Citric Acid Cycle

TRICARBOXYLIC ACID CYCLE

Names:

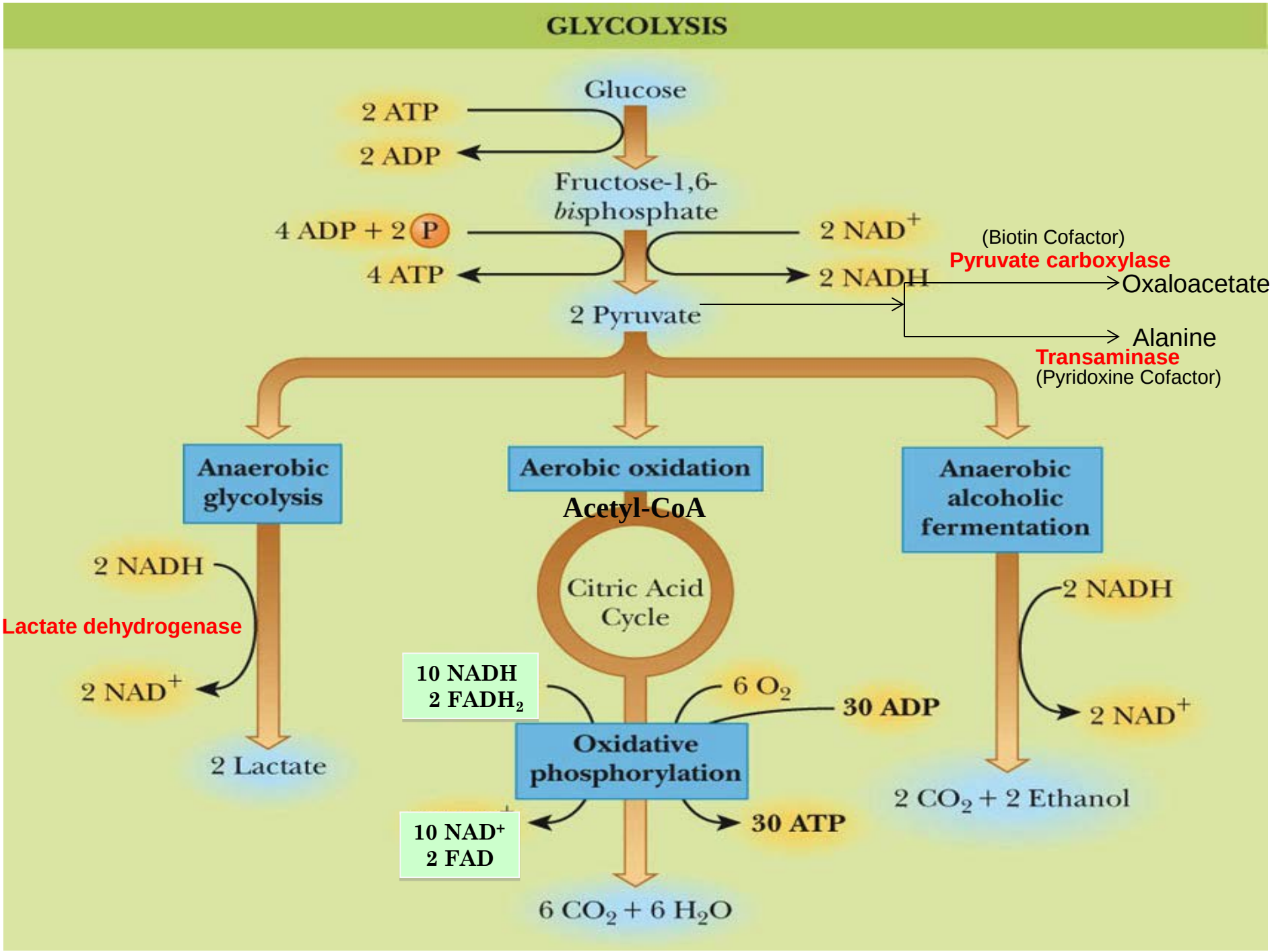
Citric Acid Cycle

Tricarboxylic Acid Cycle

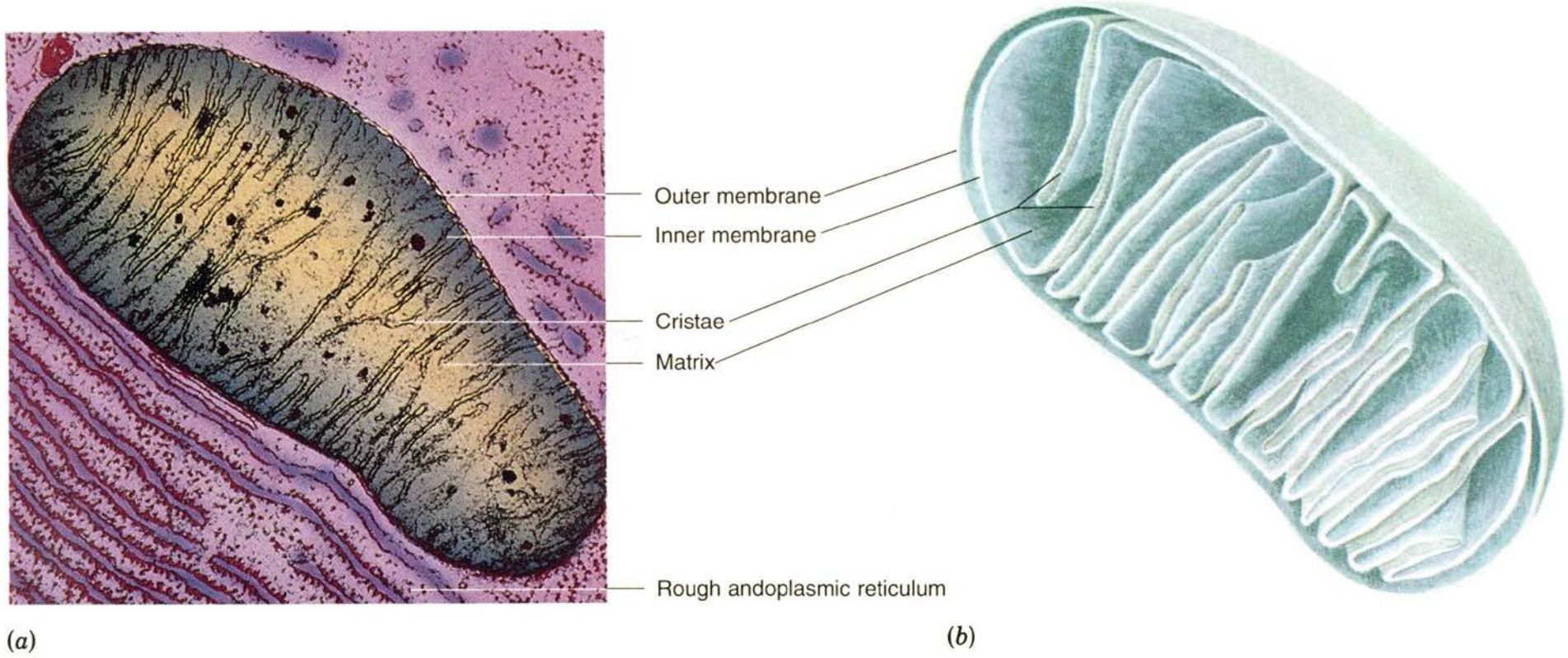
Krebs Cycle

Hans Adolf Krebs

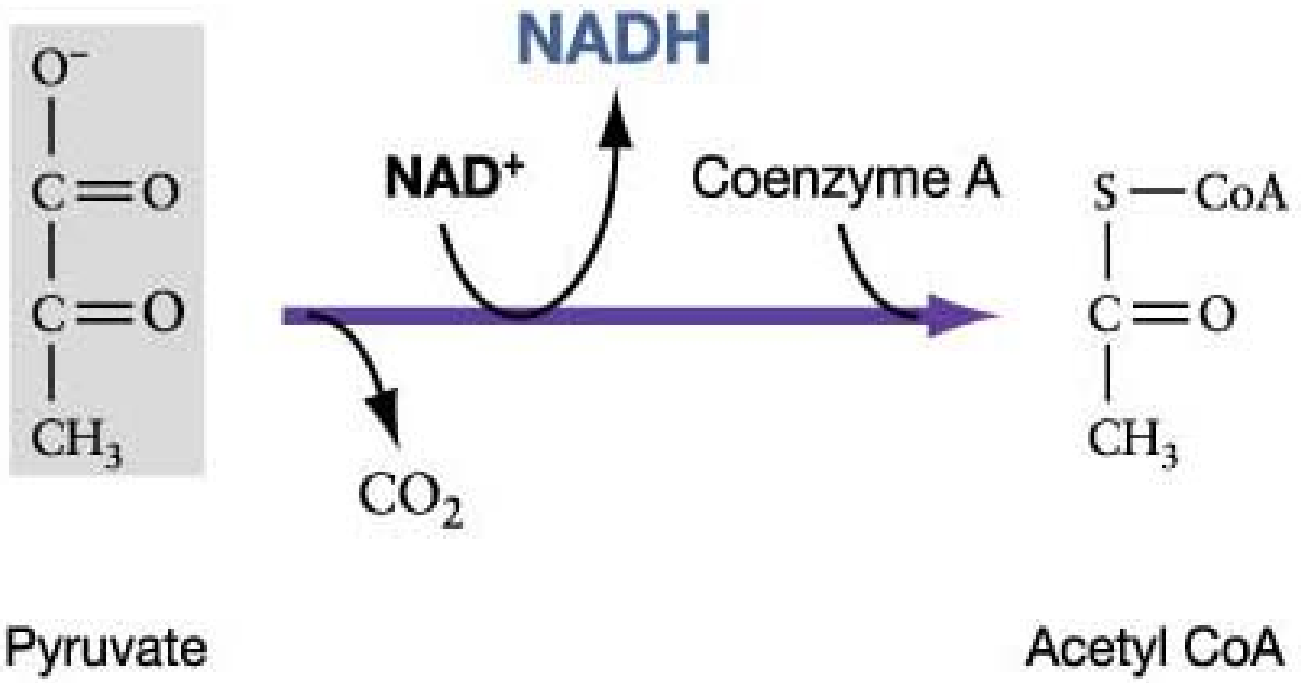
Biochemist; born in Germany. Worked in Britain. His discovery in 1937 of the 'Krebs cycle' of chemical reactions was critical to the understanding of cell metabolism and earned him the 1953 Nobel Prize for Physiology or Medicine.


GLYCOLYSIS
Glucose
2 ATP
2 ADP
Fructose-1,6-bisphosphate
4 ADP + 2 P
4 ATP
2 NAD+
2 NADH
(Biotin Cofactor)
Pyruvate carboxylase
Oxaloacetate
2 Pyruvate
Alanine
Transaminase
(Pyridoxine Cofactor)
Anaerobic glycolysis
Aerobic oxidation
Anaerobic alcoholic fermentation
Acetyl-CoA
2 NADH
Lactate dehydrogenase
2 NAD+
2 Lactate
Citric Acid Cycle
10 NADH
2 FADH2
6 O2
30 ADP
Oxidative phosphorylation
10 NAD+
2 FAD
30 ATP
6 CO2 + 6 H2O
2 NADH
2 NAD+
2 CO2 + 2 Ethanol

The citric acid cycle enzymes are found in the matrix of the mitochondria (with one exception)



Pyruvate dehyrogenase



Pyruvate dehyrogenase

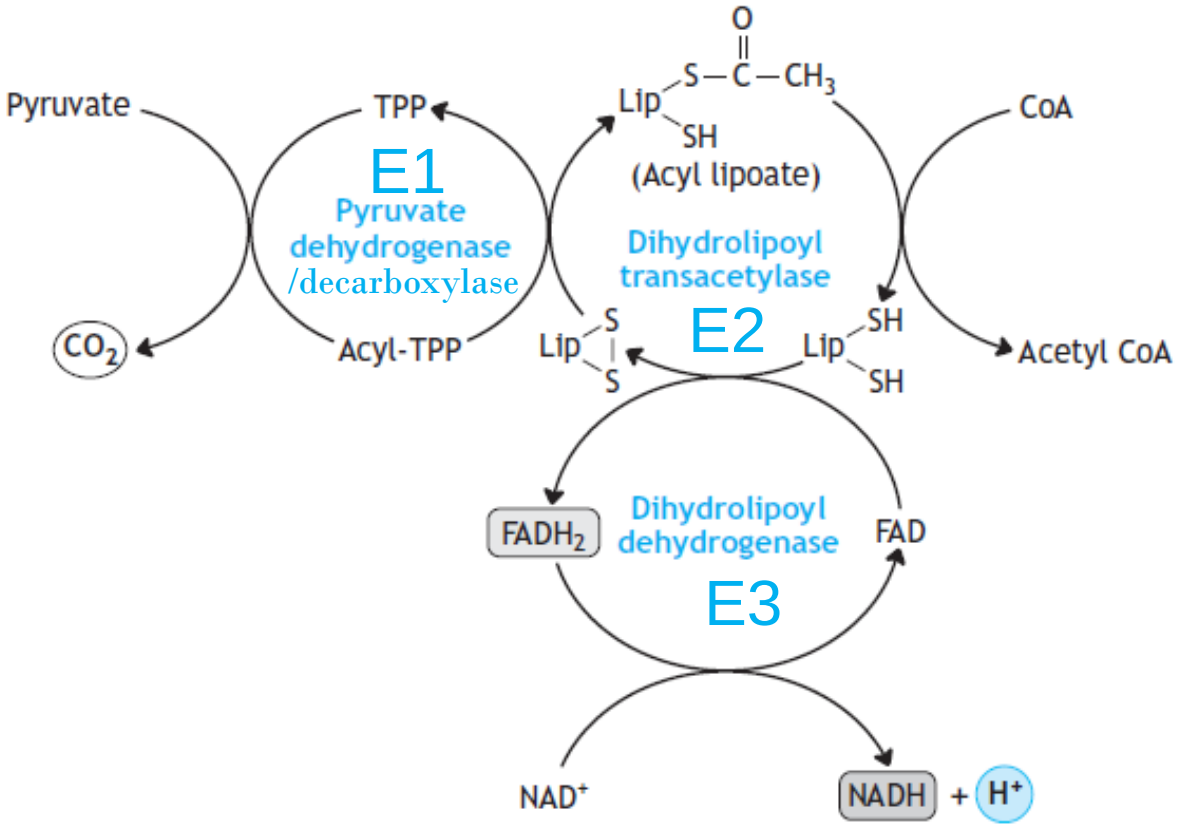


Figure 7–1. Conversion of pyruvate to acetyl CoA by the pyruvate dehydrogenase complex. The three enzymes, pyruvate dehydrogenase, dihydrolipoyl transacetylase, and dihydrolipoyl dehydrogenase, exist in a complex associated with the mitochondrial matrix. Each enzyme requires at least one coenzyme that participates in the reaction. TPP, thiamine pyrophosphate; Lip, lipoic acid; CoA, coenzyme A.

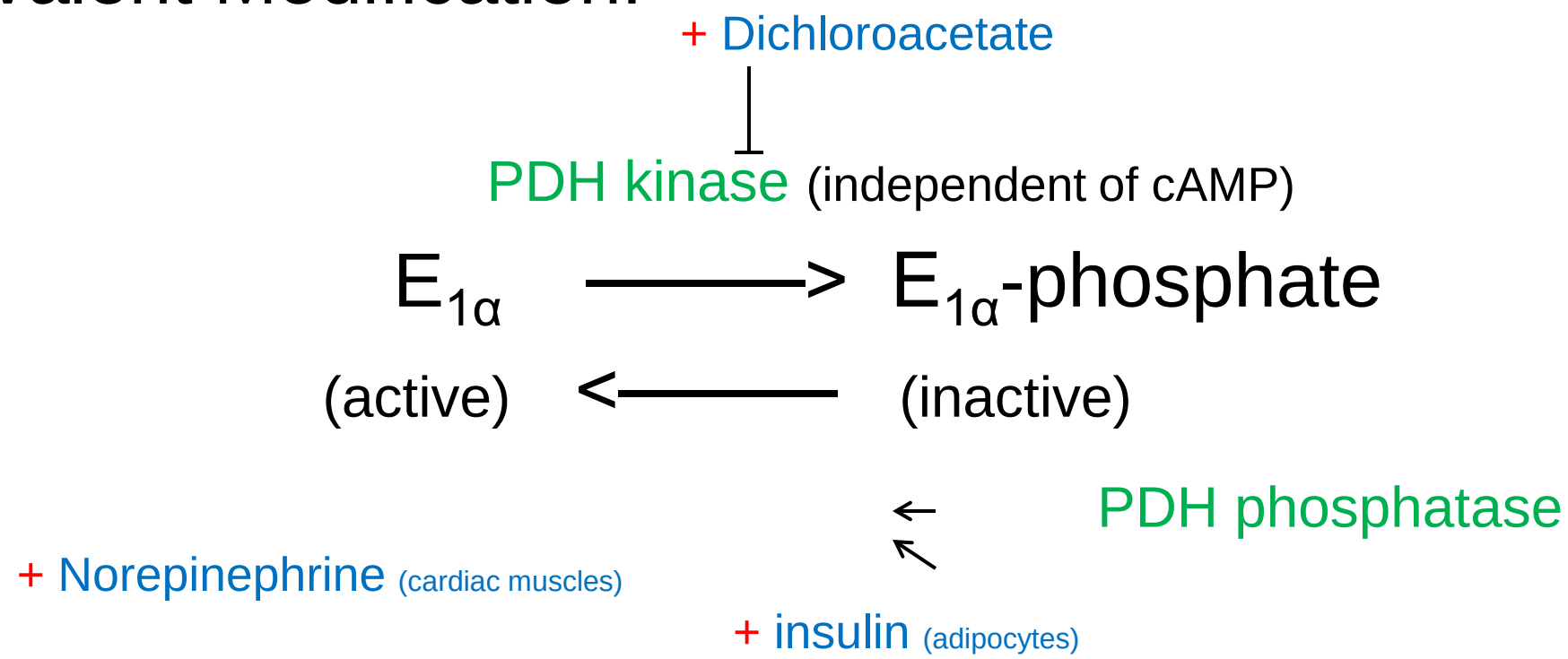
Five cofactors (derived from vitamins) participate in the reaction

Cofactor	**Vitamin (required in human nutrition)**
Thiamine pyrophosphate (TPP) (E_1)	thiamine
Lipoate (E_2)	lipoic acid (vitamin-like)
Coenzyme A *(CoA-SH)* *(E_2)*	pantothenate
Flavin adenine dinucleotide (FAD) (E_3)	riboflavin
Nicotinamide adenine dinucleotide (NAD^+) *(E_3)*	niacin

PDH Regulation

Product Inhibition: Acetyl CoA and NADH

Covalent Modification:



+ indicates increase in PDH activity

Clinical disease

- PDH deficiency – Genetic mutation in E1 (X-linked)

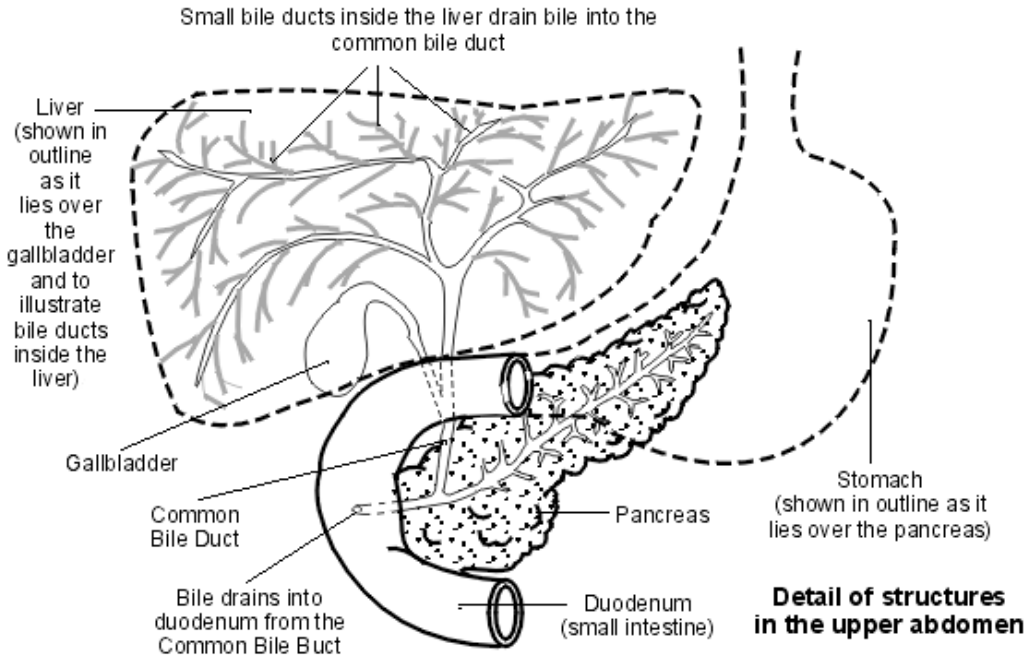
	Males	Females
Severe mutation	All cells affected Major neurological problems Not compatible with fetal survival	Not all cells affected Brain abnormalities Minimal lactic acidosis
Mild mutation	All cells affected Lactic acidosis Neurological problems Compatible with fetal survival	Not all cells affected No lactic acidosis No or minor neurological problems

Clinical disease

- Primary biliary cirrhosis

Liver---Bile in bile ductules

-----Duodenum



Bile: Cholesterol

Phospholipids

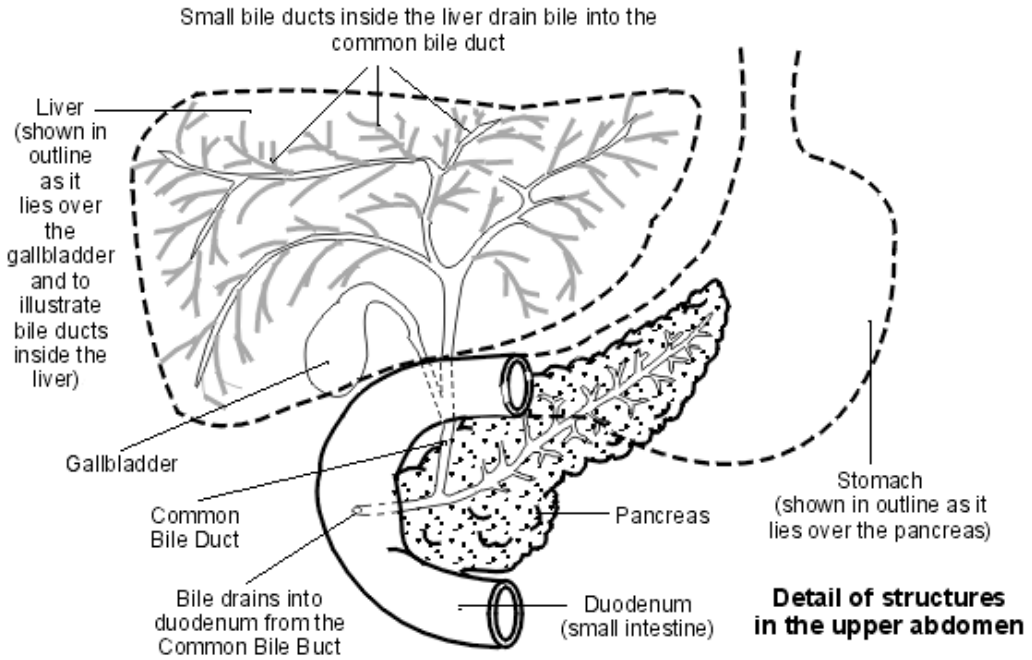
Bile acids (fat and fat soluble vitamin absorption)

Bile pigment-Bilirubin (excreted as stercobilin)

Primary biliary cirrhosis is an autoimmune disorder against E2 subunit of PDH

Bile flow prevented:

cholestasis

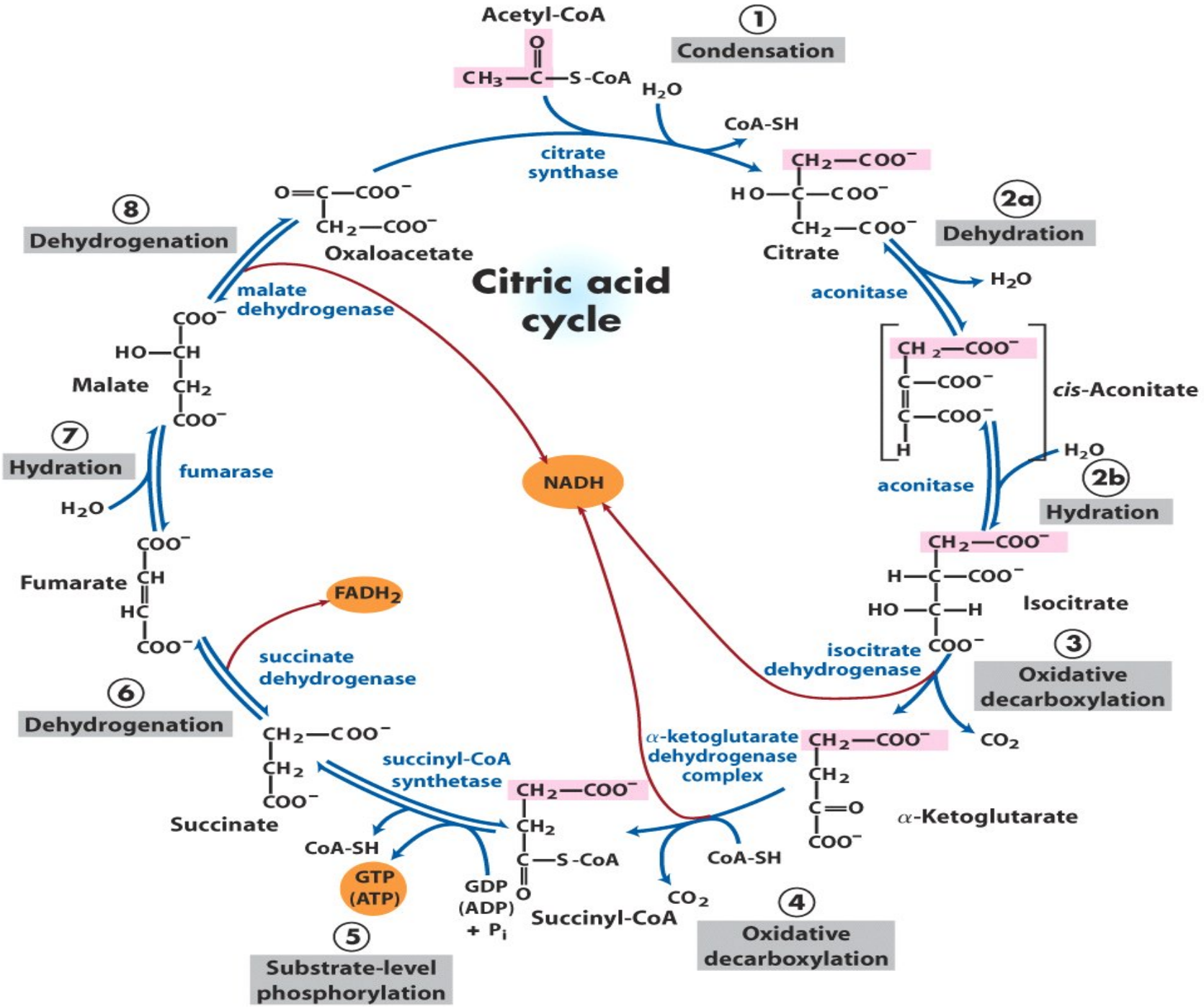


Cholesterol (hypercholesterolemia)

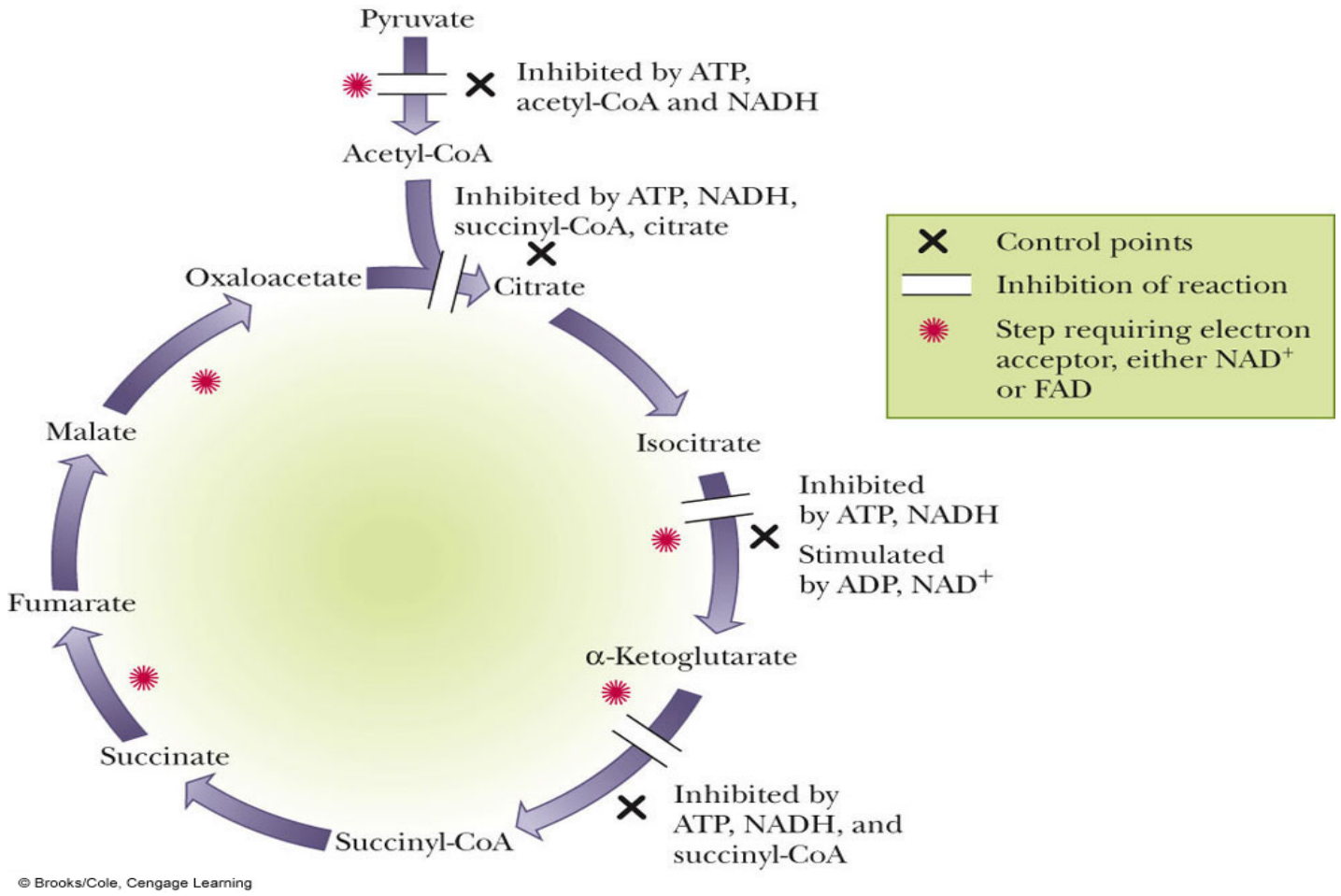
Phospholipids (hyperlipidemia)

Bile acids (pruritus, steatorrhea, Vit A,D,E,K deficiency)

Bile pigment-Bilirubin (jaundice)


Citric acid cycle
Acetyl-CoA
1
Condensation
H_2O
CoA-SH
citrate synthase
Citrate
2a
Dehydration
aconitase
H_2O
cis-Aconitate
aconitase
H_2O
2b
Hydration
Isocitrate
isocitrate dehydrogenase
3
Oxidative decarboxylation
CO_2
α-ketoglutarate dehydrogenase complex
α-Ketoglutarate
CoA-SH
CO_2
4
Oxidative decarboxylation
Succinyl-CoA
GDP (ADP) + P_i
GTP (ATP)
CoA-SH
succinyl-CoA synthetase
5
Substrate-level phosphorylation
Succinate
succinate dehydrogenase
$FADH_2$
6
Dehydrogenation
Fumarate
7
Hydration
fumarase
H_2O
Malate
malate dehydrogenase
8
Dehydrogenation
Oxaloacetate
NADH

Control of the Citric Acid Cycle



Oxidative decarboxylation of α-ketoglutarate into succinyl CoA by αKGDH

The reaction mechanism for the conversion of α-ketoglutarate into succinyl CoA is exactly similar to that seen in the conversion of pyruvate into acetyl CoA

Both reactions require five coenzymes: NAD^+, FAD, CoA, Thiamine pyrophosphate, and lipoic acid
Hence, just like pyruvate dehydrogenase, α-ketoglutarate dehydrogenase also requires five vitamins: Niacin, riboflavin, pantothenic acid, thiamine and lipoic acid

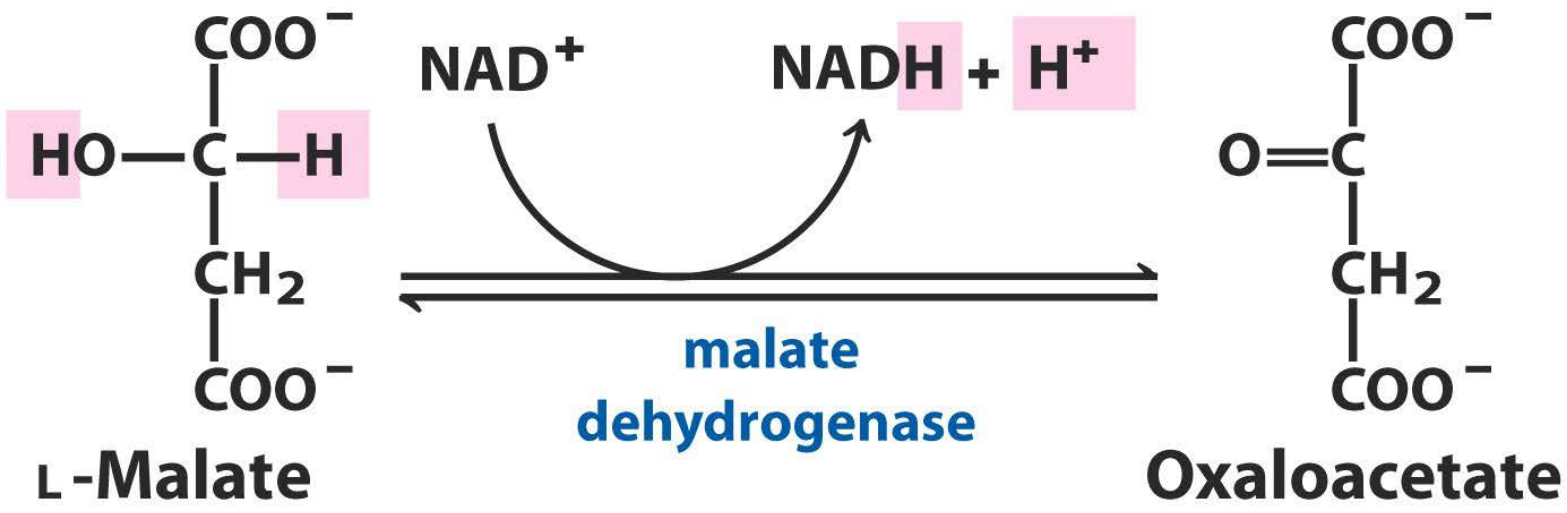
Thiamine deficiency (beri beri) would interfere with both reactions

Dehydrogenation of succinate to fumarate

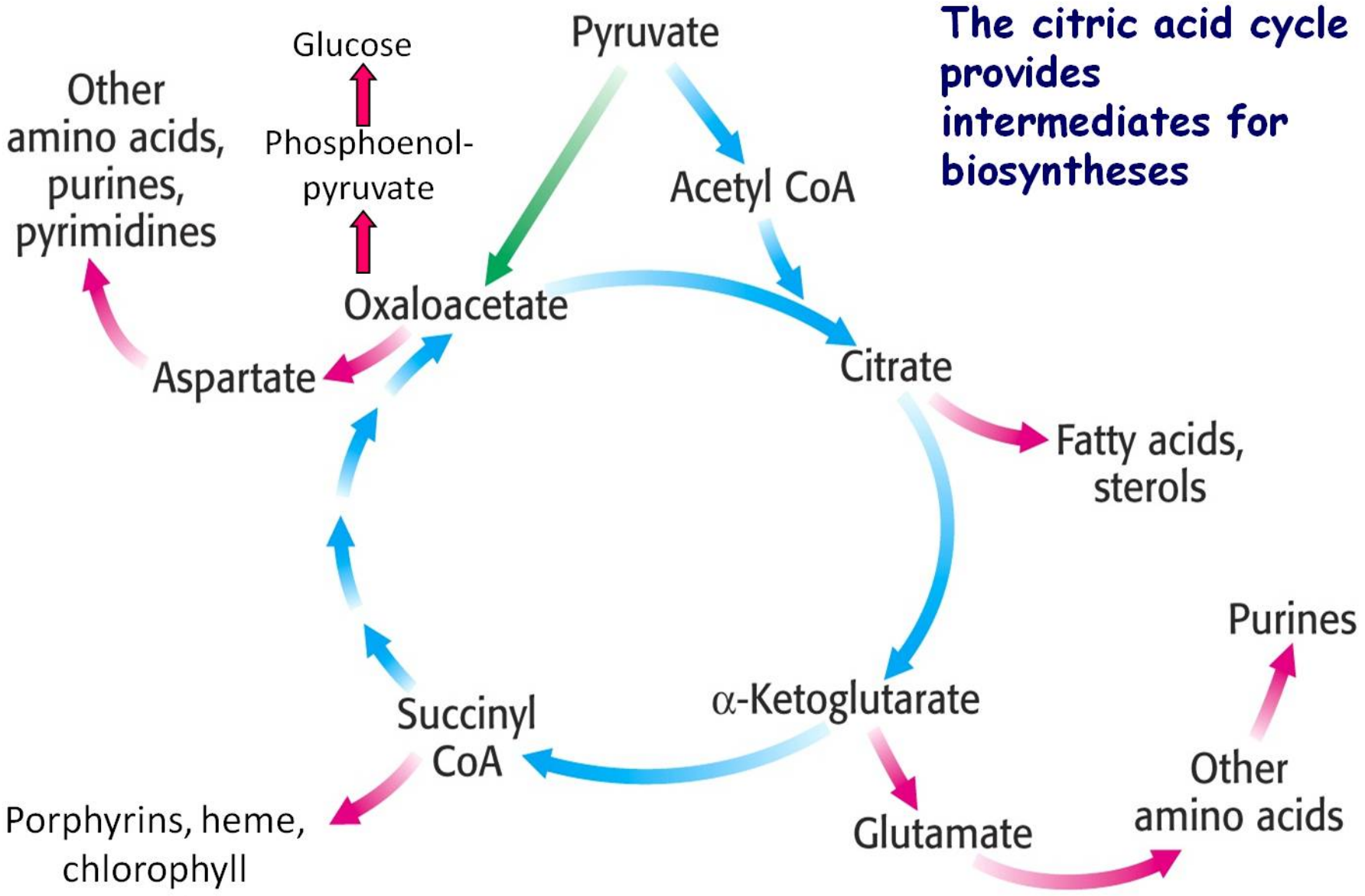
- This reaction is mediated by succinate dehydrogenase
- It is a FAD-dependent enzyme
- It is inhibited by malonate competitively
- It is the only enzyme in the citric acid cycle that is not present in the mitochondrial matrix; instead, it is associated with the inner mitochondrial membrane
- It is also called Complex II, a part of the electron transport chain; like other complexes of ETC, succinate dehydrogenase (Complex II) is also in IMM
- Among all five complexes of ETC, succinate dehydrogenase (i.e., Complex II) is the only complex that is not encoded by mitochondrial DNA

Dehydrogenation of malate to oxaloacetate

Malate is oxidized to form **oxaloacetate**. MDH has a positive value for ΔG^{o}; still the reaction occurs in the forward direction in citric acid cycle. This is because oxaloacetate is removed efficiently, thus reducing the levels of the product and hence keeping the value of ΔG negative.



Krebs Cycle is a Source of Biosynthetic Precursors



Why fatty acids (with even number of carbon atoms) cannot be converted into glucose?

Fatty acids with even number of carbon atoms go through oxidation to generate acetyl CoA

If acetyl CoA can be converted into pyruvate, then pyruvate can go through oxaloacetate and then gluconeogenesis to make glucose; but acetyl CoA cannot be converted into pyruvate because pyruvate dehydrogenase is essentially an irreversible enzyme.

If acetyl CoA can be converted into oxaloacetate via citric acid cycle, it can be converted into glucose; but when acetyl CoA goes through citric acid cycle, it has to use one molecule of oxaloacetate in the first reaction of the cycle to make citrate, which then goes through the cycle to generate oxaloacetate after losing two carbon atoms in the form of CO_2. Thus, there is no net synthesis of oxaloacetate from acetyl CoA in the citric acid cycle. Therefore, this pathway also does not lead to the conversion of acetyl CoA into glucose.

Fatty acids with an odd number of carbon atoms may be used to make glucose because when such fatty acids go through oxidation, it results in acetyl CoA and propionyl CoA, the latter of which can be used to make glucose.