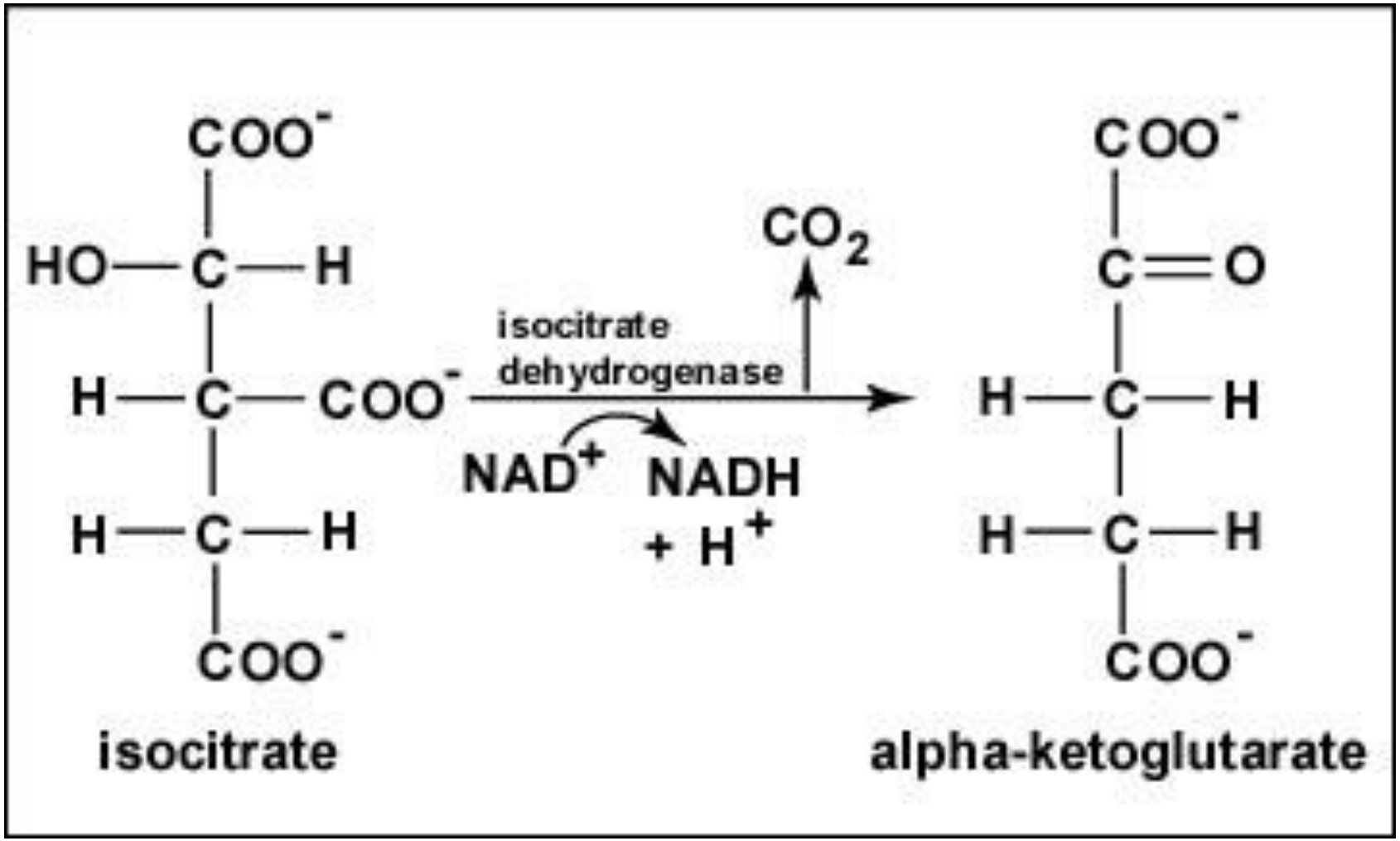


Citrate ***cis*-Aconitate** **Isocitrate**

Formation of isocitrate occur in two steps dehydration followed by hydration through formation of cis-aconitate.

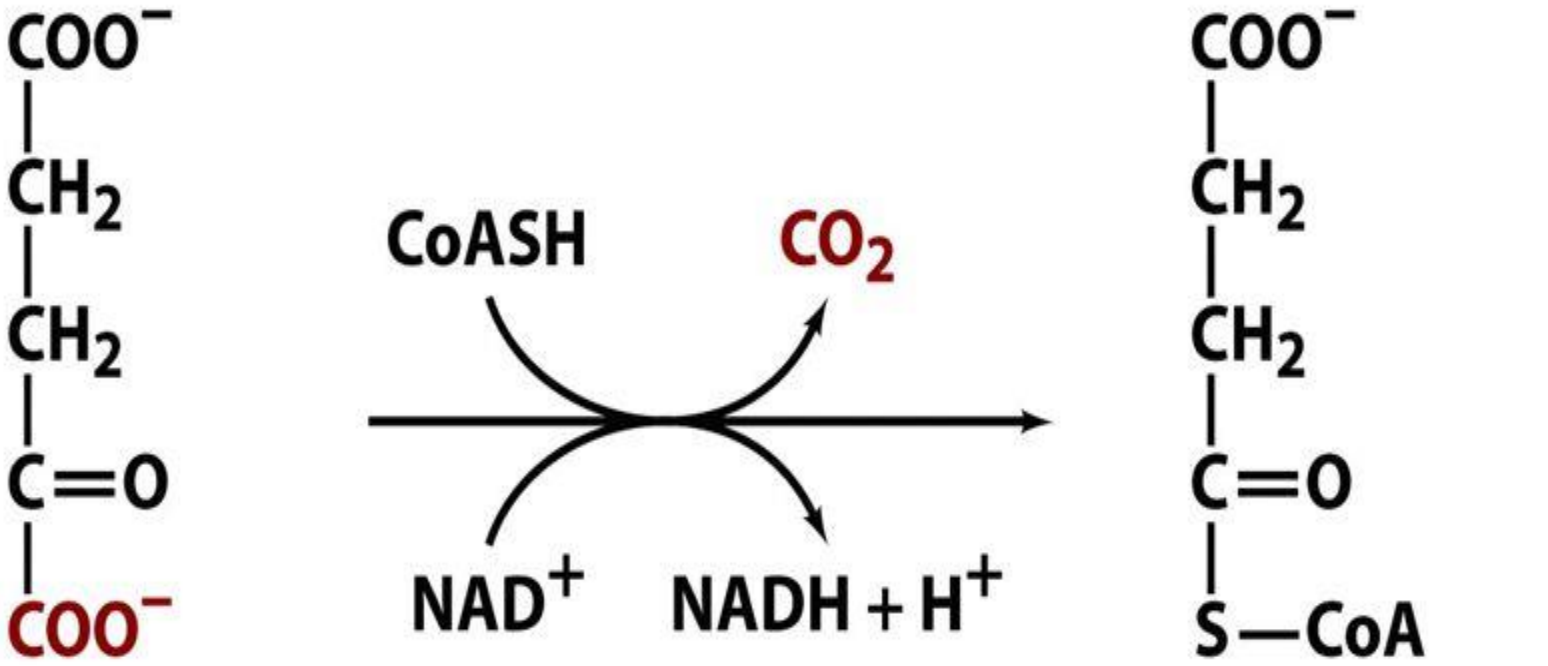


3- Oxidation of iscoitrate to α-ketoglutarate



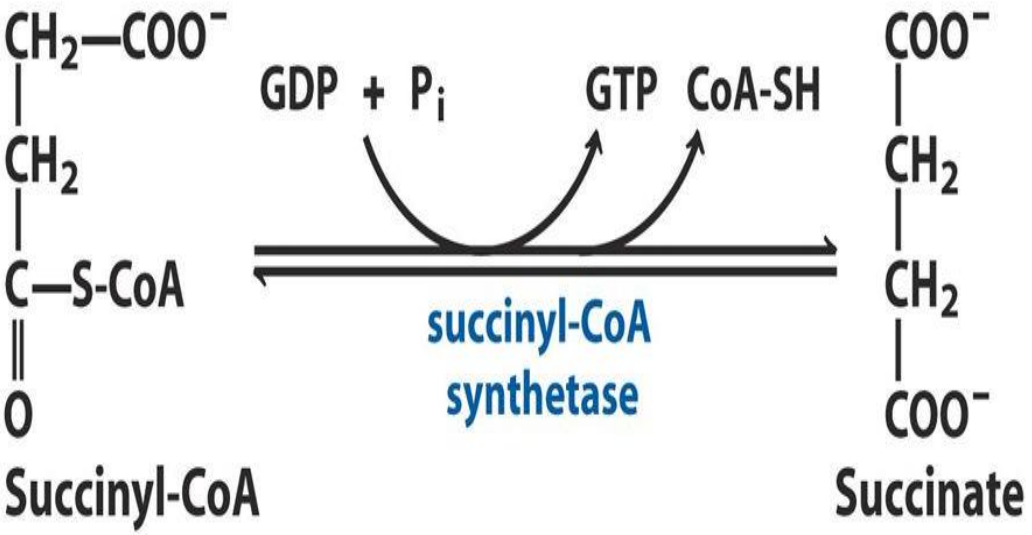
Step 4: α-ketoglutarate → succinyl-CoA

The enzyme is α-ketoglutarate dehydrogenase, which resembles and uses some subunits of the pyruvate dehydrogenase complex



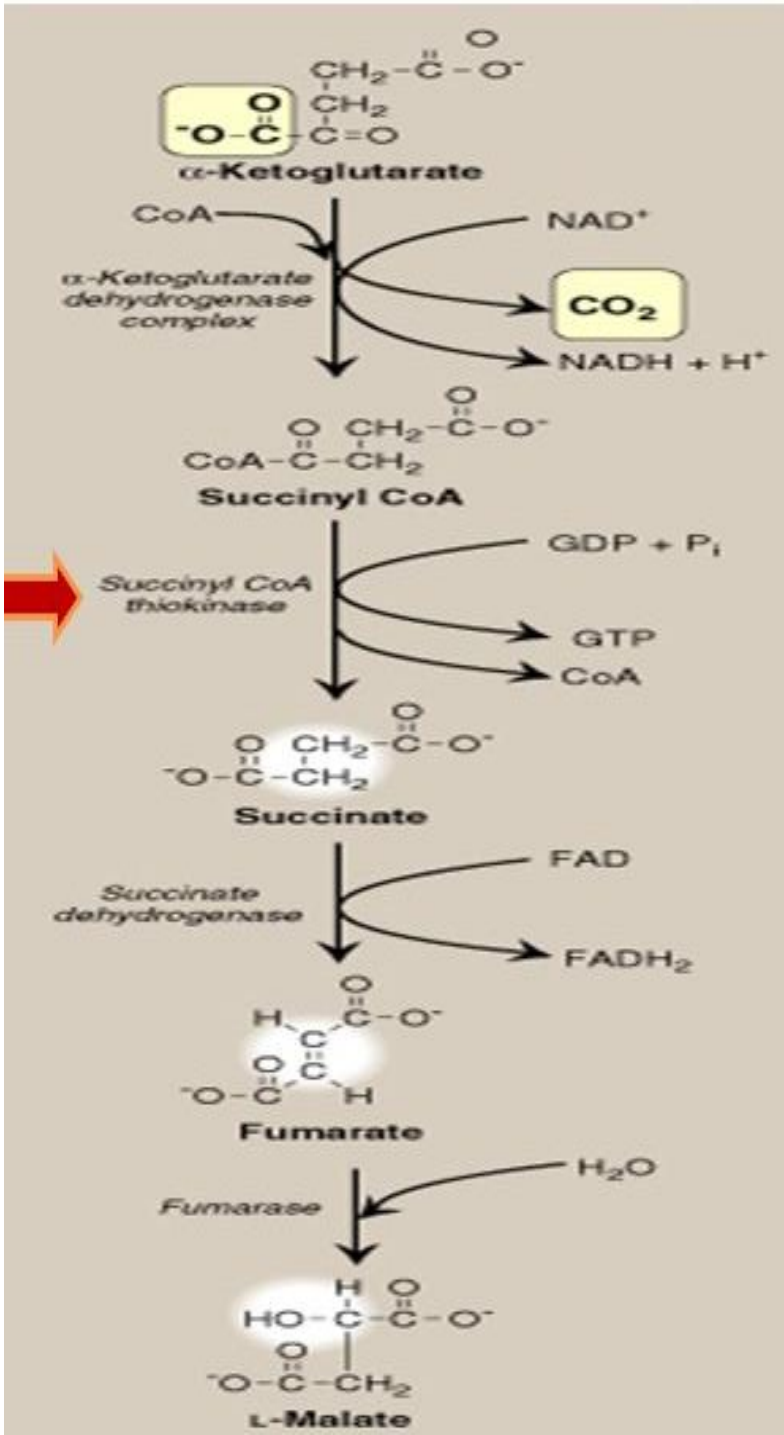
α-Ketoglutarate **Succinyl-CoA**

Conversion of Succinyl-CoA to Succinate



$\Delta G'^{\circ} = -2.9$ kJ/mol

Substrate level phosphorylation
-- GTP is equivalent to ATP.

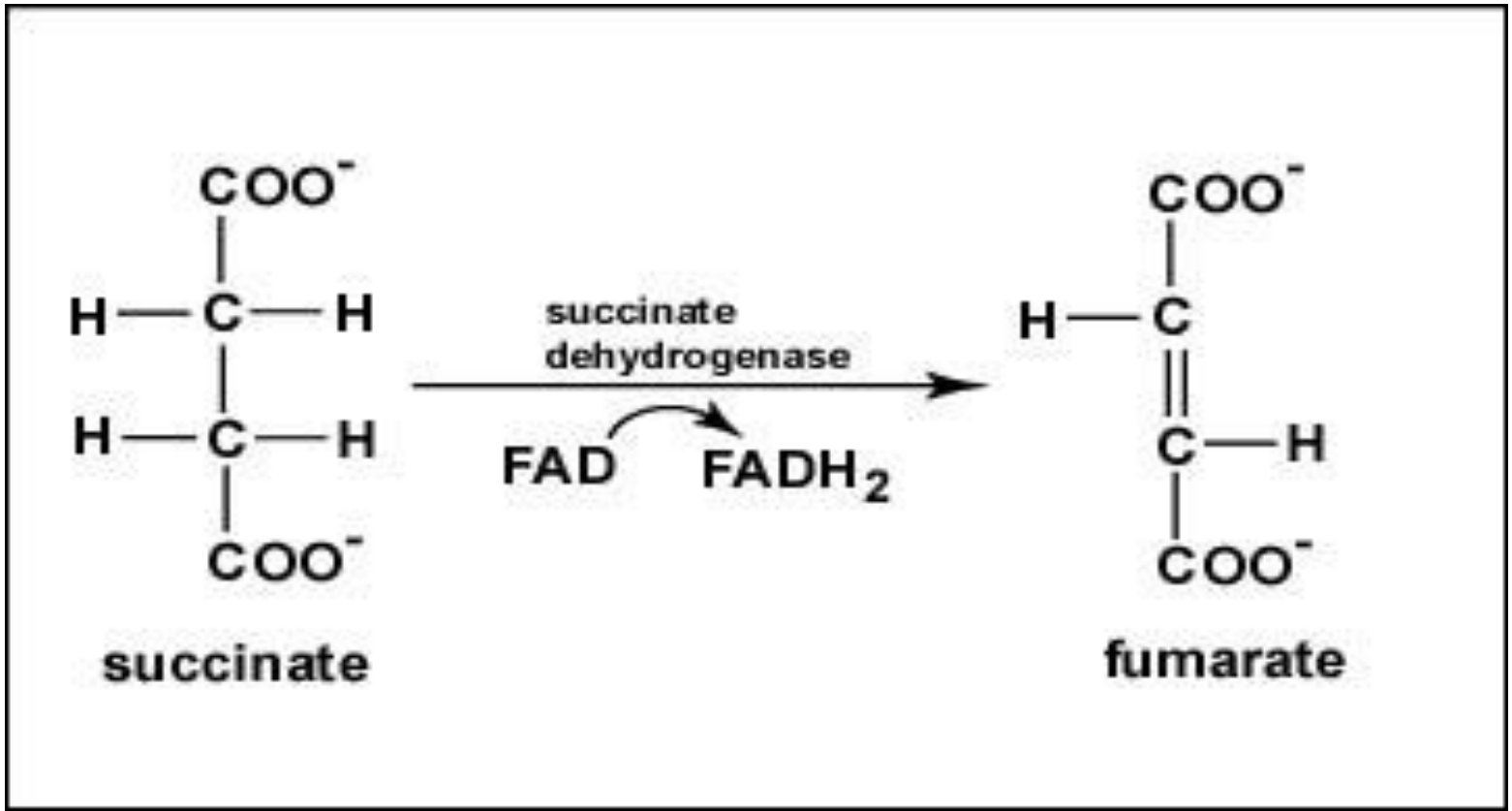


Oxidation of succinate to fumarate

Enzyme = succinate dehydrogenase, bound to inner mit.memb.

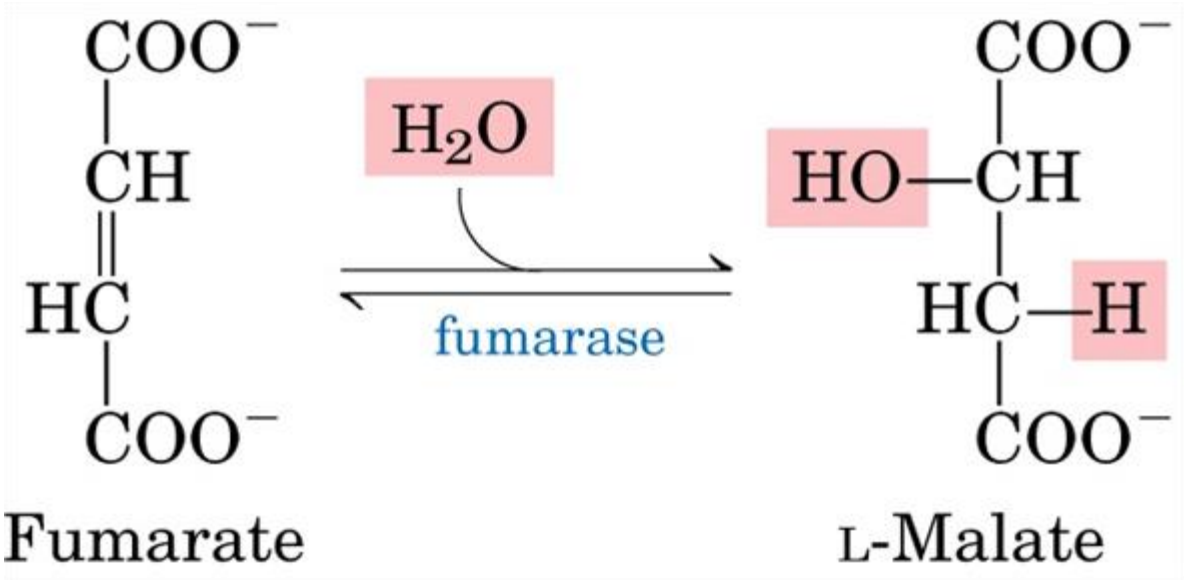
has FAD & Fe-S protein.

•a *dehydrogenation* rxn involving transfer of H from substrate to flavoprteins instead of NAD.

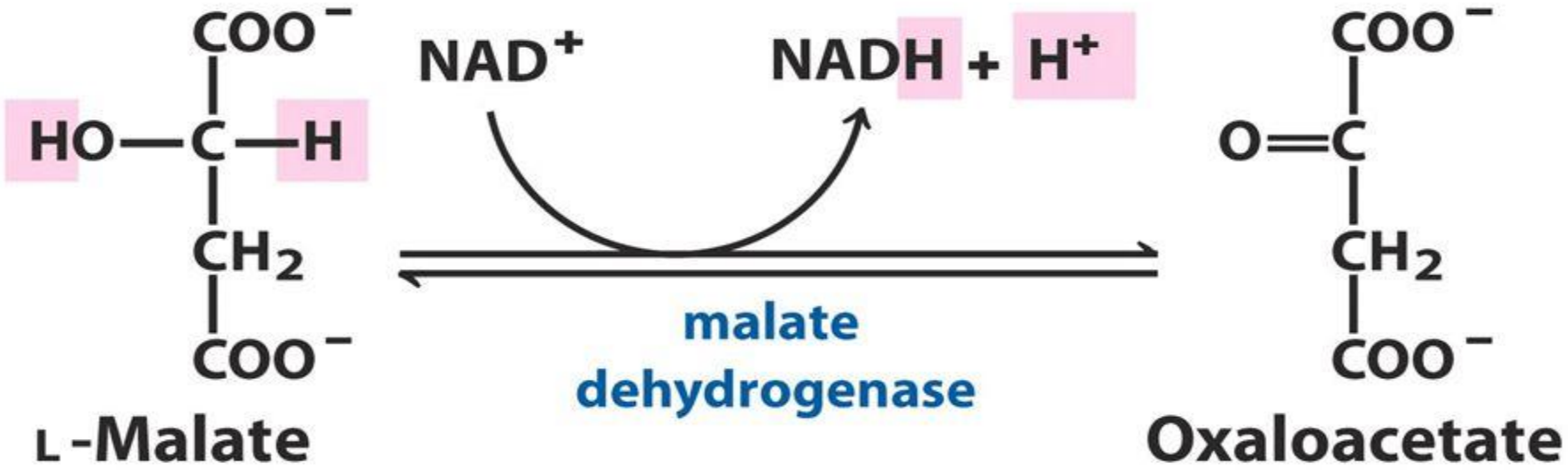


Hydration.

Enzyme = fumarase



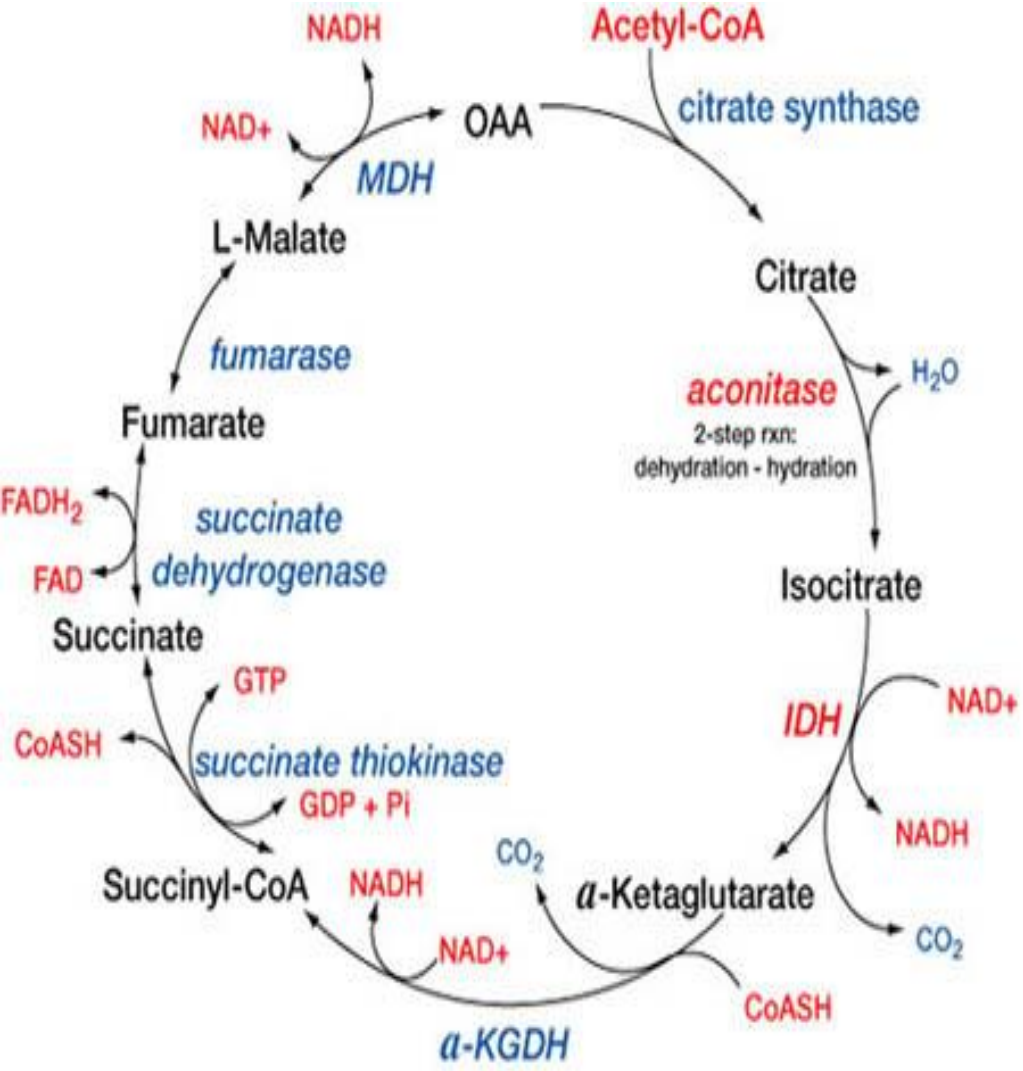
Oxidation of Malate to Oxaloacetate



Enzyme = malate dehydrogenase $\Delta G'^{\circ} = 29.7$ kJ/mol

fourth oxidation; another pair of electrons is made available in NADH.

ENERGY PRODUCED BY THE TCA



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

ROLE OF VITAMINS IN THE TCA

- Four vitamins belonging to vitamin B complex are essential for the TCA cycle

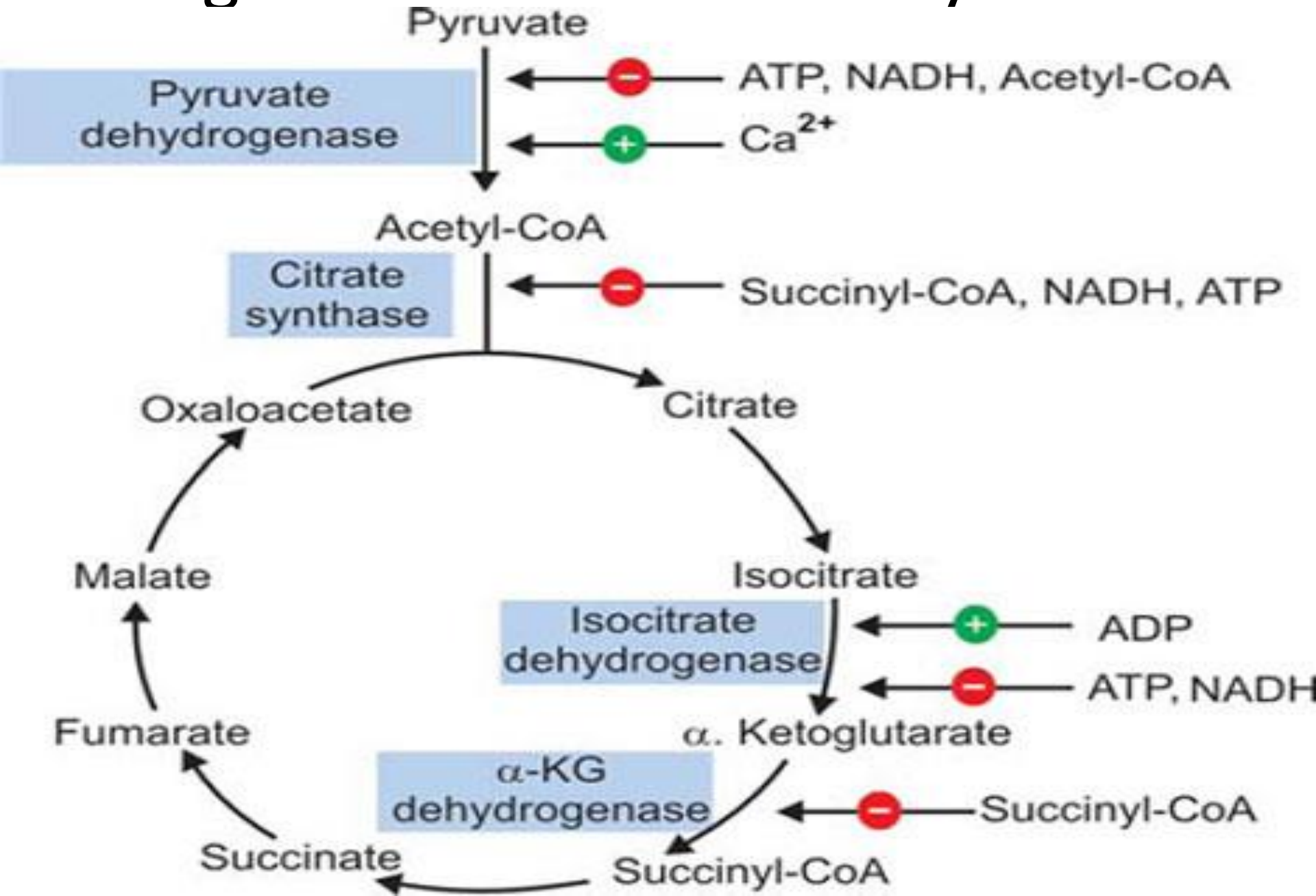
- ***Riboflavin*** : in the form of ***FAD*** _____
  co-factor for ***succinate dehydrogenase***

- ***Niacin*** : in the form of ***NAD*** _____ electron acceptor for *isocitrate, alpha-ketoglutarate and malate dehydrogenases*

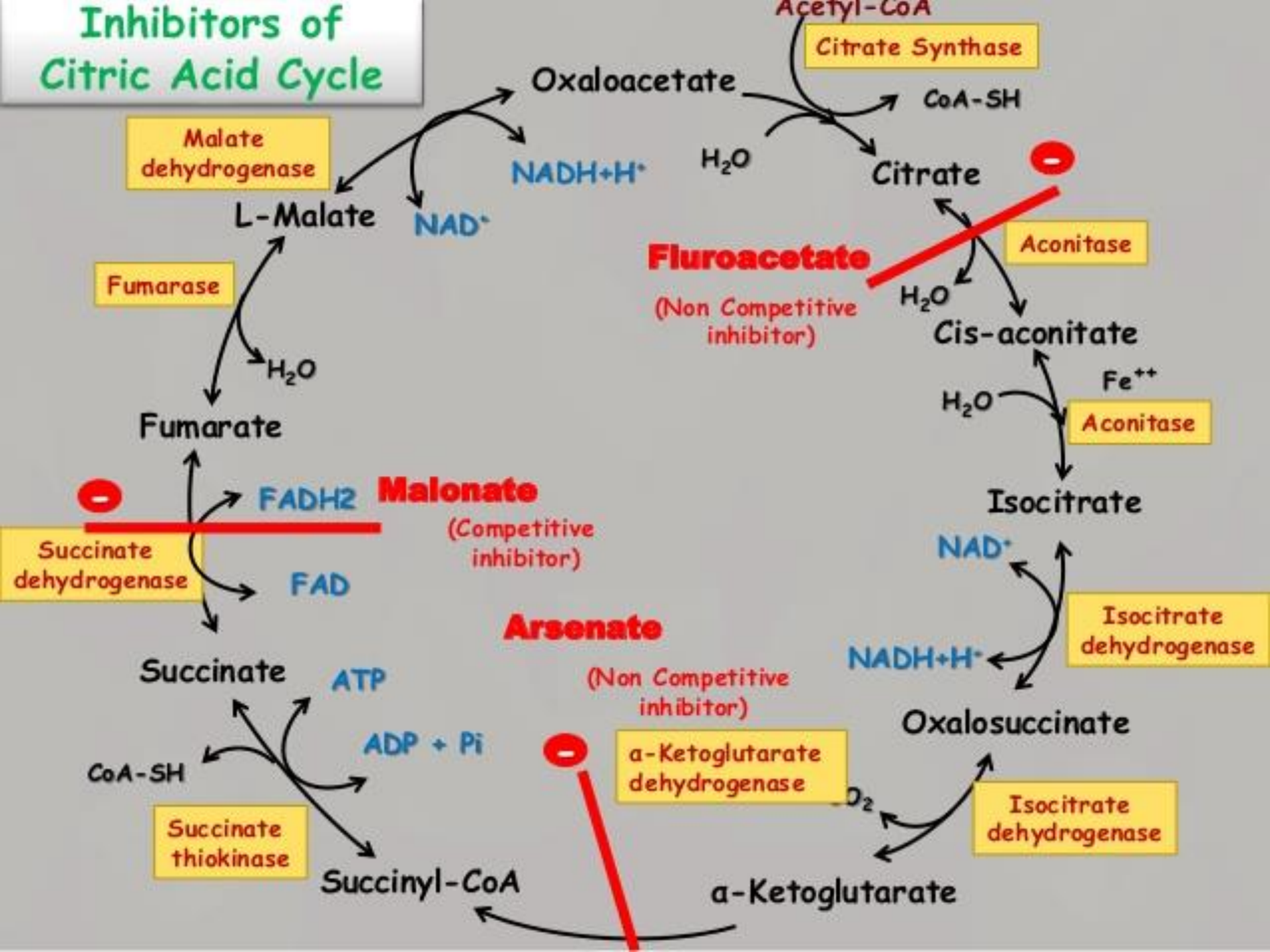
- ***Thiamin (vit B1)*** : as ***thiamin di-phosphate*** which is the co-enzyme for decarboxylation in ***the alpha-ketoglutarate dehydrogenase rxn***

- ***Pantothenic acid*** : as part of ***coenzyme A***,the co-factor attached to active carboxylic acid residues such as ***acetyl- CoA and succinyl-CoA***

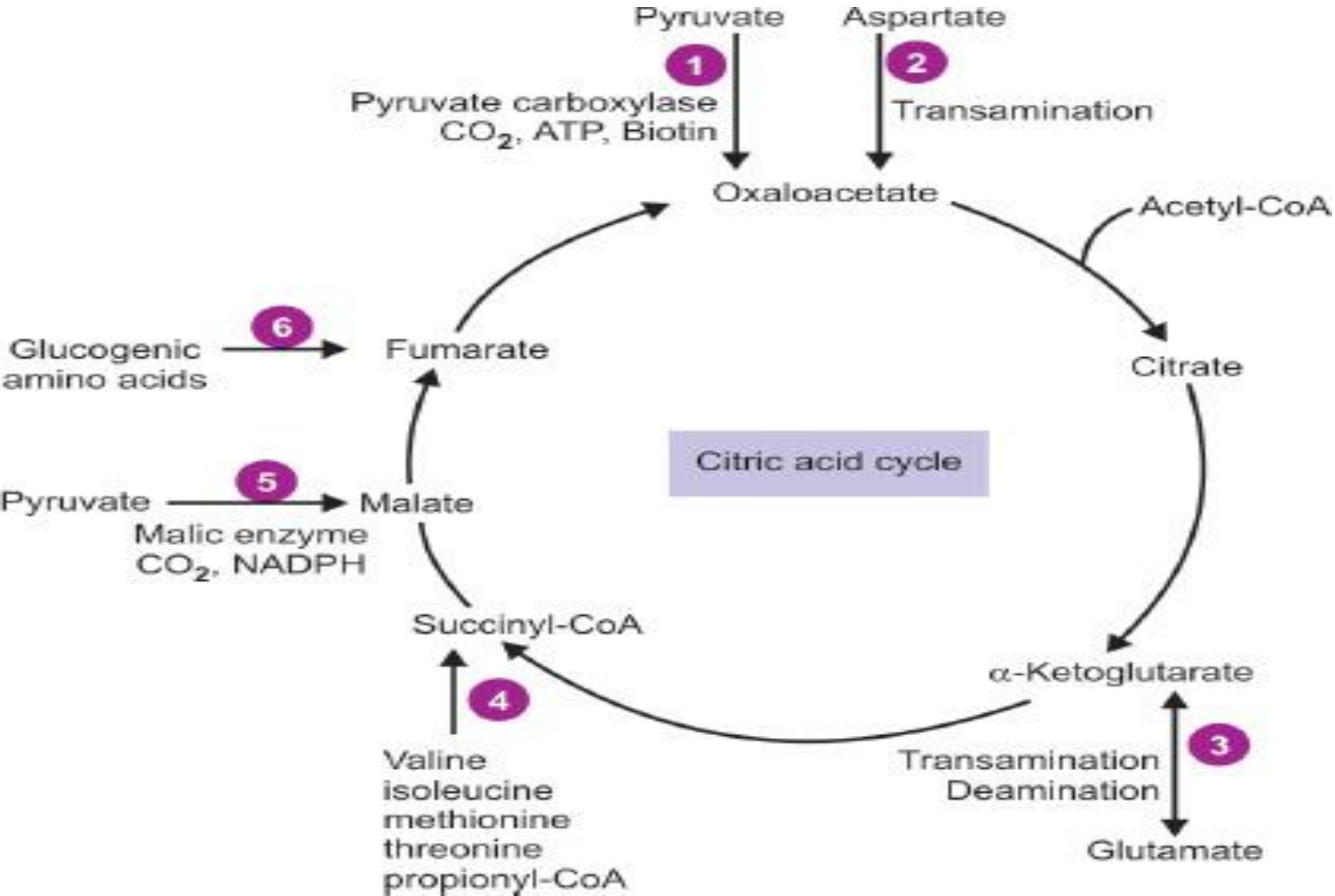
Regulation of citric acid cycle



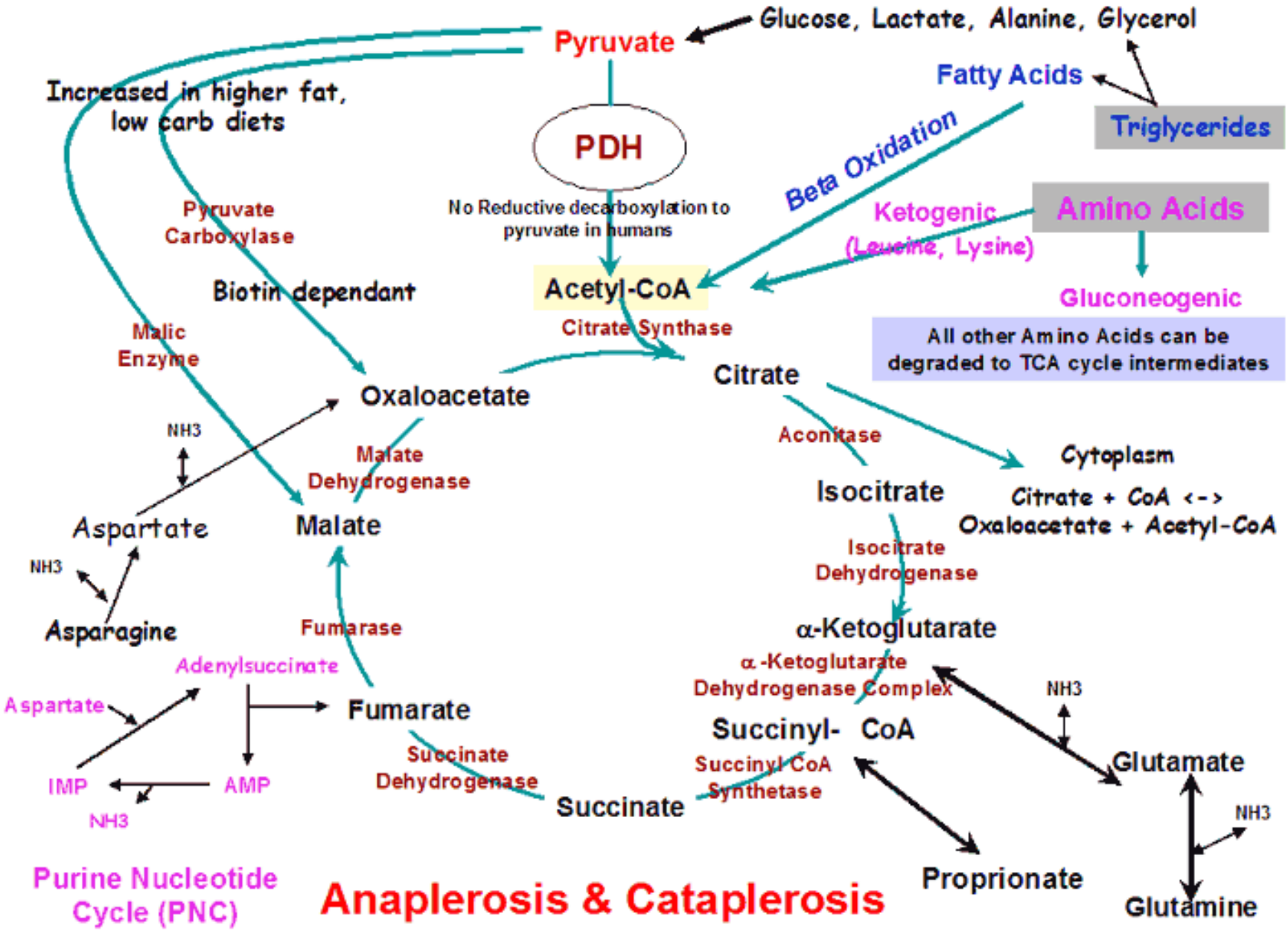
Inhibitors of Citric Acid Cycle



Anaplerotic reactions



Amphibolic nature of citric acid cycle




Thank
You