Chapter 9. The citrate cycle

* TCA cycle (Krebs cycle, Citrate cycle)의 기능
  - Energy production (에너지 생산)
  - Cycle intermediates are substrates in a variety of biosynthetic reaction
* **Cellular respiration (세포호흡)** : 연료가 연소되어 CO_2 와 물로 전환되면서 ATP를 생산하는 것 (2 steps 으로 구성)

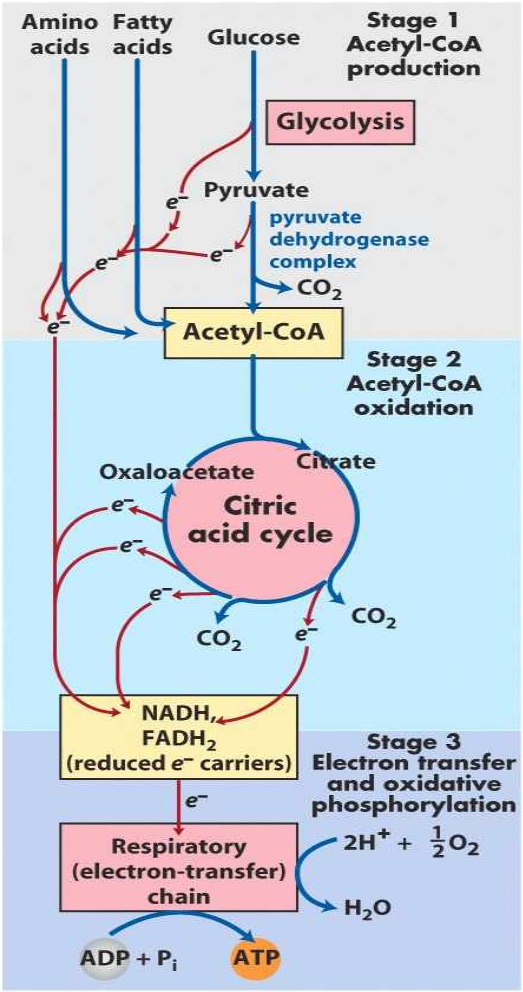


Fig. Catabolism of proteins, fats, and carbohydrates occurs in the three stages of cellular respiration.

Stage 1 : Oxidation of fatty acids, glucose, and some amino acids

Stage 2 : Oxidation of acetyl groups via the citric acid cycle includes four steps in which electrons are abstracted

Stage 3 : Electrons carried by NADH and $FADH_2$ are funneled in to a chain of mitochondrial electron carriers-the respiratory chain-ultimately reducing O_2 to H_2O.

* This electron flow drives the synthesis of ATP in the process of oxidative phosphorylation.

I. Citric acid cycle(구연산회로)

◎ 학습목표

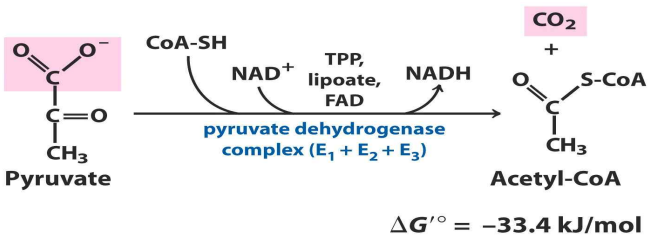
- 왜 피르브산 탈수소효소 복합체가 대사의 중요한 연결부위를 촉매 하는가?
- 어떻게 pyruvate dehydrogenase complex가 조절되는가?
- 시트르산회로에서 아세틸 CoA 산화의 장점은 무엇인가?
- Citrate cycle이 어떻게 조절되는가?

◎ Citrate회로의 기능

- 탄소 연료로부터 높은 에너지전자(high-energy electron)를 생성한다.
- 세포물질대사의 중심으로 모든 연료분자들의 호기성물질대사의 관문이다.
- 아미노산, 핵산, 포리피린(헴)과 같은 다른 분자들의 생합성 전구체이다.
- 이 회로의 구성성분인 OAA는 glucose 합성의 전구체이다.

1. Pyruvate is oxidized to acetyl CoA and CO_2

- 이 반응은 대사의 결정적인 반응으로 탄수화물에 있는 탄소원자가 시트르산 회로를 통하여 산화되거나 지방의 합성에 이용되도록 한다.



* The overall reaction (전체반응)

- Pyruvate + NAD^+ + CoASH → Acetyl-CoA + NADH + CO_2 + H_2O + H^+
- **catalyzed by the pyruvate dehydrogenase complex**
- oxidative decarboxylation, an irreversible oxidation process

1) Pyruvate dehydrogenase complex requires five coenzyme

① **NAD, FAD : electron carriers**
② **TPP : decarboxylation, coenzyme**
③ **Pantothenate : an essential component of coenzyme A**
④ **Lipoate : has two thiol groups,**
can serve both as electron carrier and as an acyl carrier

2) Pyruvate dehydrogenase complex consists of three distinct enzymes

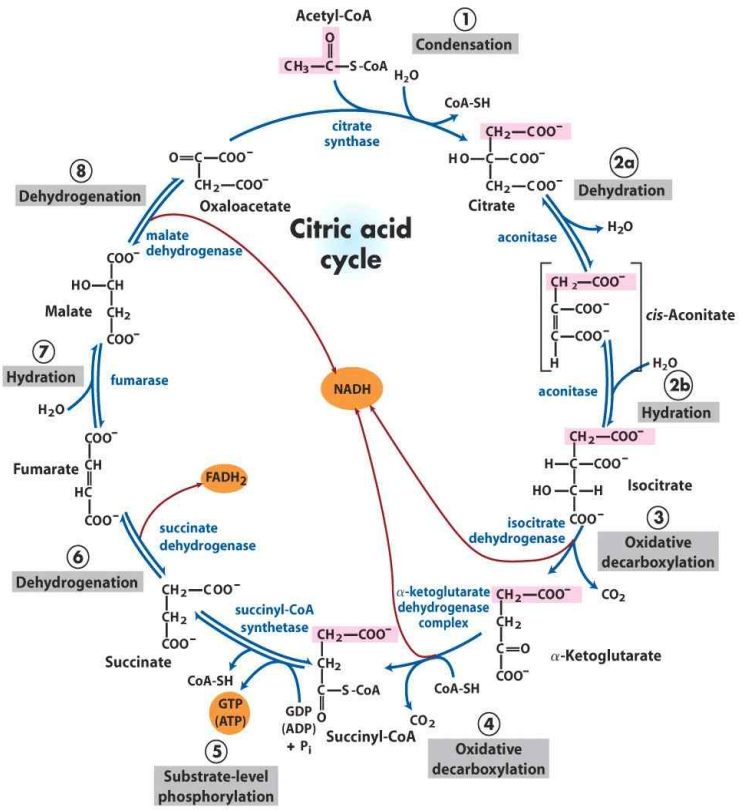
Table 15–1 Subunit composition of the *E. coli* pyruvate dehydrogenase complex

Enzyme	Coenzyme(s)	Molecular weight of subunit	Number of subunits per complex
Pyruvate dehydrogenase (E_1)	TPP	96,000	24
Dihydrolipoyl transacetylase (E_2)	Lipoate, CoA	65,000–70,000	24
Dihydrolipoyl dehydrogenase (E_3)	FAD, NAD	56,000	12

Source: Modified from Eley, M.H., Namihira, G., Hamilton, L., Munk, P., & Reed, L.J. (1972) α-Ketoacid dehydrogenases. XVIII: subunit composition of the *E. coli* pyruvate dehydrogenase complex. *Arch. Biochem. Biophys.* **152,** 655–669.

2. Reaction of citric acid cycle

- begins with the condensation of acetyl-CoA with OAA to form citrate
- The citric acid cycle has eight steps
- Amphibolic pathways can function in both anabolic and catabolic processes



1) Energy yielding in citrate cycle

① PVA	→	Acetyl CoA	1 NADH
② Isocitrate	→	α-ketoglutarate	〃
③ α-KGA	→	Succinyl CoA	〃
④ Malate	→	Oxaloactate	〃
⑤ Succinate	→	Fumarate	1 FADH2
⑥ Succinyl CoA	→	Succinate	1 GTP
		Total ATP	12.5 ATP (15 ATP)

2) Citric acid cycle components are important biosynthetic intermediates
(시트르산 회로의 구성성분은 중요한 생합성 중간체이다)

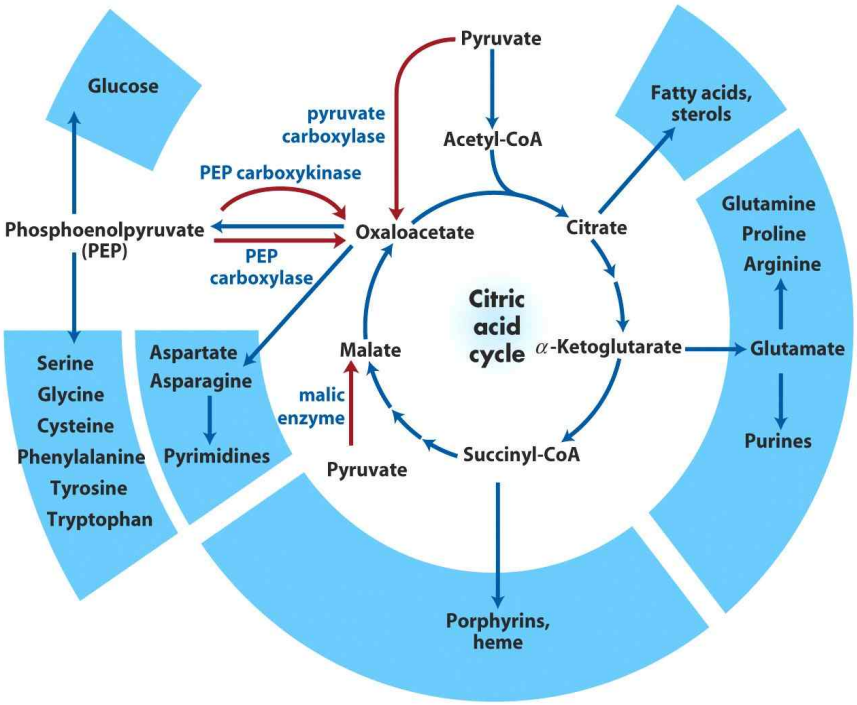


Fig. 동화작용에서 ctrate 회로의 역할

- 시트르산회로의 중간체는 많은 생합성경로의 중간체로 빠져나가면 음영을 한 부분에 있는 생성물을 만들게 된다.
- 적색으로 표시된 것은 시트르산회로의 고갈된 중간체를 보급하는 4종류의 보충대사반응이다

3) Anaplerotic reaction (보충대사반응)

구연산회로의 중간산물이 생합성 전구체로서 작용하기위해 고갈되면 중간산물들은 보충대사반응에 의하여 보충된다.

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 prokaryotes

* **Biotin carries CO_2 group**

4) Regulation of the TCA cycle (TCA 회로의 조절)

- substrate availability (기질 이용능력)
- inhibition by accumulating product (생성물의 축적에 의한 억제)
- allosteric feedback inhibition of early enzyme by later intermediates

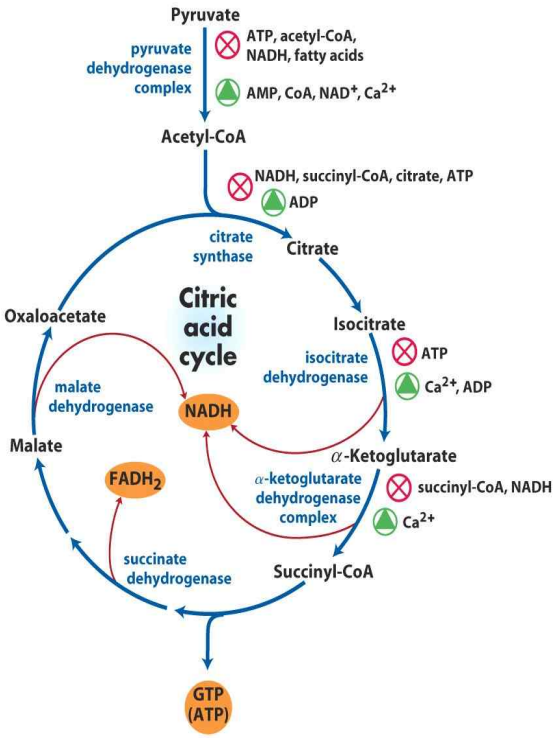


Fig. Regulation of metabolic flow from pyruvate through the citric acid cycle.

① Three enzymes of the citric acid cycle are regulated

* Citrate synthase : ADP에 의해 활성화, ATP, NADH는 경쟁적으로 저해
* Isocitrate dehydrogenase : ADP, Ca^{++}에 의해 활성화, ATP에 의해 저해
* α-ketoglutarate dehydrogenase : Succinyl CoA, NADH에 의해 저해

② Two enzymes outside the citric acid cycle profoundly affect its regulation

* **Pyruvate dehydrogenase** : PVA ⟶ Acetyl CoA
  - inhibited by ATP, acetyl CoA, NADH
  - activated by AMP, **pyruvate,** CoA, NAD^+, Ca^{++}
  - **입체다른자리 조절과 공유결합기전**에 의하여 조절된다.

◎ **Pyruvate dehydrogenase (PDH) complex 조절**

- PDH 복합체는 [ATP/ADP], [NADH/NAD+], [Acetyl-CoA/CoA] 비가 높을 때 **입체다른자리 기전**으로 억제된다
- **공유결합기전**은 인산화 및 탈인산화에 의한 조절된다

* **Pyruvate carboxylase** : PVA ⟶ oxaloacetic acid

II. The Glyoxylate cycle (글리옥실산회로)

* **Glyoxylate cycle** bypasses the two decarboxylation steps of the citric acid cycle
* **Two molecules of the acetyl-CoA** enter the glyoxylate cycle
* The glyoxylate cycle consists of five reactions
* **In Plants, the glyoxylate cycle occurs in organelles called glyoxysomes**
* **High plant & m/o : 존재, Animal : nothing**
* **특히 고등식물종자의 발아 중 lipid가 탄수화물로 전환되는 기작**

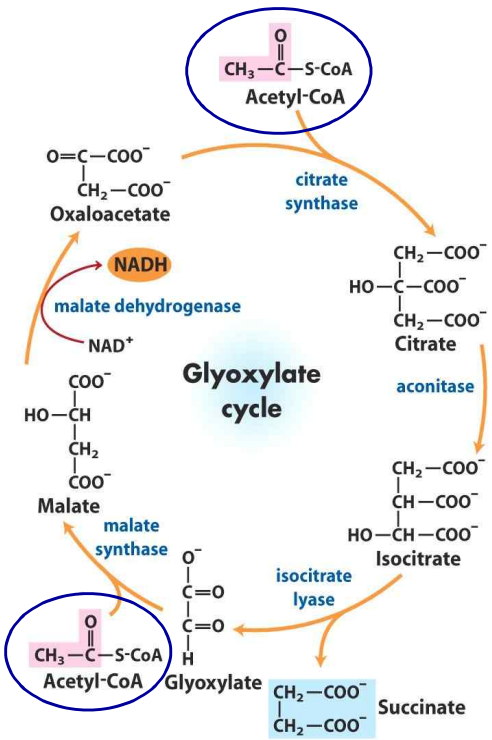


Fig. Glyoxylate cycle.

☞ The key enzymes (isocitrate lyase and malate synthase) are unique to the glyoxylate cycle

☞ The citric acid cycle and glyoxylate cycles are coordinately regulated (시트르산 회로와 글리옥실산 회로는 협조적으로 조절된다)

☞ Glyoxylate 회로를 가지고 있는 생물은 두 탄소를 가진 분자(acetyl-CoA)를 이용하여 살 수 있다.

☞ 글리옥실산회로는 아세트산으로부터 4-탄소화합물을 생성한다.

☞ Glyoxylate cycle function : lipid → carbohydrate

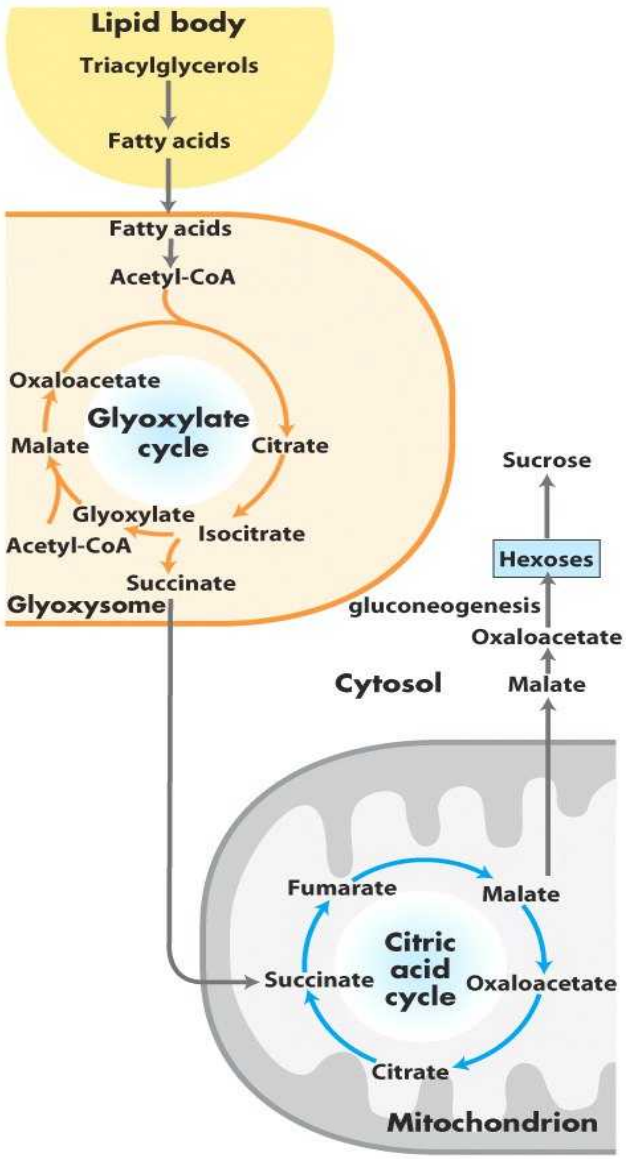


Fig. Relationship between the glyoxylate and citric acid cycles.
(글라이옥실산회로와시트르산회로사이의관계)

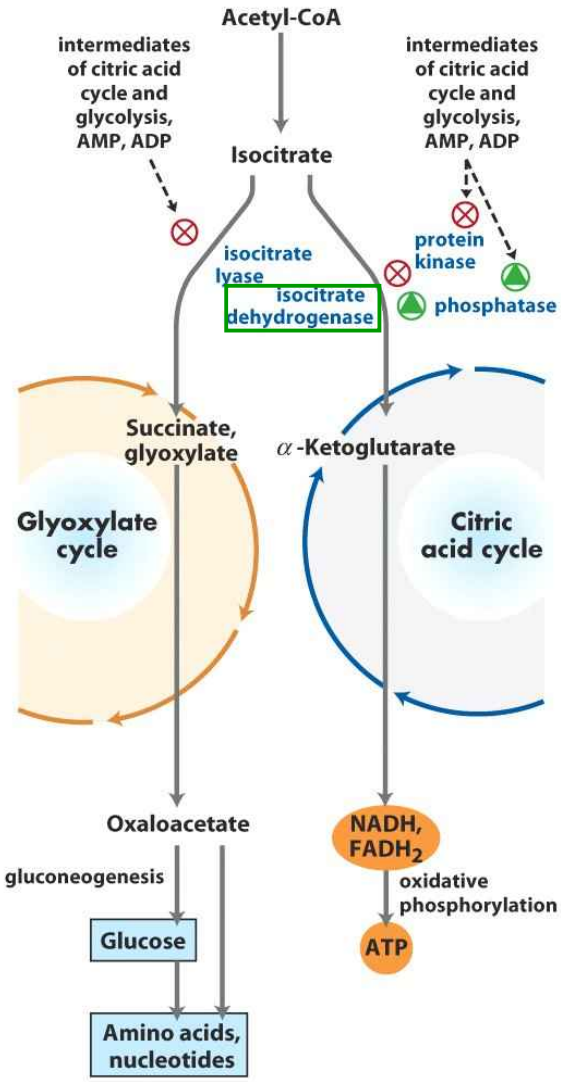


Fig. Coordinated regulation of glyoxylate and citric acid cycle
(글라이 옥실산 회로와 시트르산회로의 협조적 조절)
- Isocitrate dehydrogenase가 두 회로의 분배를 결정한다