Tricarboxylic Acid (TCA) Cycle
Kreb's Cycle/Citric Acid Cycle

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Introduction

- Organisms derive the majority of their energy from the Kreb's Cycle, also known as the TCA cycle.
- Glycolysis oxidizes sugar to pyruvate which is converted to acetyl-CoA in mitochondria.
- Proteins and fatty acid are also broken down to yield Acetyl CoA.
- **TCA cycle produce energy by oxidizing acetyl-CoA.**
- Provides NADH (reducing equivalents) which is carried to the electron transport chain (ETC) for synthesis of ATP by the process called oxidative phosphorylation.
- Also, generates energy (GTP).
- Also, provides intermediates for amino acid synthesis.

Discovered CAC in Pigeon Flight Muscle

Hans Krebs, 1900–1981

Hans Krebs, 1900–1981

Unnumbered 16 p633
Lehninger Principles of Biochemistry, Sixth Edition

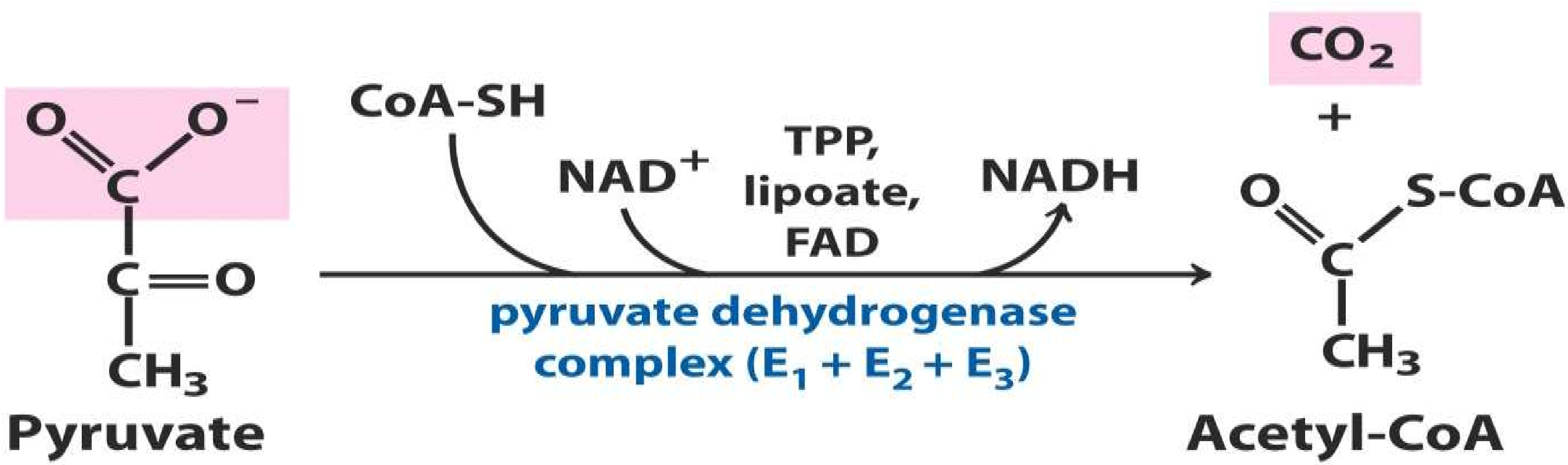
Krebs or TCA Cycle

- **Location:** In Mitochondria of eukaryotes
- The Kreb's Cycle is an aerobic process
- The reason oxygen is required is because the NADH and [$FADH_2$] produced in the Kreb's Cycle are able to be oxydized in the ETC thus replenishing the supply of NAD^+ and [FAD].
- In order to enter the Kreb's Cycle pyruvate must first be converted into Acetyl-CoA by pyruvate dehydrogenase complex found in the mitochondria which is an oxidative process wherein NADH and CO_2 are formed.

Krebs or TCA Cycle

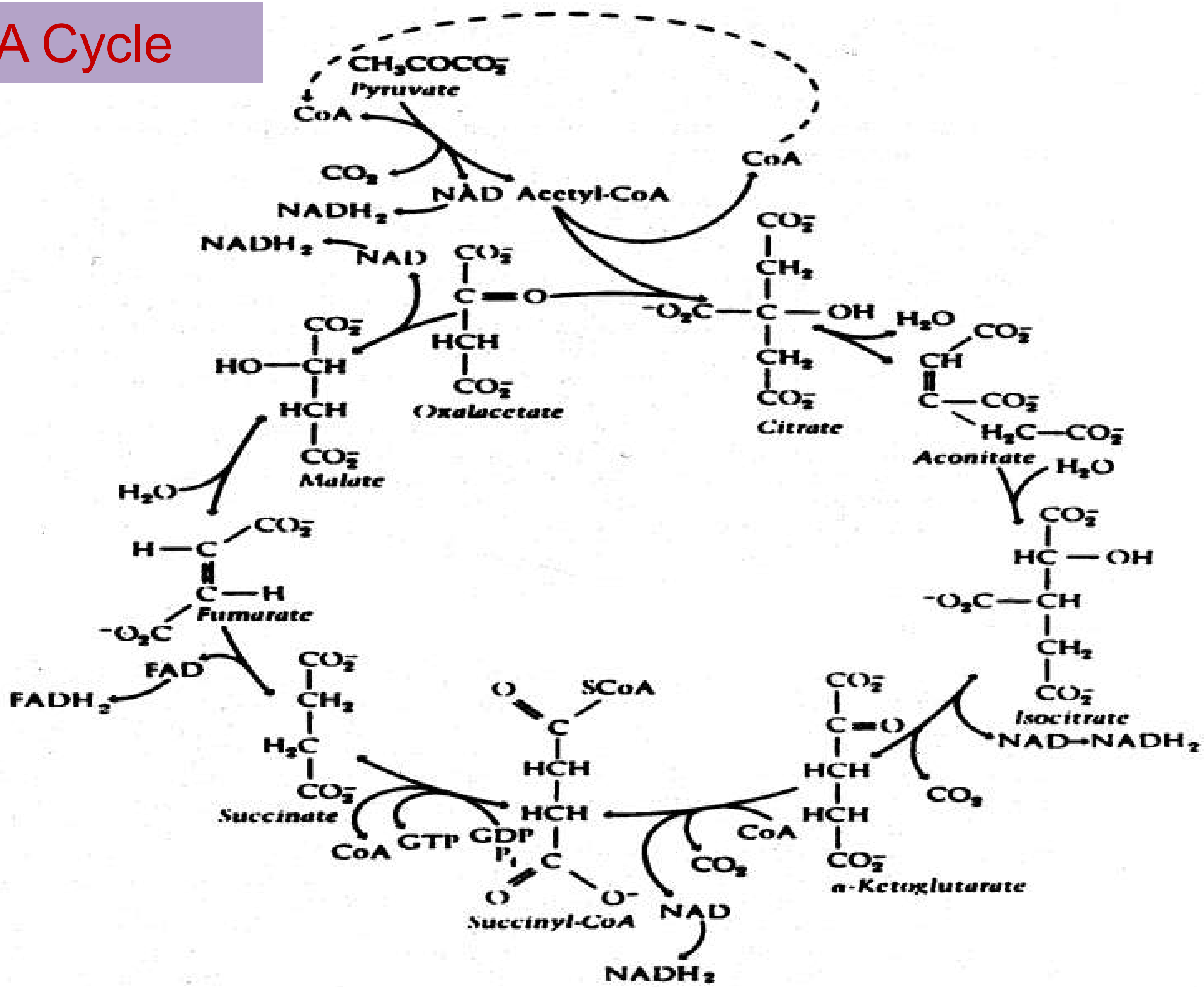
Pyruvate is decarboxylated to Acetyl-Co which enters into TCA cycle.
The reaction is Catalyzed by large enzyme-Pyruvate dehydrogenase (PDH) complex (mitochondrial matrix).

PDH is a Complex Enzyme



$$\Delta G'^{\circ} = -33.4 \text{ kJ/mol}$$

Krebs or TCA Cycle

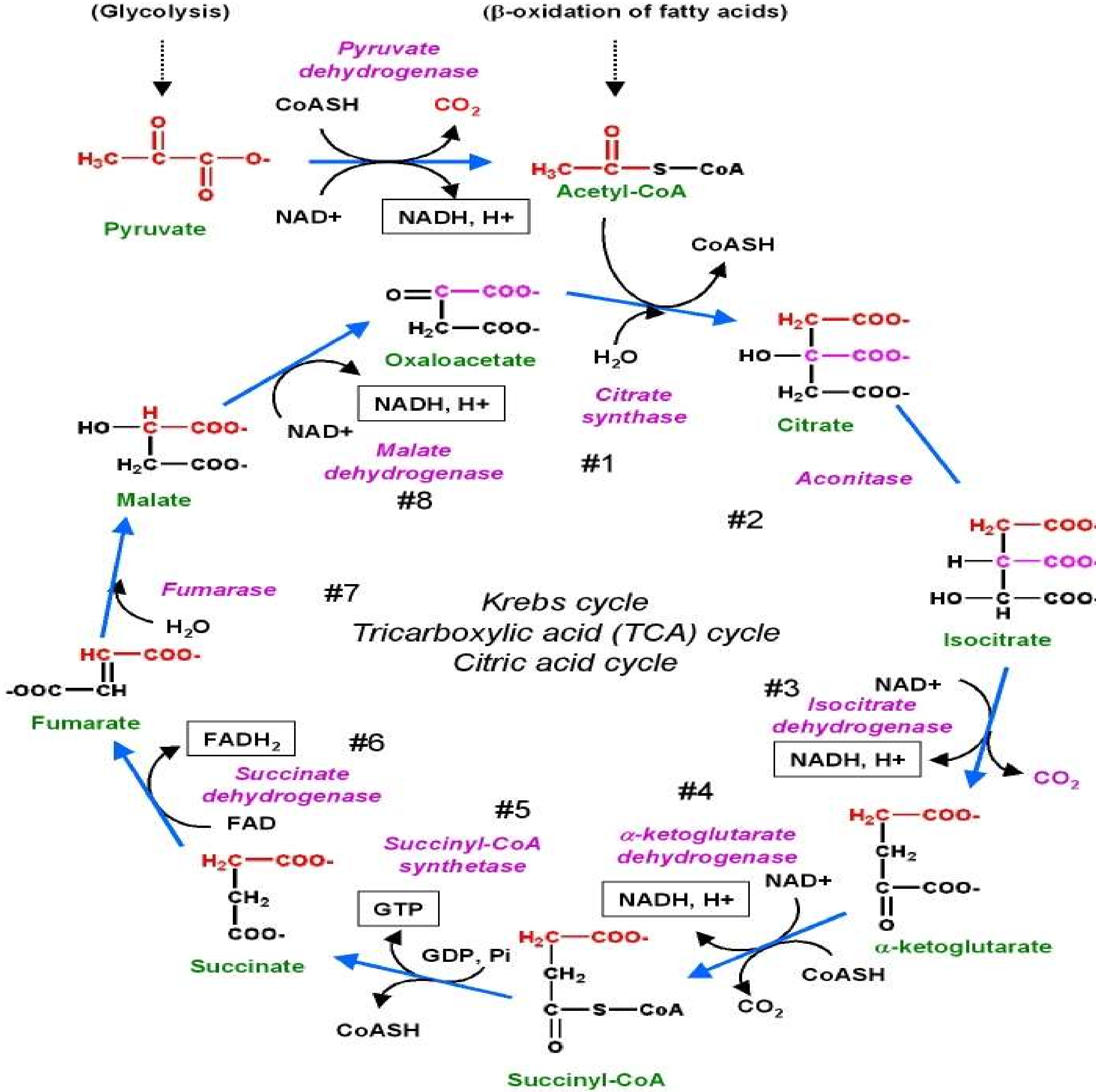


Overall reaction: Pyruvate + 4NAD + FAD → $3CO_2$ + $4NADH_2$ + $FADH_2$

GDP + phosphate → GTP

GTP + ADP → GDP + ATP

Oxidative phosphorylation: $4NADH_2$ ≡ 12ATP; $FADH_2$ ≡ 2ATP | 15ATP



(Glycolysis)
(β-oxidation of fatty acids)
Pyruvate dehydrogenase
CoASH
CO2
NAD+
NADH, H+
Pyruvate
Acetyl-CoA
CoASH
H2O
Citrate synthase
#1
Oxaloacetate
NADH, H+
NAD+
Malate dehydrogenase
#8
Malate
Citrate
Aconitase
#2
Isocitrate
Fumarase
#7
H2O
Krebs cycle
Tricarboxylic acid (TCA) cycle
Citric acid cycle
Fumarate
#3
NAD+
Isocitrate dehydrogenase
NADH, H+
CO2
FADH2
#6
Succinate dehydrogenase
FAD
#4
#5
Succinyl-CoA synthetase
α-ketoglutarate dehydrogenase
NADH, H+
NAD+
GTP
GDP, Pi
CoASH
Succinate
CO2
CoASH
α-ketoglutarate
Succinyl-CoA

TCA Cycle: Overall reaction

- Acetyl CoA + 3NAD$^+$ + FAD + GDP + Pi + 2H_2O

$$\downarrow$$

- 2CO_2 + CoA + 3NADH + $FADH_2$ + GTP + H^+

TCA Cycle: Energetics

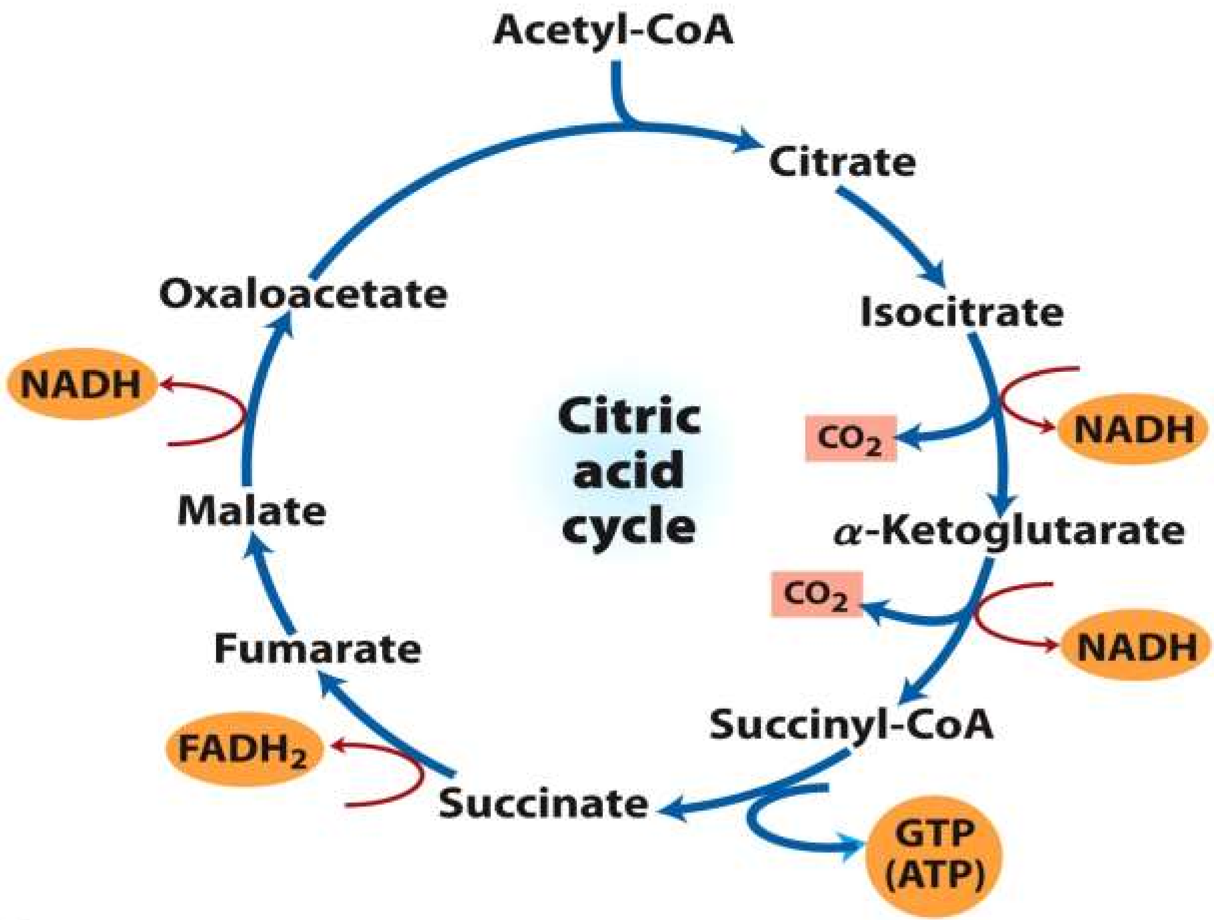


Figure 16-14
Lehninger Principles of Biochemistry, Sixth Edition

- The *Kreb's Cycle* gives **3 moles of NADH**, **1 mole of FADH** and **1 mole of ATP** *per cycle of substrate i.e per* **1 mole of Acetyl CoA**.

Energetics of Glycolysis and TAC in ATPs

TABLE 16–1 **Stoichiometry of Coenzyme Reduction and ATP Formation in the Aerobic Oxidation of Glucose via Glycolysis, the Pyruvate Dehydrogenase Complex Reaction, the Citric Acid Cycle, and Oxidative Phosphorylation**

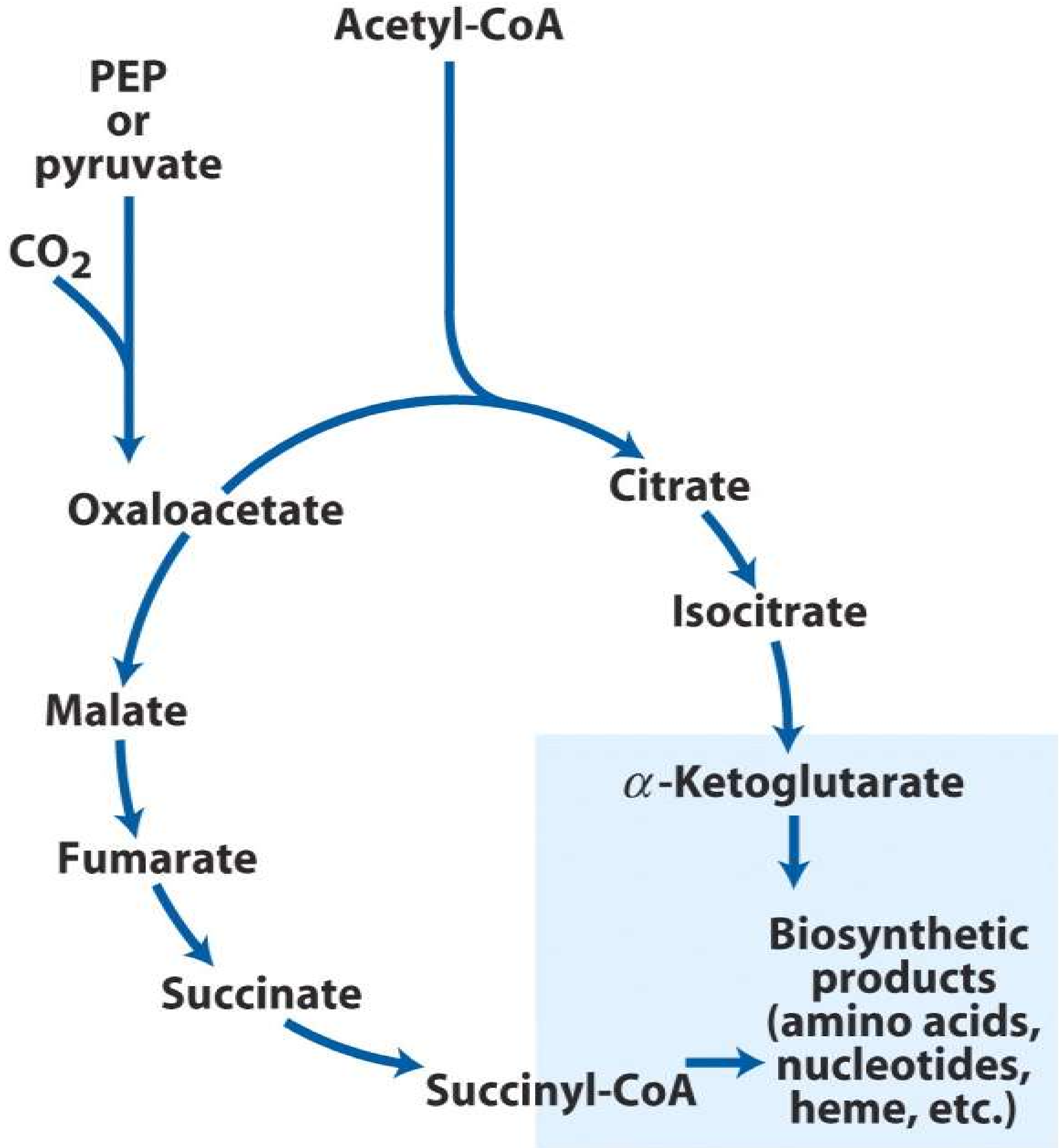
Reaction	Number of ATP or reduced coenzyme directly formed	Number of ATP ultimately formed*
Glucose → glucose 6-phosphate	−1 ATP	−1
Fructose 6-phosphate → fructose 1,6-bisphosphate	−1 ATP	−1
2 Glyceraldehyde 3-phosphate → 2 1,3-bisphosphoglycerate	2 NADH	3 or 5†
2 1,3-Bisphosphoglycerate → 2 3-phosphoglycerate	2 ATP	2
2 Phosphoenolpyruvate → 2 pyruvate	2 ATP	2
2 Pyruvate → 2 acetyl-CoA	2 NADH	5
2 Isocitrate → 2 α-ketoglutarate	2 NADH	5
2 α-Ketoglutarate → 2 succinyl-CoA	2 NADH	5
2 Succinyl-CoA → 2 succinate	2 ATP (or 2 GTP)	2
2 Succinate → 2 fumarate	2 $FADH_2$	3
2 Malate → 2 oxaloacetate	2 NADH	5
Total		30–32

*This is calculated as 2.5 ATP per NADH and 1.5 ATP per $FADH_2$. A negative value indicates consumption.

†This number is either 3 or 5, depending on the mechanism used to shuttle NADH equivalents from the cytosol to the mitochondrial matrix; see Figures 19–30 and 19–31.

Table 16-1
Lehninger Principles of Biochemistry, Sixth Edition

TAC in Anaerobic Not-Respiratory Organisms



Anaplerotic Reactions

TABLE 16–2 Anaplerotic Reactions

Reaction	Tissue(s)/organism(s)
Pyruvate + HCO_3^- + ATP $\xrightleftharpoons{\text{pyruvate carboxylase}}$ oxaloacetate + ADP + P_i	Liver, kidney
Phosphoenolpyruvate + CO_2 + GDP $\xrightleftharpoons{\text{PEP carboxykinase}}$ oxaloacetate + GTP	Heart, skeletal muscle
Phosphoenolpyruvate + HCO_3^- $\xrightleftharpoons{\text{PEP carboxylase}}$ oxaloacetate + P_i	Higher plants, yeast, bacteria
Pyruvate + HCO_3^- + NAD(P)H $\xrightleftharpoons{\text{malic enzyme}}$ malate + $NAD(P)^+$	Widely distributed in eukaryotes and bacteria

Table 16-2
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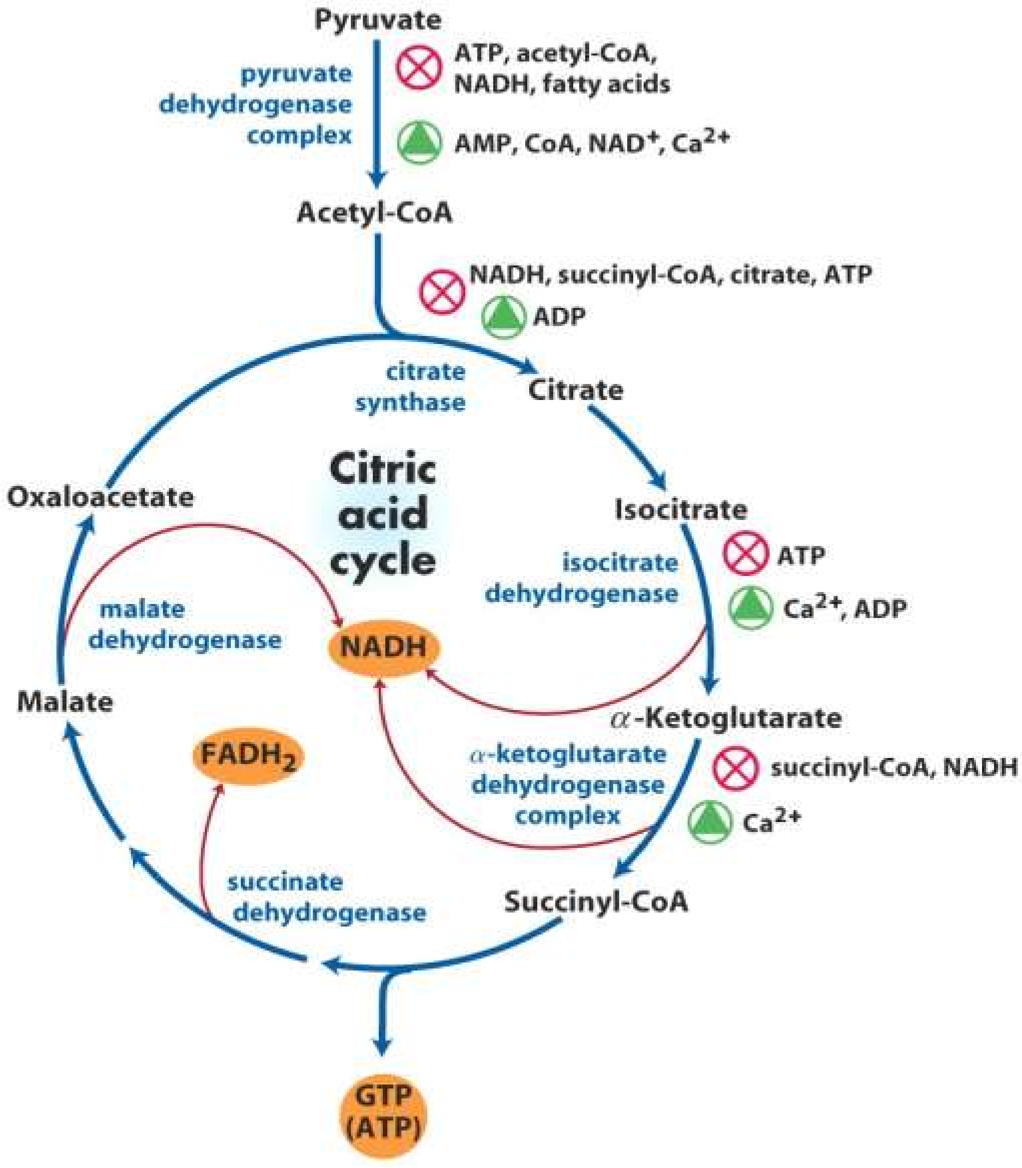
Regulation of Citric Acid Cycle



Control of the Pyruvate Dehydrogenase complex

- Regulation by its products

NADH & Acetyl-CoA : inhibit

While

NAD^+ & CoA stimulate

- Regulation by energy charge

ATP : inhibit

While

AMP : stimulate

Regulation of Citric Acid Cycle

Three Control sites:

$$\text{Acetyl CoA + Oxaloacetate} \longrightarrow \text{Citrate}$$

Site 1 - Reaction 1

- Enzyme: citrate synthase
- Inhibited by ATP

Site 2 - Reaction 3

$$\text{Isocitrate} \longrightarrow \alpha\text{-Ketoglutarate}$$

- Enzyme: isocitrate dehydrogenase
- Inhibited by ATP & NADH
- Stimulated by ADP & NAD^+

Regulation of Citric Acid Cycle

Site 3 - Reaction 4

- α-Ketoglutarate $\longrightarrow$ Succinyl CoA

- Enzyme: α-Ketoglutarate dehydrogenase
- Similar to PDH complex
- Inhibited by Succinyl CoA & NADH also high-energy charge.

- In the Kreb's Cycle is inhibited by a high energy charge and stimulated by a low energy charge