Chem 352 - Lecture 8
Carbohydrate Metabolism
Part III: Citric Acid Cycle

Introduction

The citric acid cycle has both catabolic and anabolic functions.

- **Catabolic** – Oxidizes the 2-carbon acetyl group to CO_2 and produces reduced nucleotides (NADH + H^+ and $FADH_2$)
- **Anabolic** – The citric acid cycle intermediates serve as starting material for the biosynthesis of amino acids, heme groups, glucose, et al.

Introduction

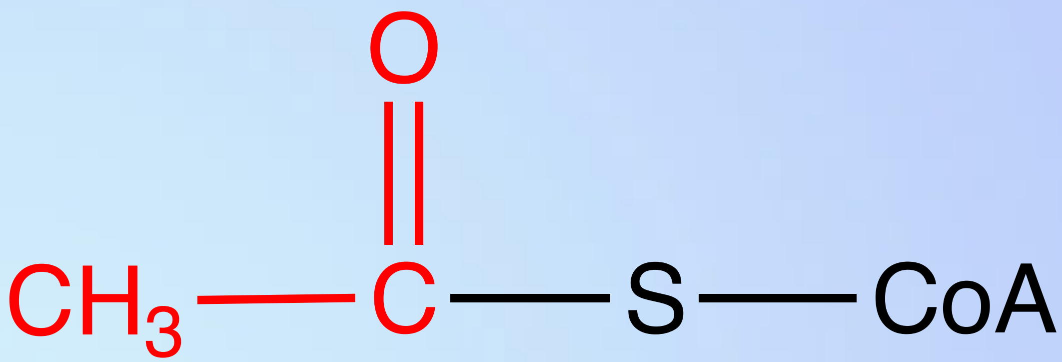
The citric acid cycle was discovered by Hans Kreb's and colleagues in 1937.

- Citric acid cycle is also called the Kreb's Cycle and the TCA (tricarboxylic acid) Cycle.

Hans Krebs (1900-1981)
Nobel Prize in Physiology and Medicine, 1953

Acetyl CoA

- The entry point of carbon into the citric acid cycle is acetyl CoA



Acetyl CoA

Questions:

Acetyl CoA contains a thioester group. What can you say about the thermodynamics for the hydrolysis of thioester groups?

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TABLE 10.3 Standard Gibbs free energies of hydrolysis for common metabolites

Metabolite	$\Delta G^{\circ\prime}_{\text{hydrolysis}}$ ($kJ\ mol^{-1}$)
Phosphoenolpyruvate	−62
1,3-*Bis*phosphoglycerate	−49
ATP to AMP + PP_i	−45
Phosphocreatine	−43
Phosphoarginine	−32
Acetyl CoA	−32
ATP to ADP + P_i	−32
Pyrophosphate	−29
Glucose 1-phosphate	−21
Glucose 6-phosphate	−14
Glycerol 3-phosphate	−9

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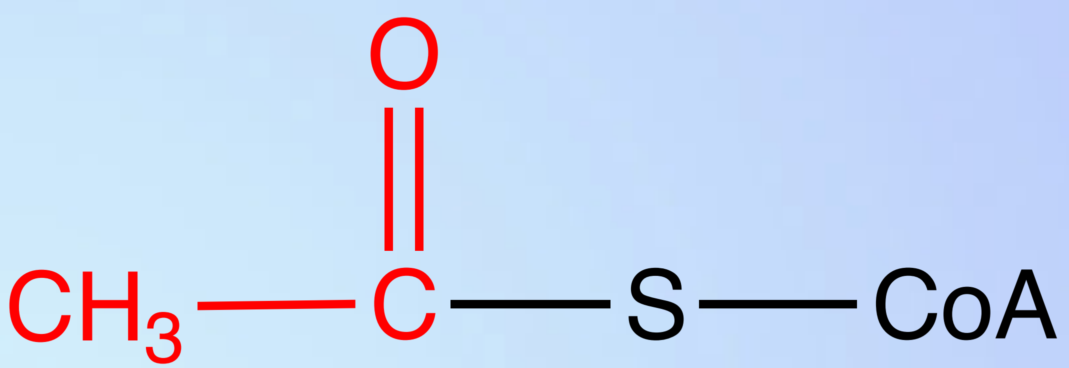

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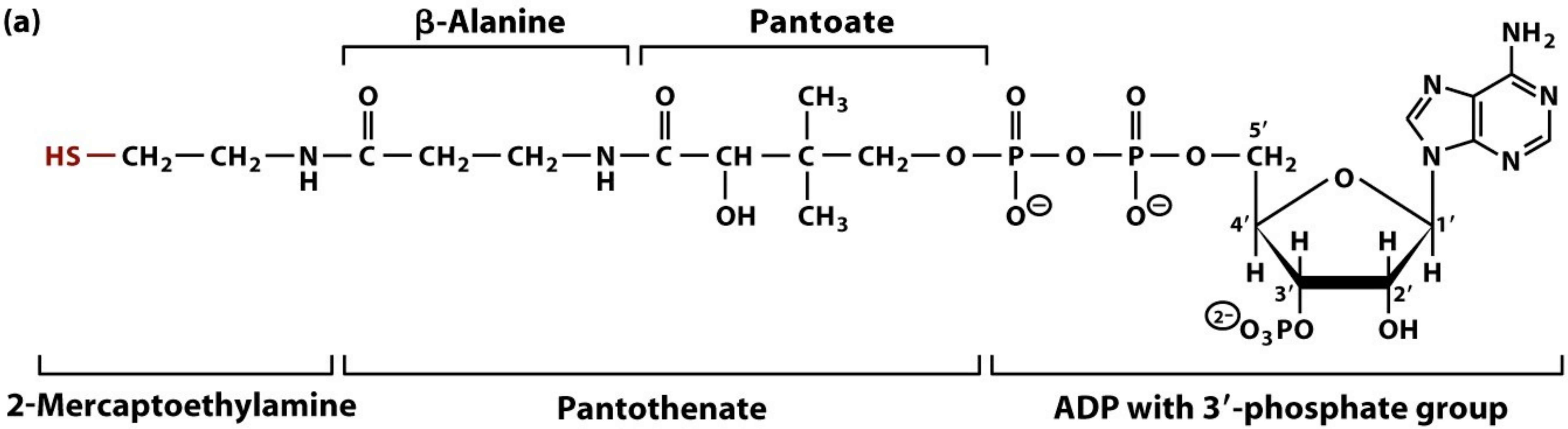

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Acetyl CoA

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Uridine diphosphate glucose	—	Transfer of glycosyl groups	Cosubstrate
Nicotinamide adenine dinucleotide ($NAD^{\oplus}$) and nicotinamide adenine dinucleotide phosphate ($NADP^{\oplus}$)	Niacin	Oxidation-reduction reactions involving two-electron transfers	Cosubstrate
Flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD)	Riboflavin (B_2)	Oxidation-reduction reactions involving one- and two-electron transfers	Prosthetic group
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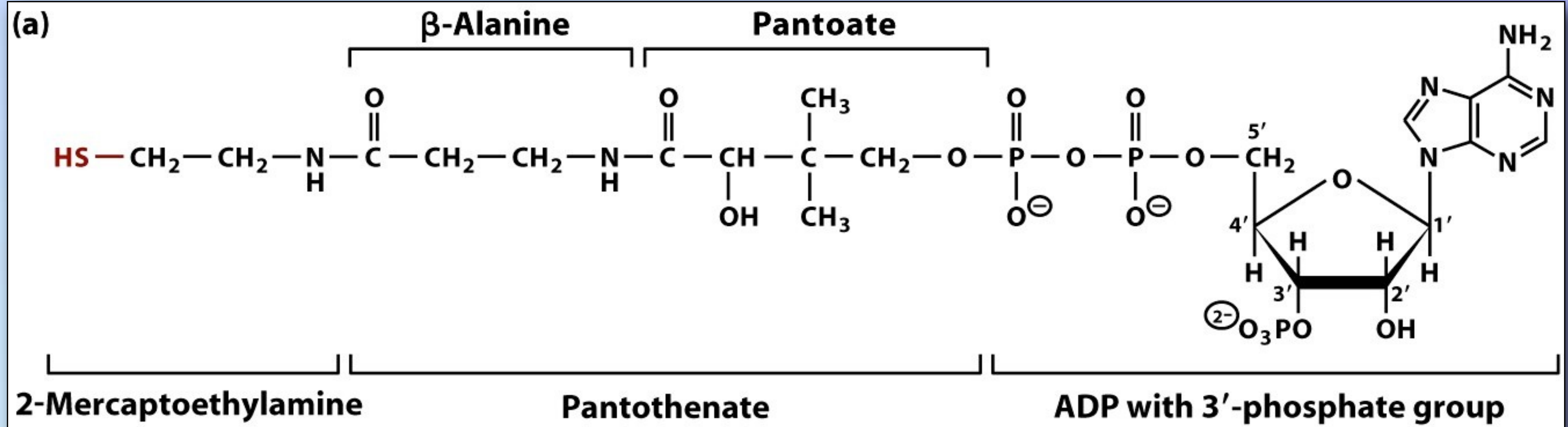

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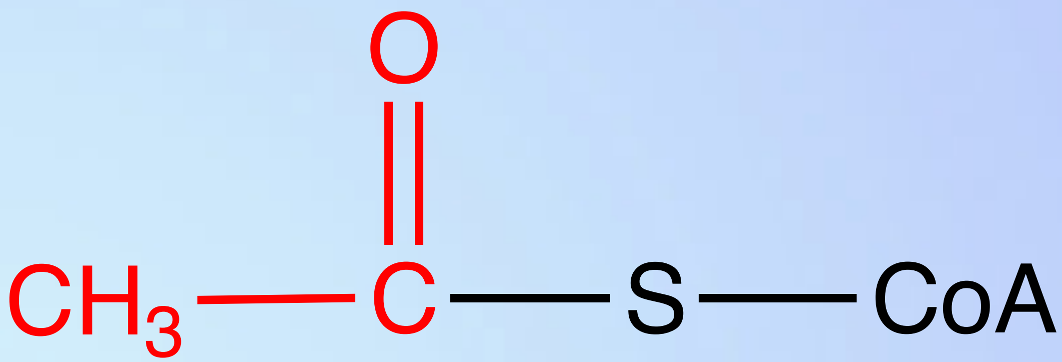


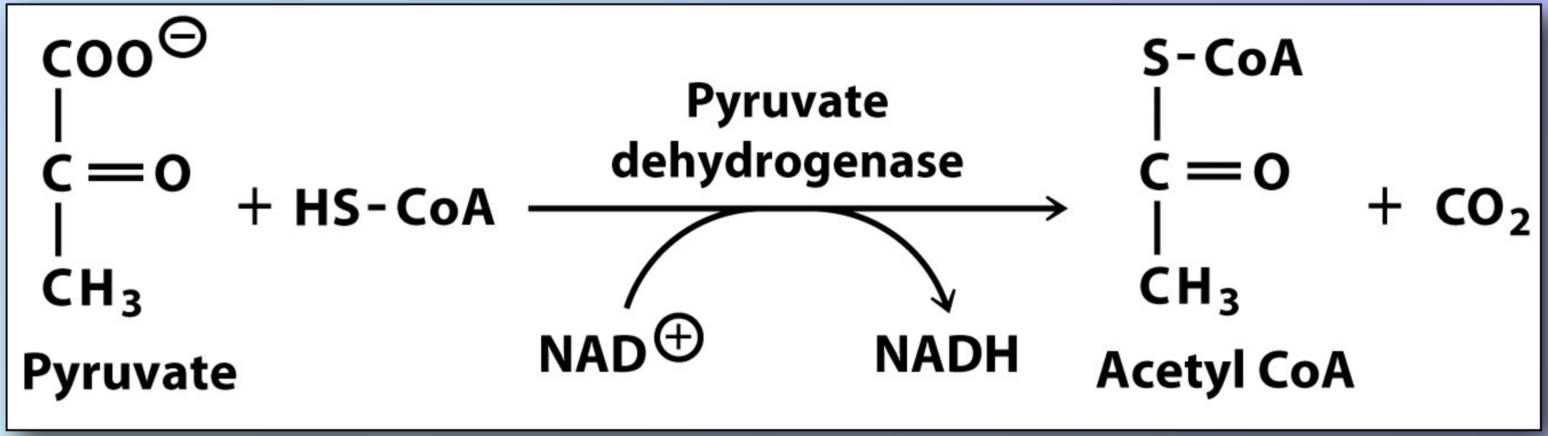
Acetyl CoA

- The entry point of carbon into the citric acid cycle is acetyl CoA

- Acetyl CoA is produced from
  - The oxidative decarboxylation of pyruvate from the glycolysis pathway.
  - The degradation of fatty acids

Conversion of Pyruvate to Acetyl CoA

- Pyruvate dehydrogenase is a large enzyme complex that converts pyruvate to acetyl-CoA and CO_2.



  - This is the catabolic entry point into the citric acid cycle of carbon coming from glycolysis.

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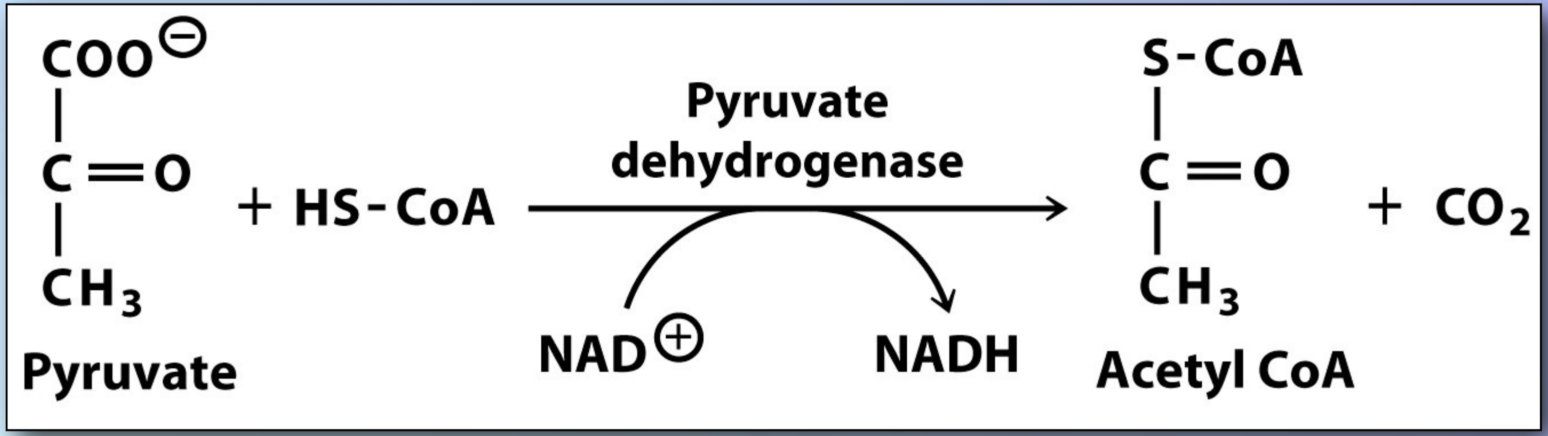
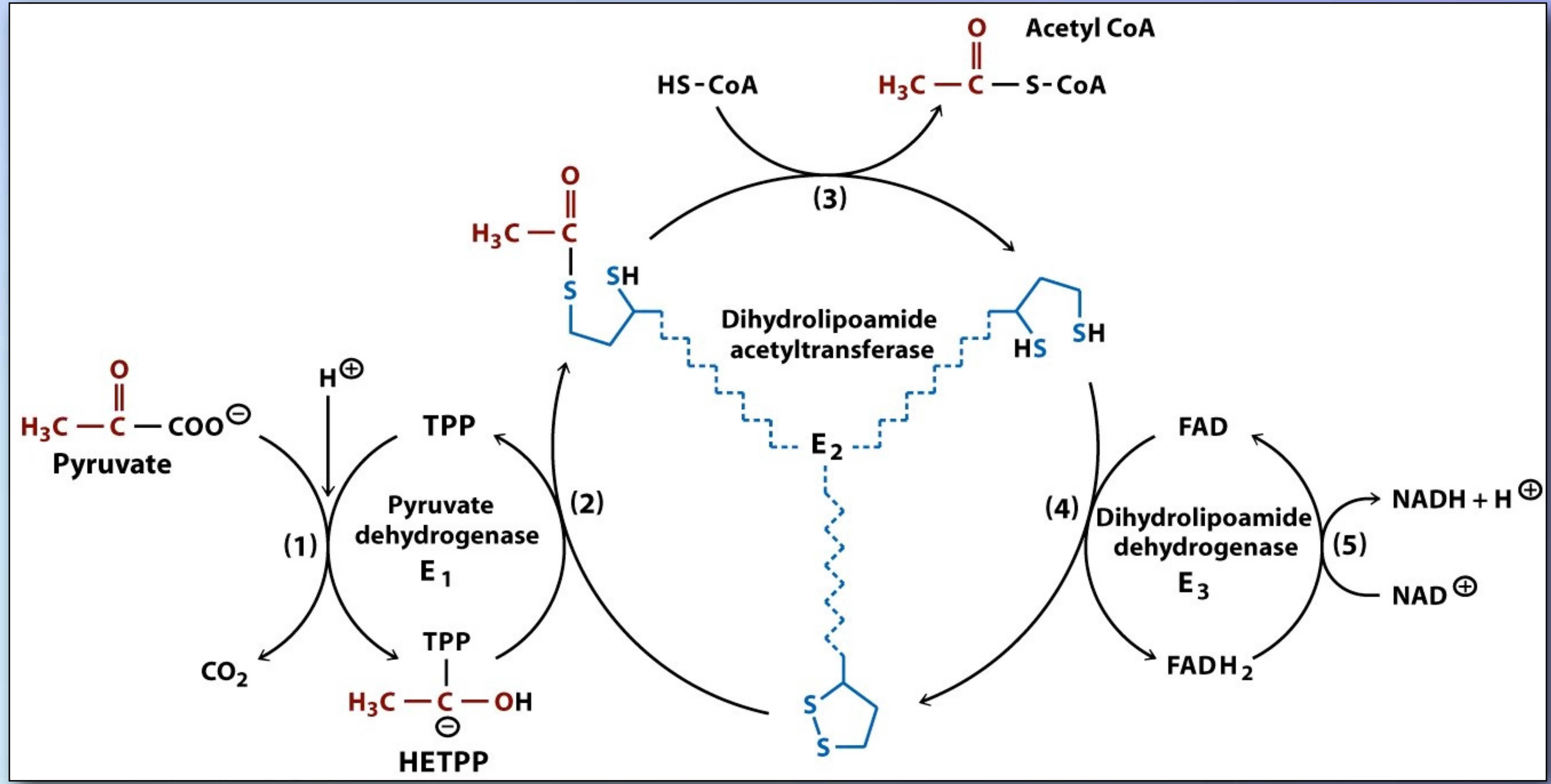


- ✦ Three different subunits catalyze five sub-reactions to to carry out this overall reaction.

Conversion of Pyruvate to Acetyl CoA

- Pyruvate Dehydrogenase



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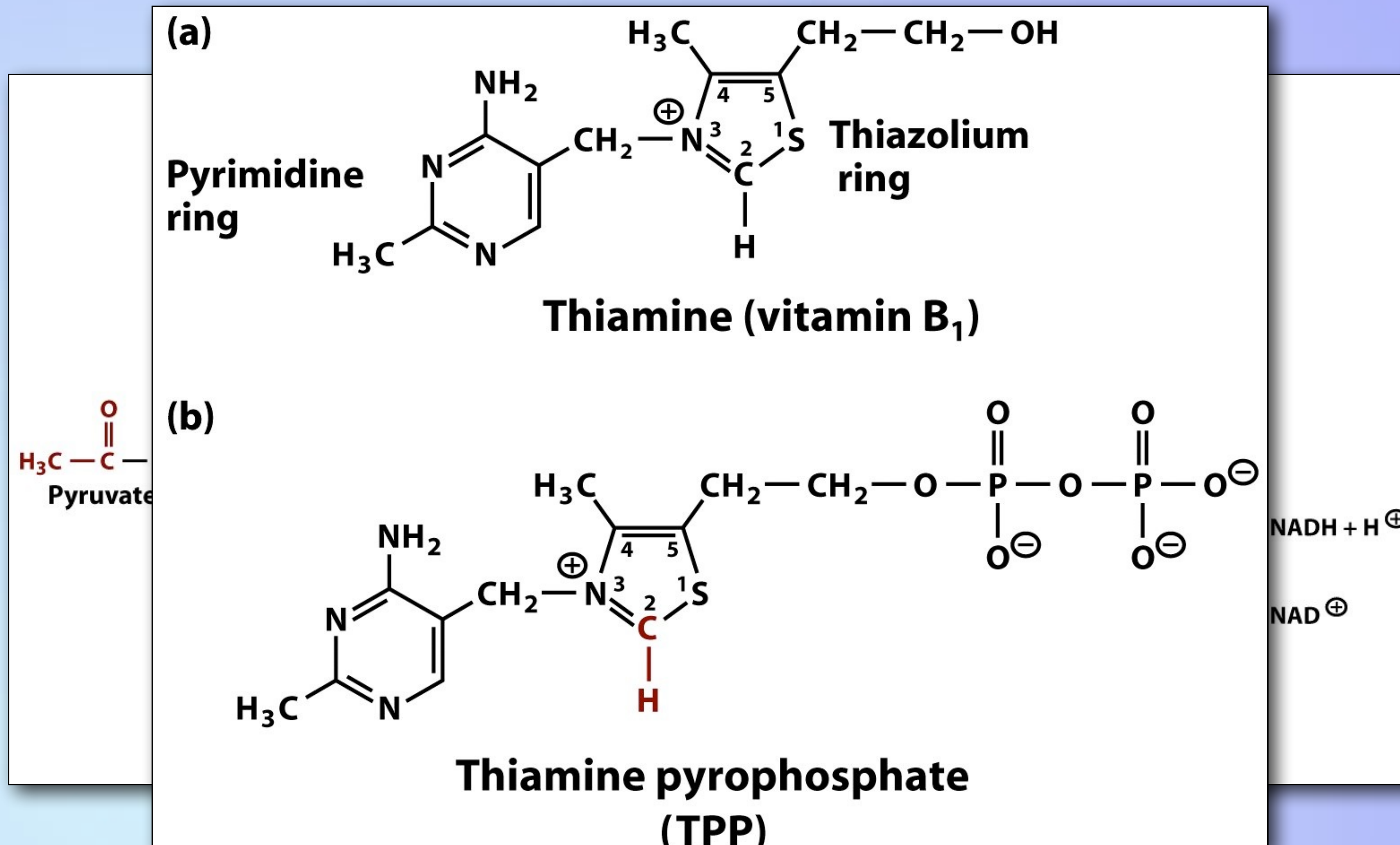

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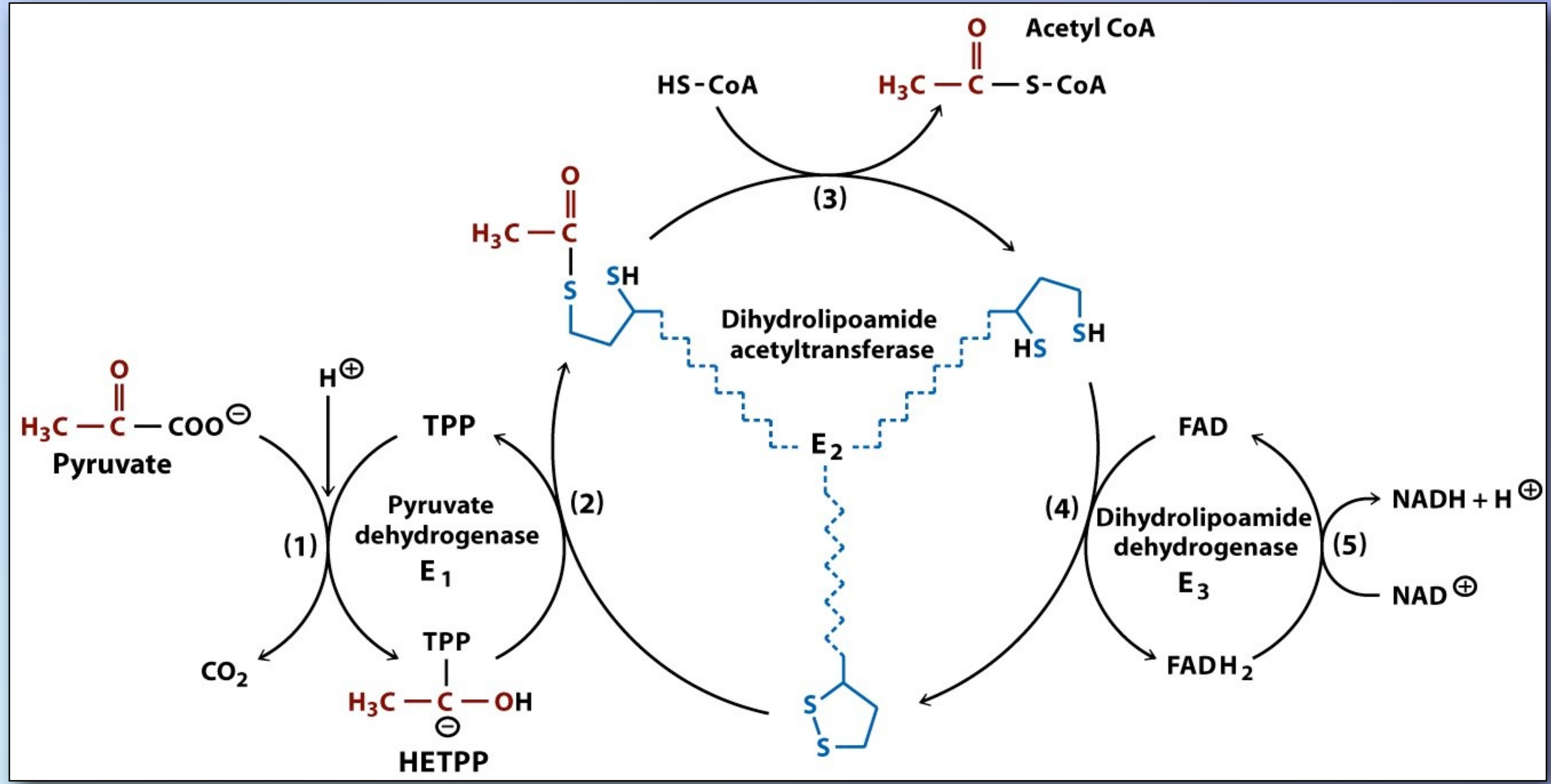

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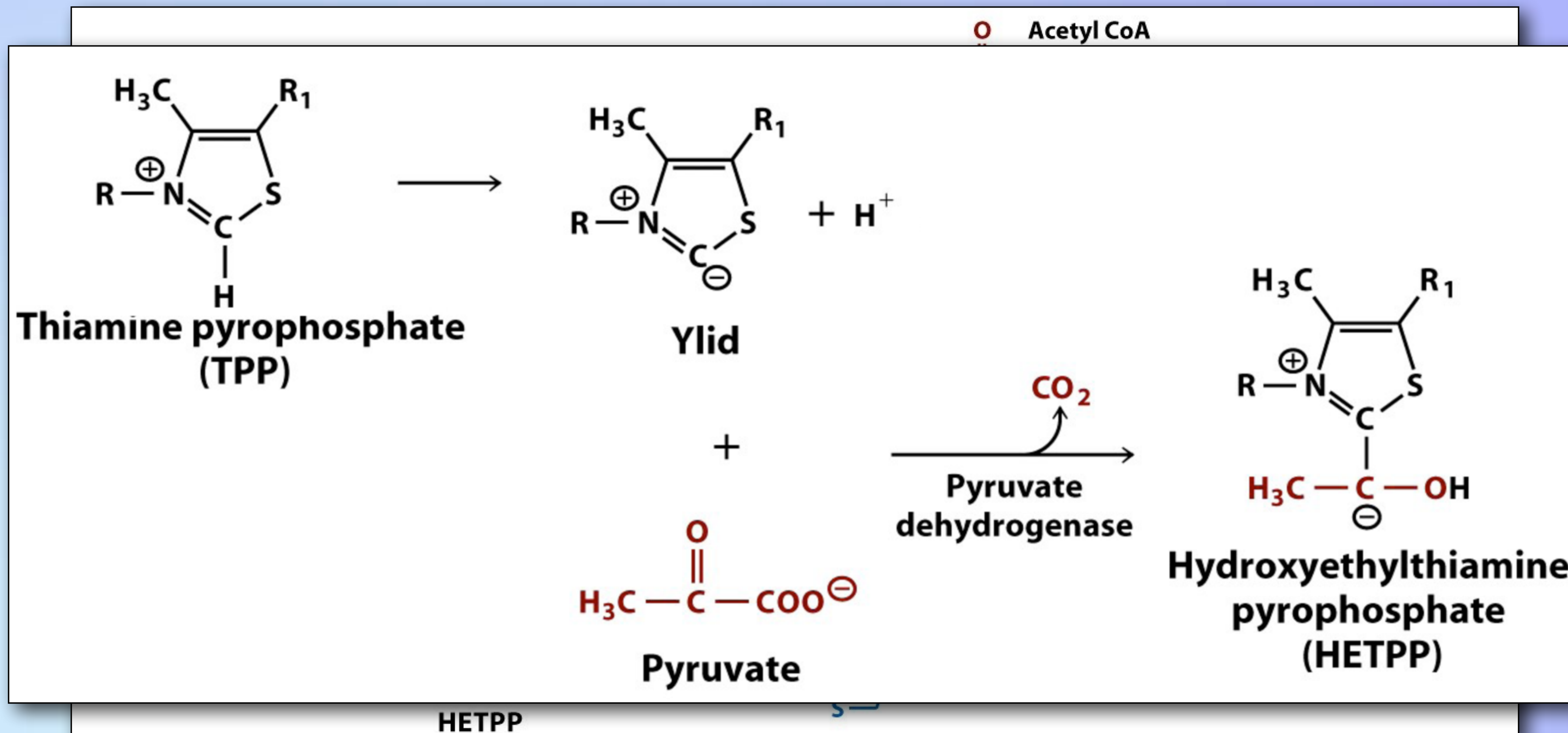

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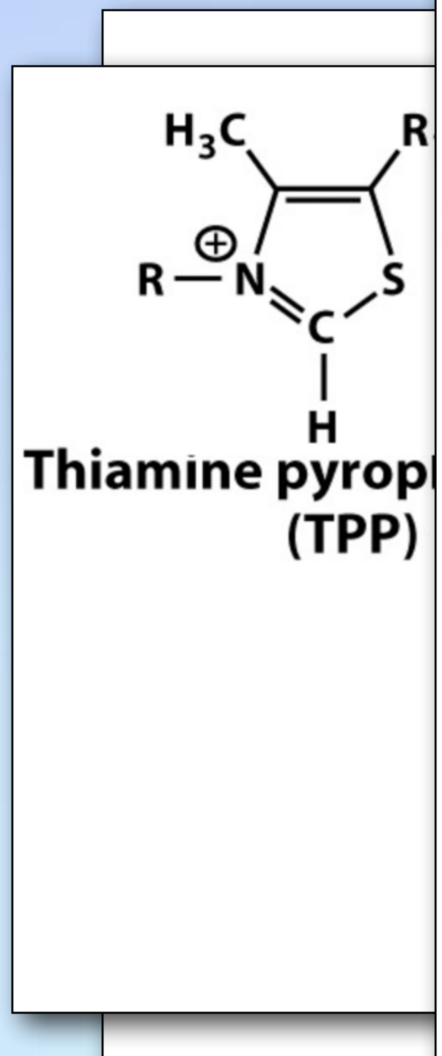

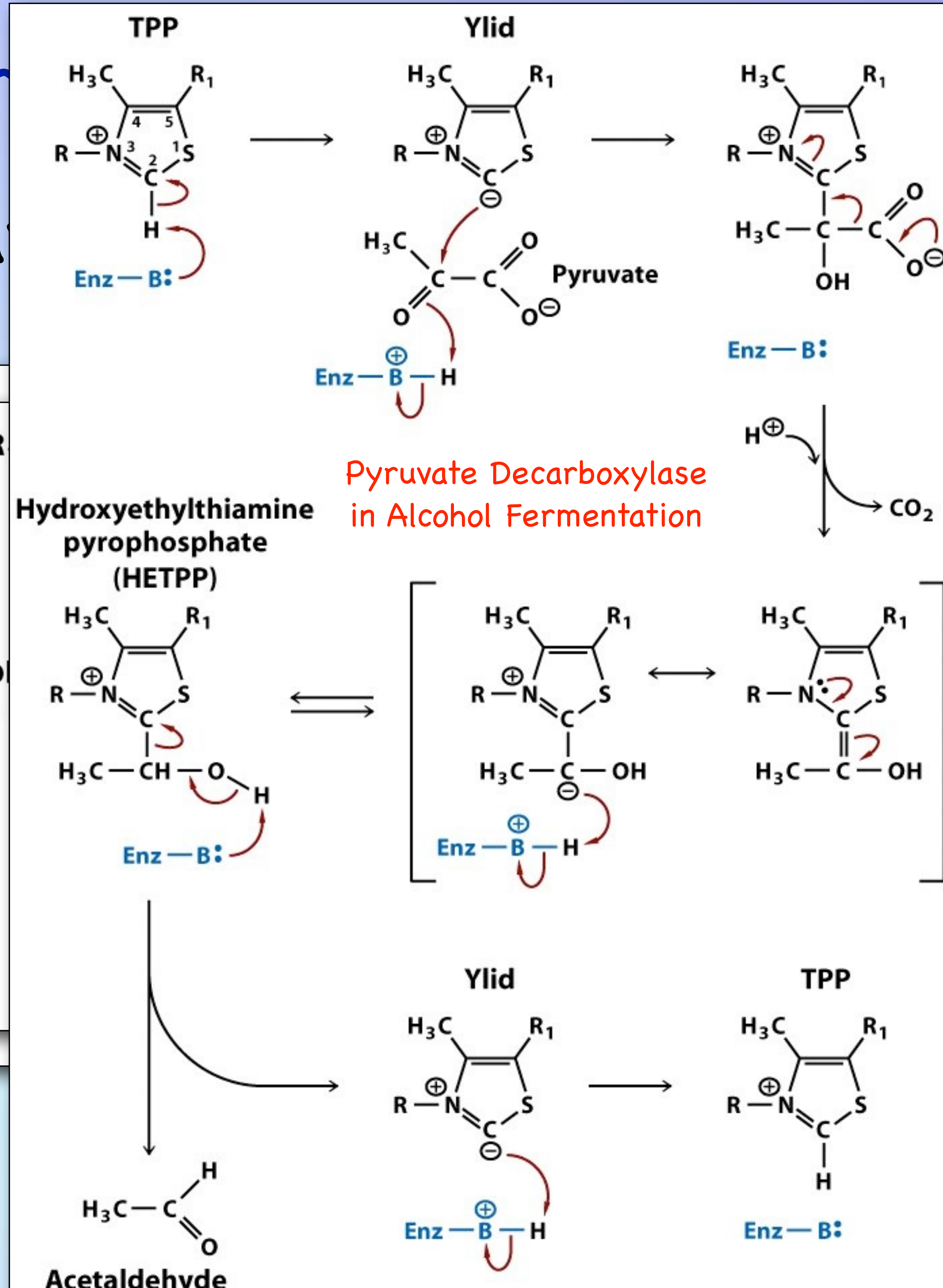

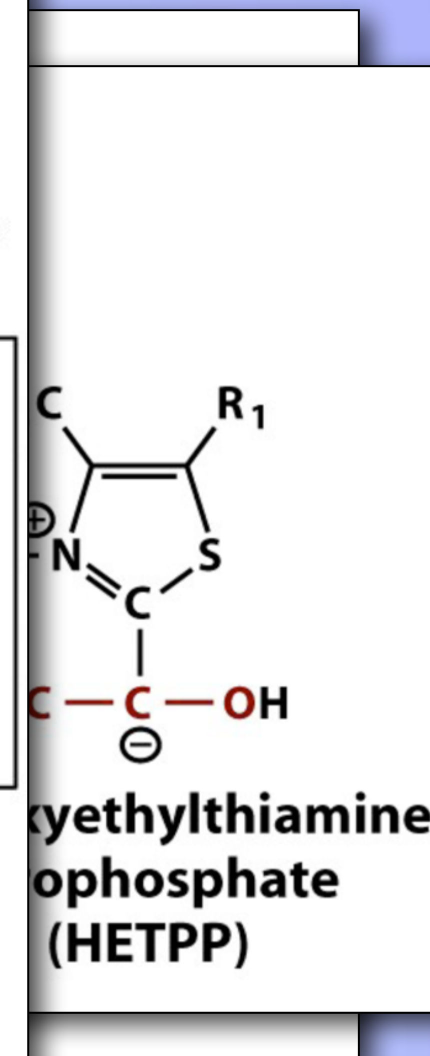

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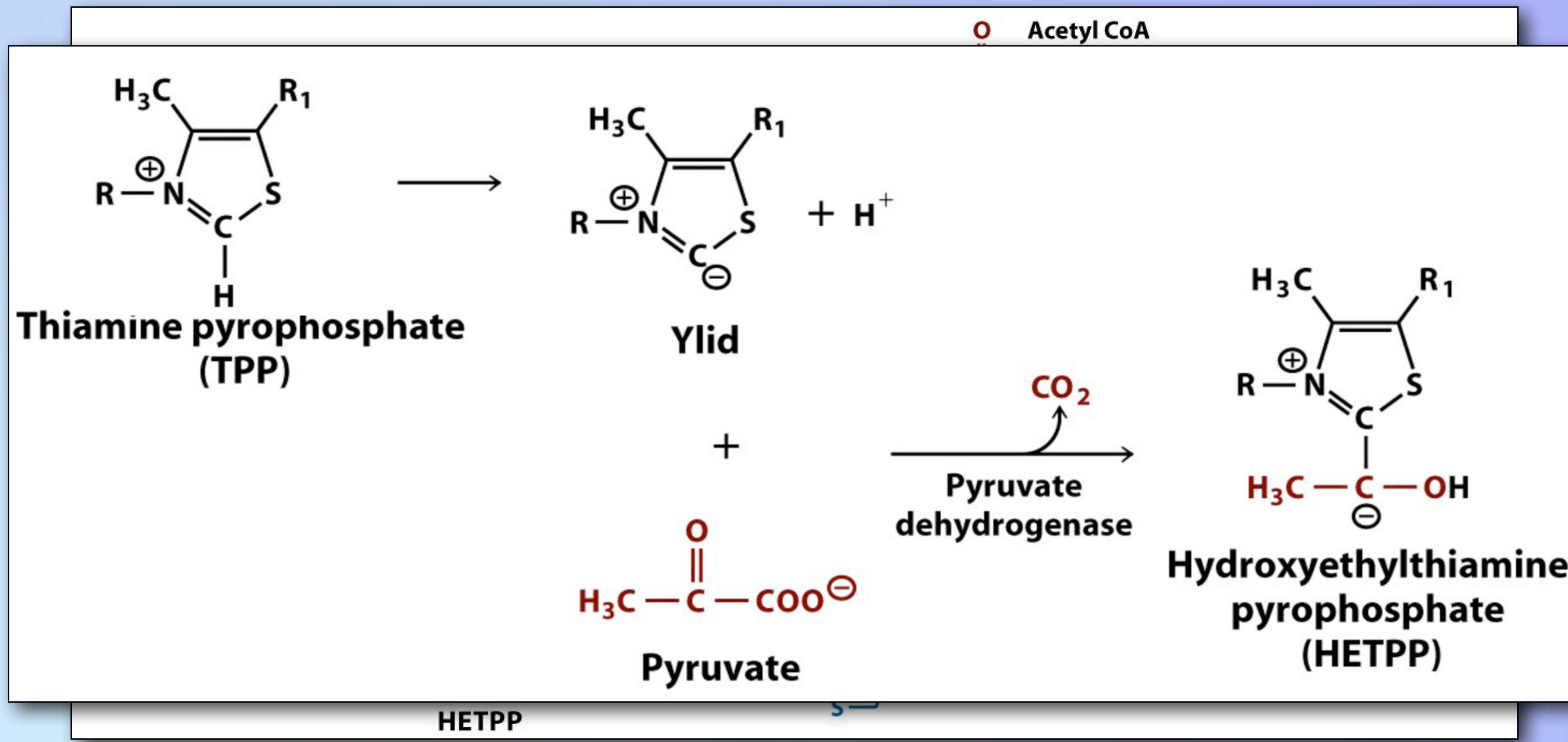

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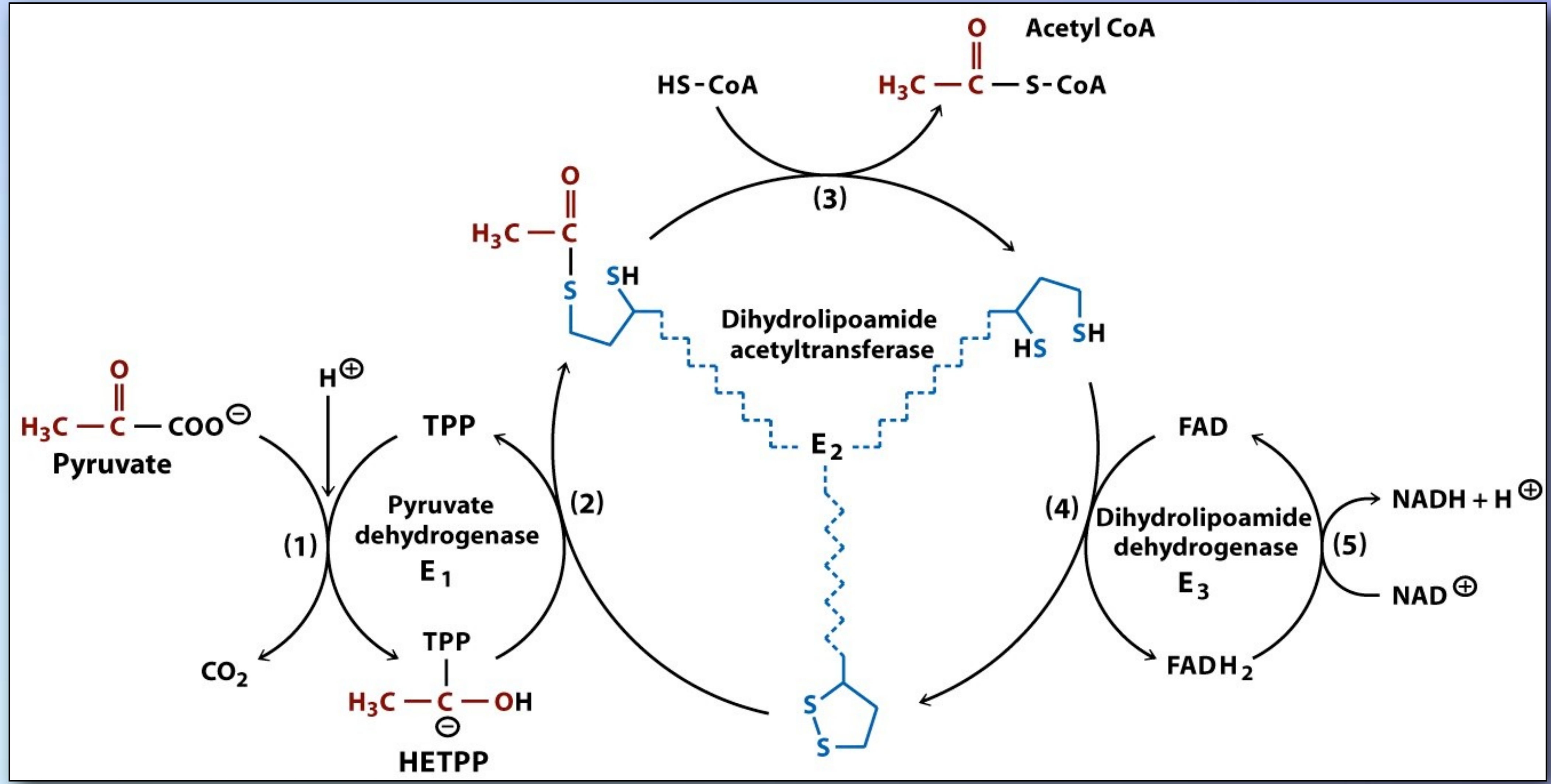

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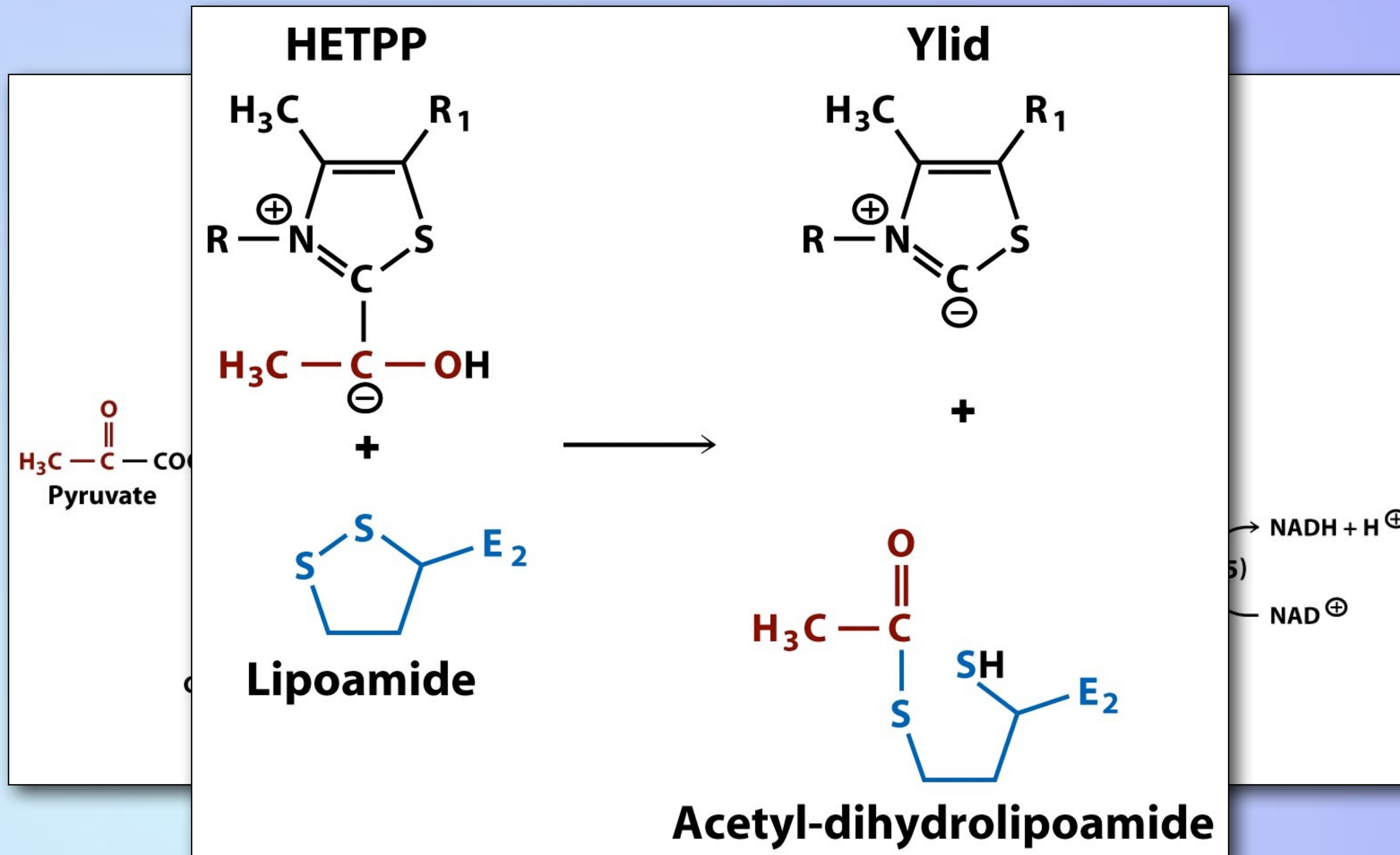

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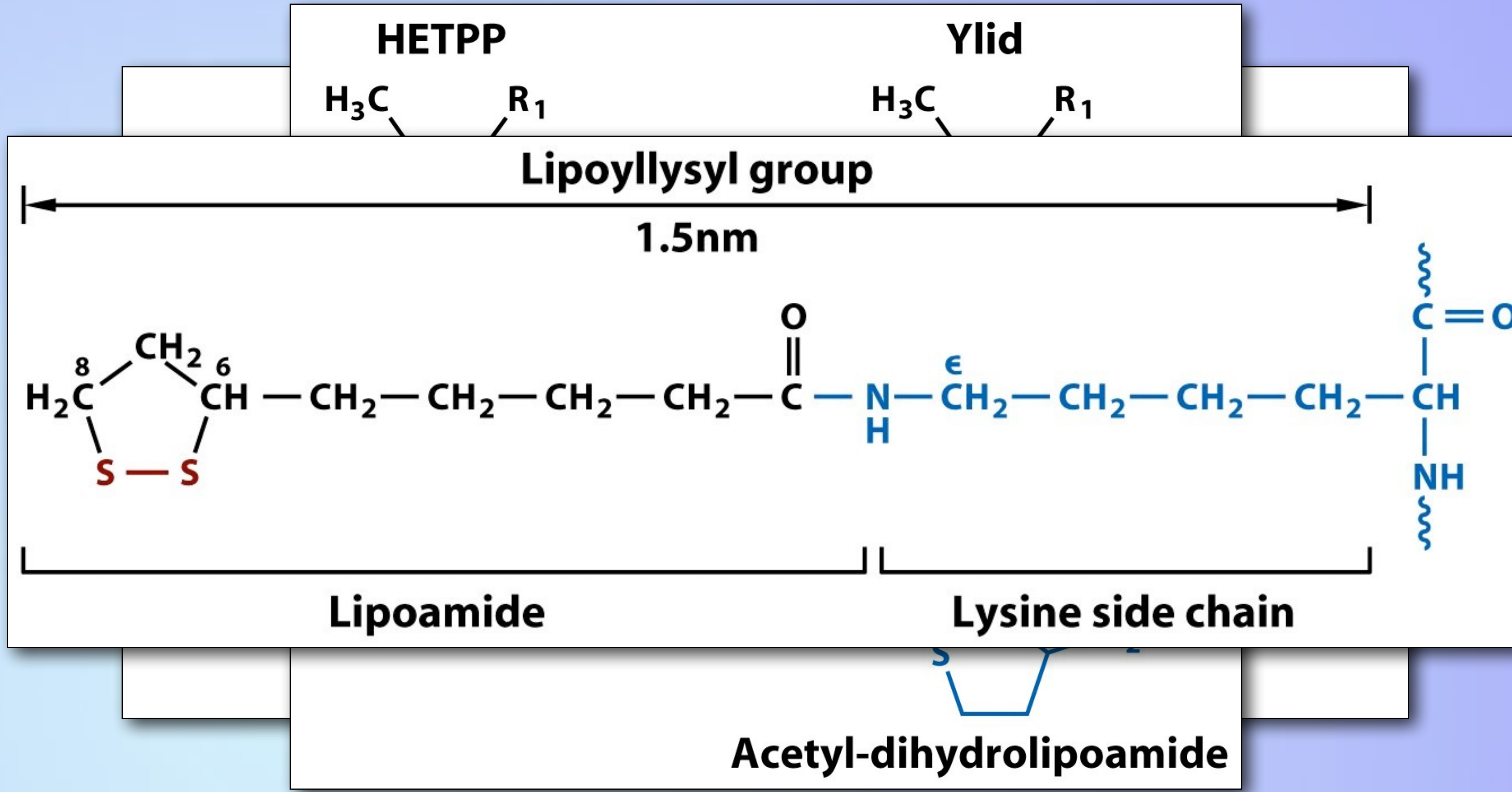

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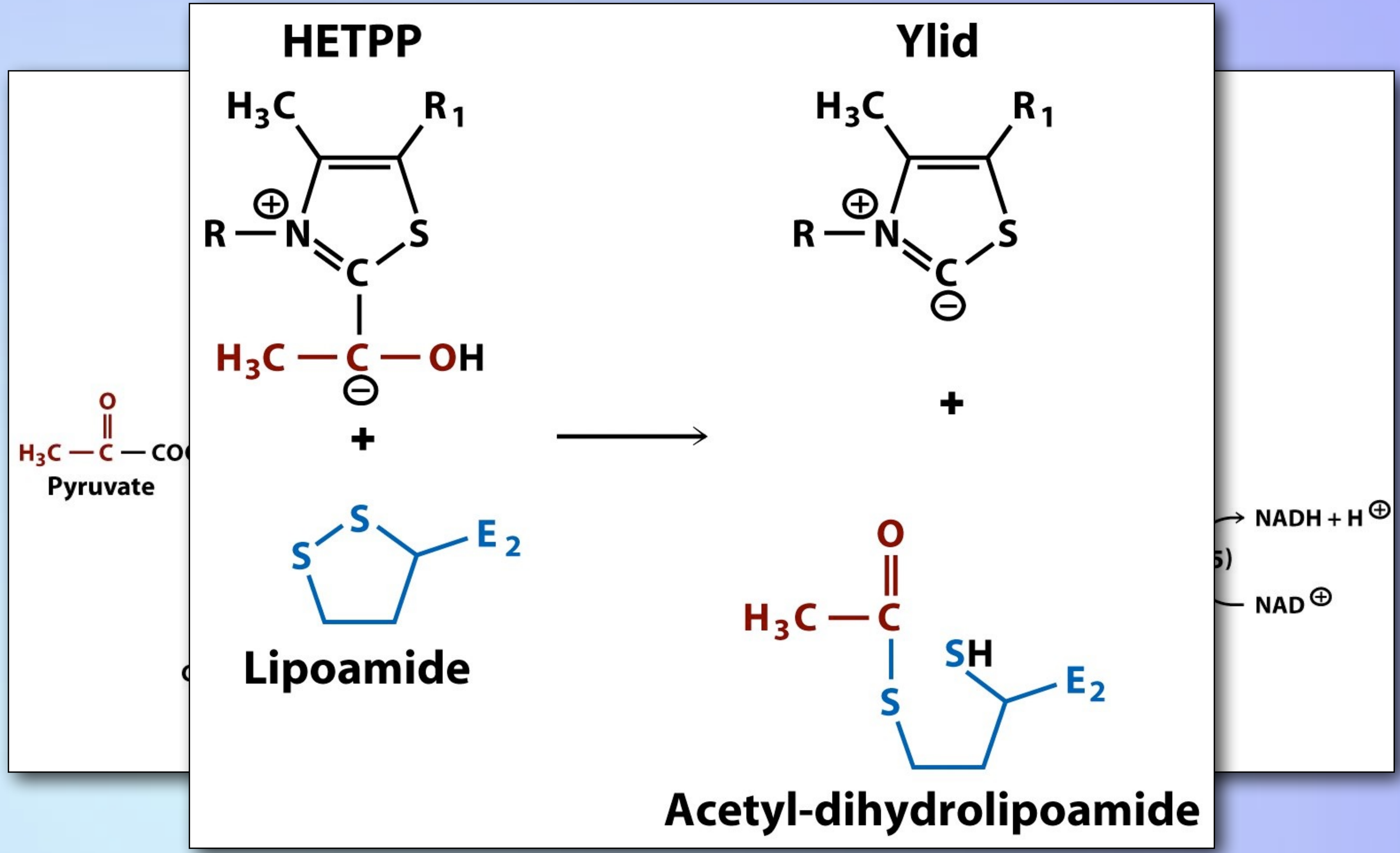

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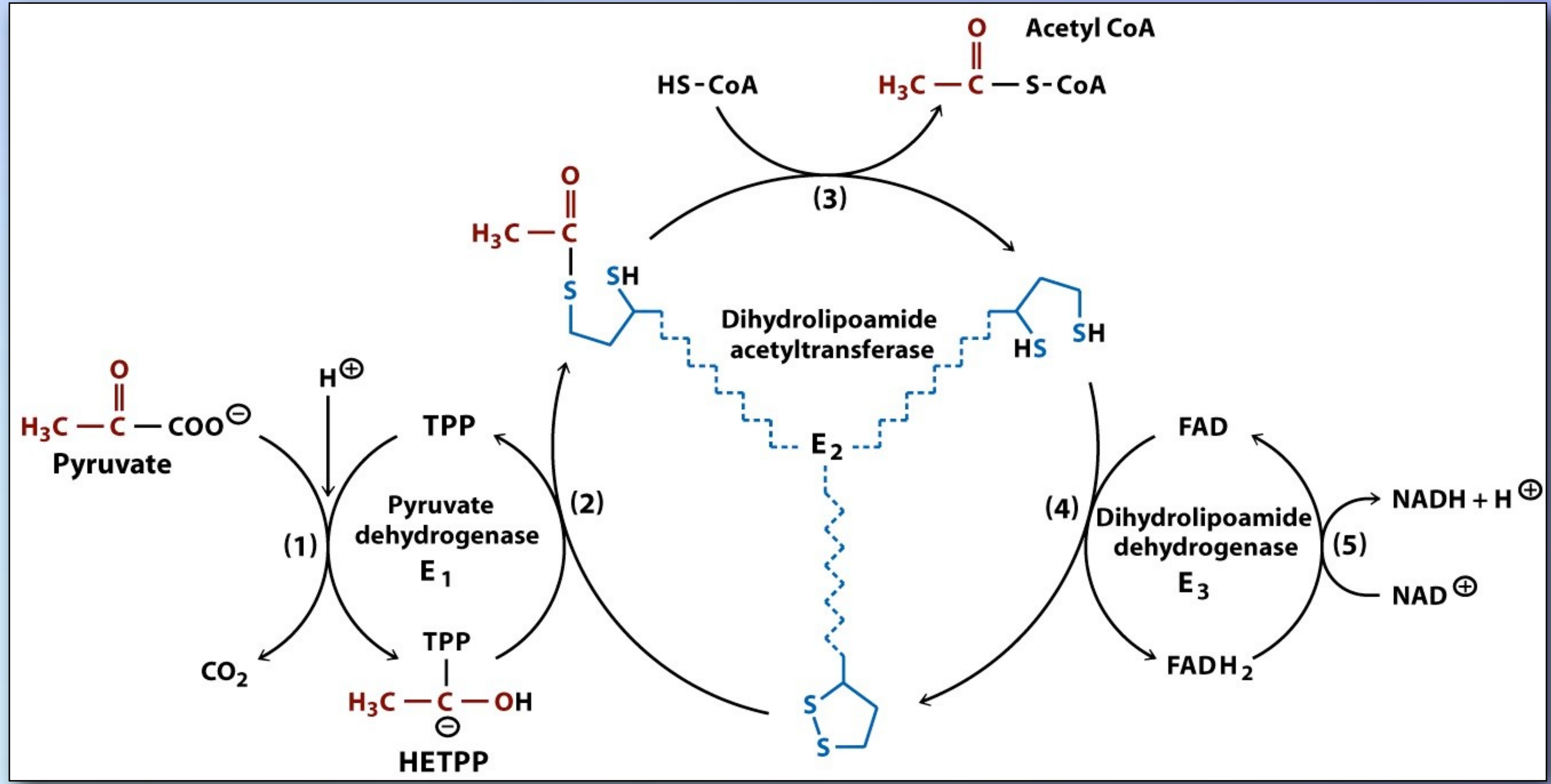

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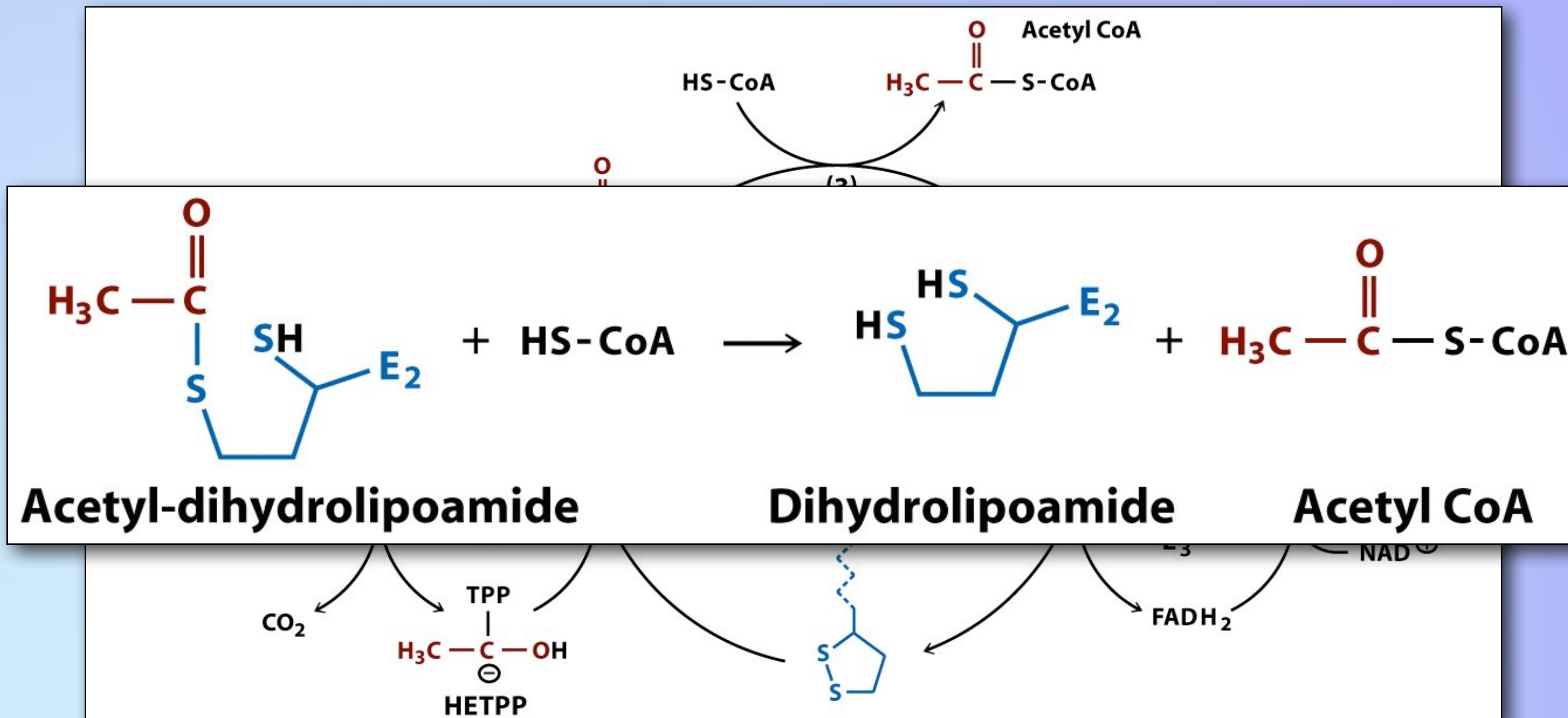

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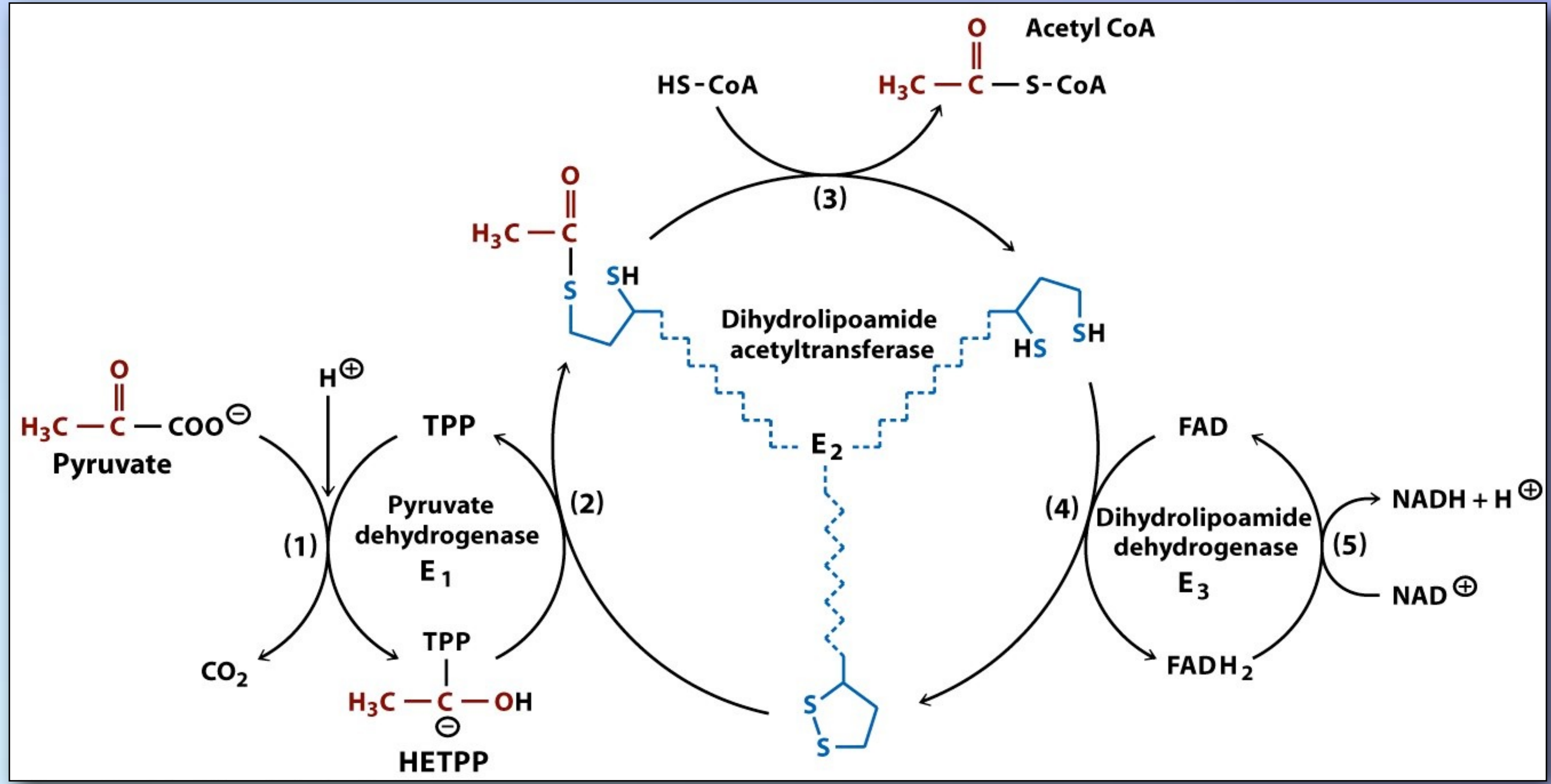

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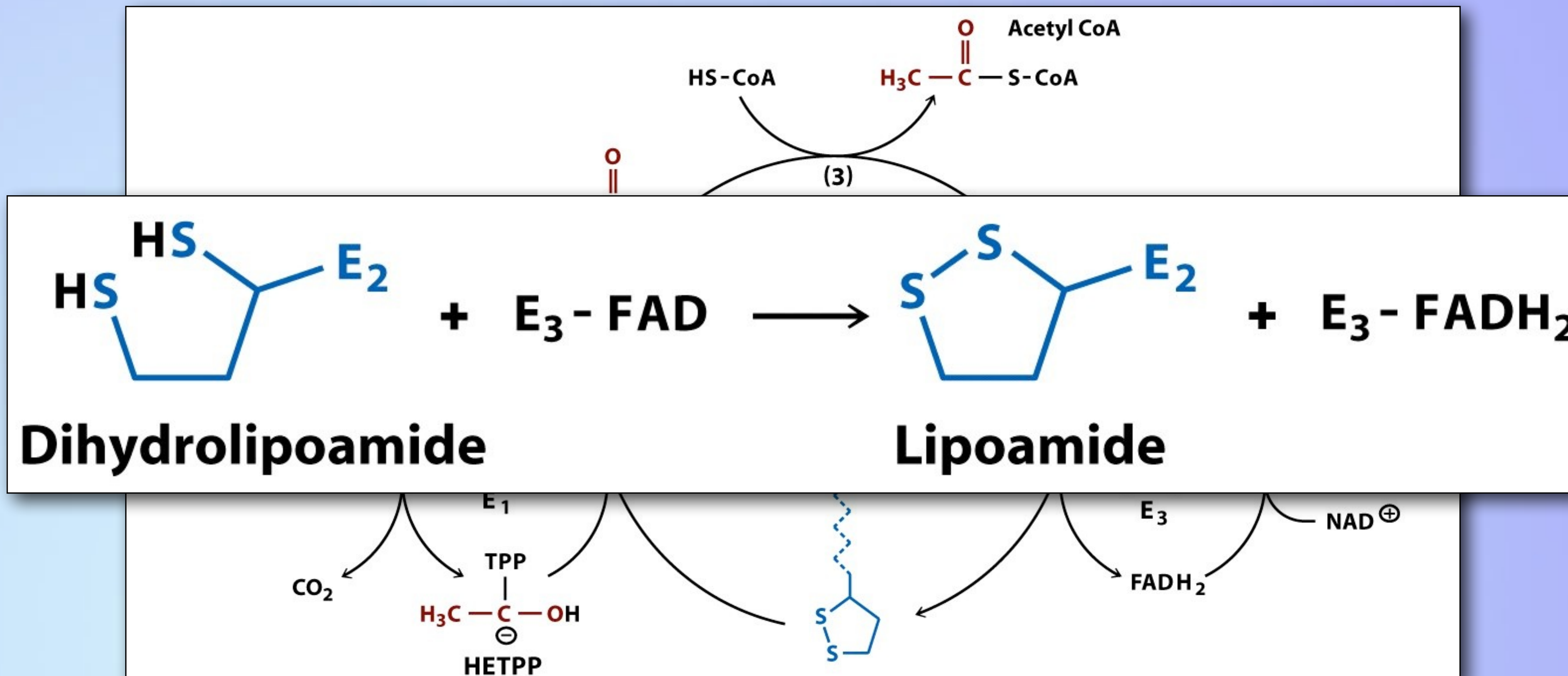

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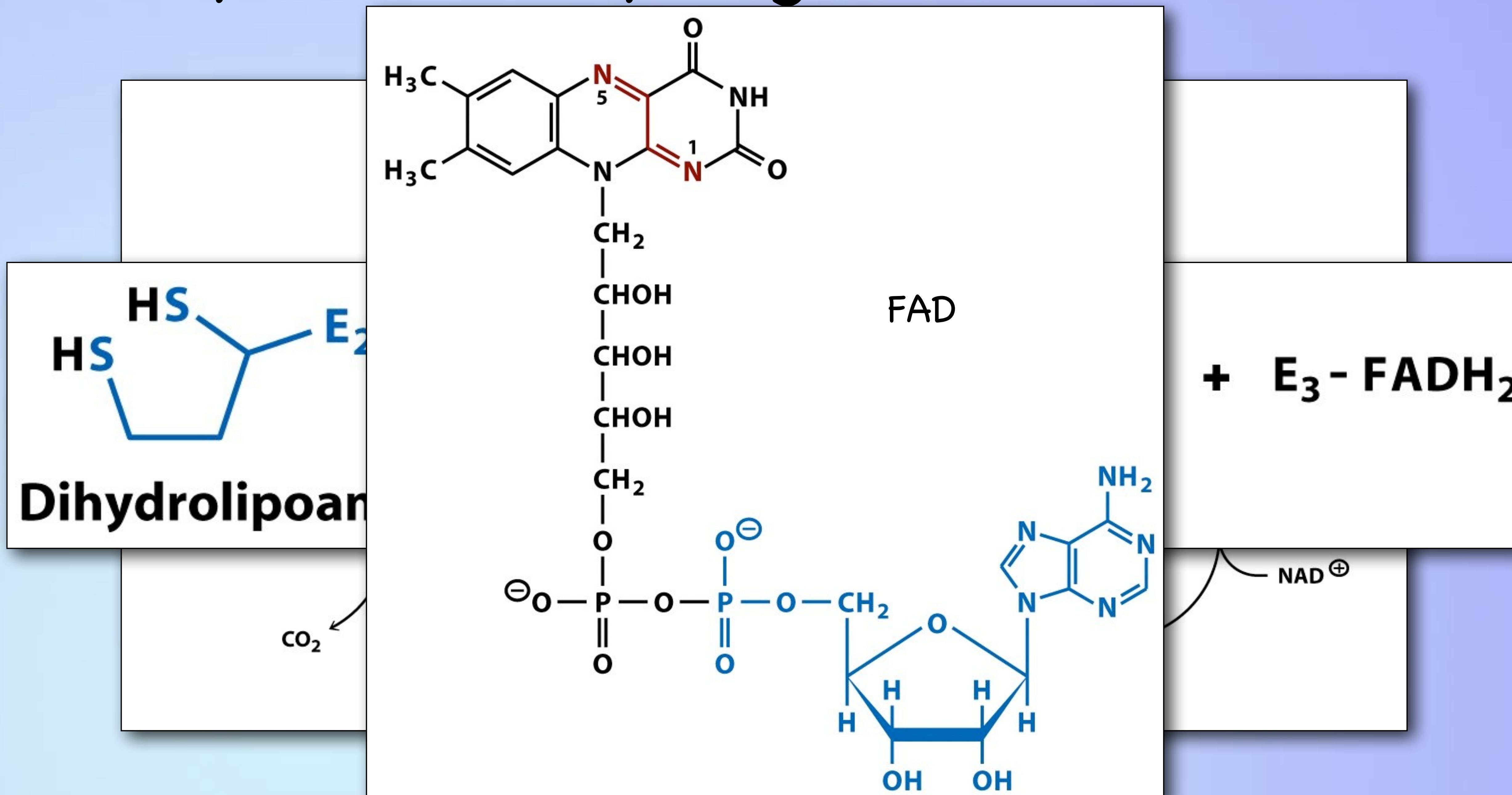

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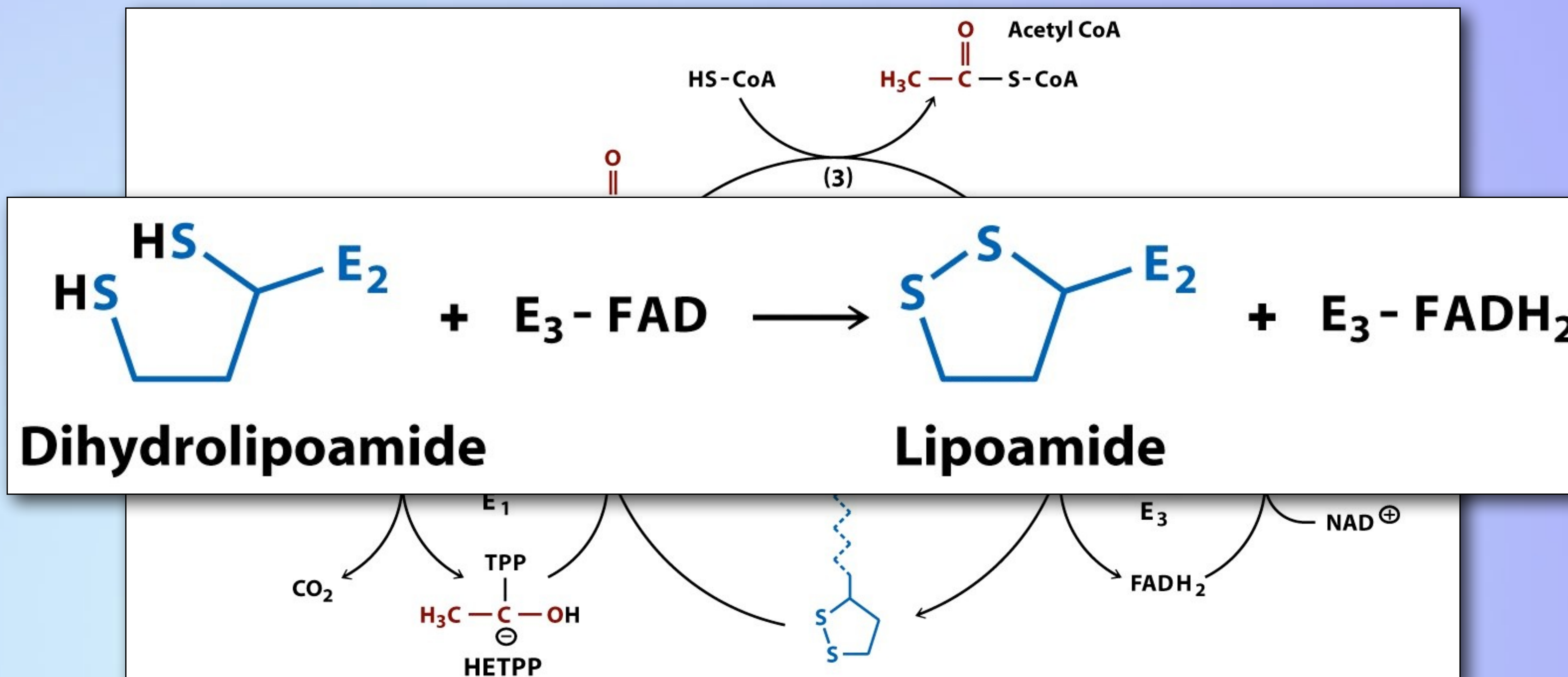

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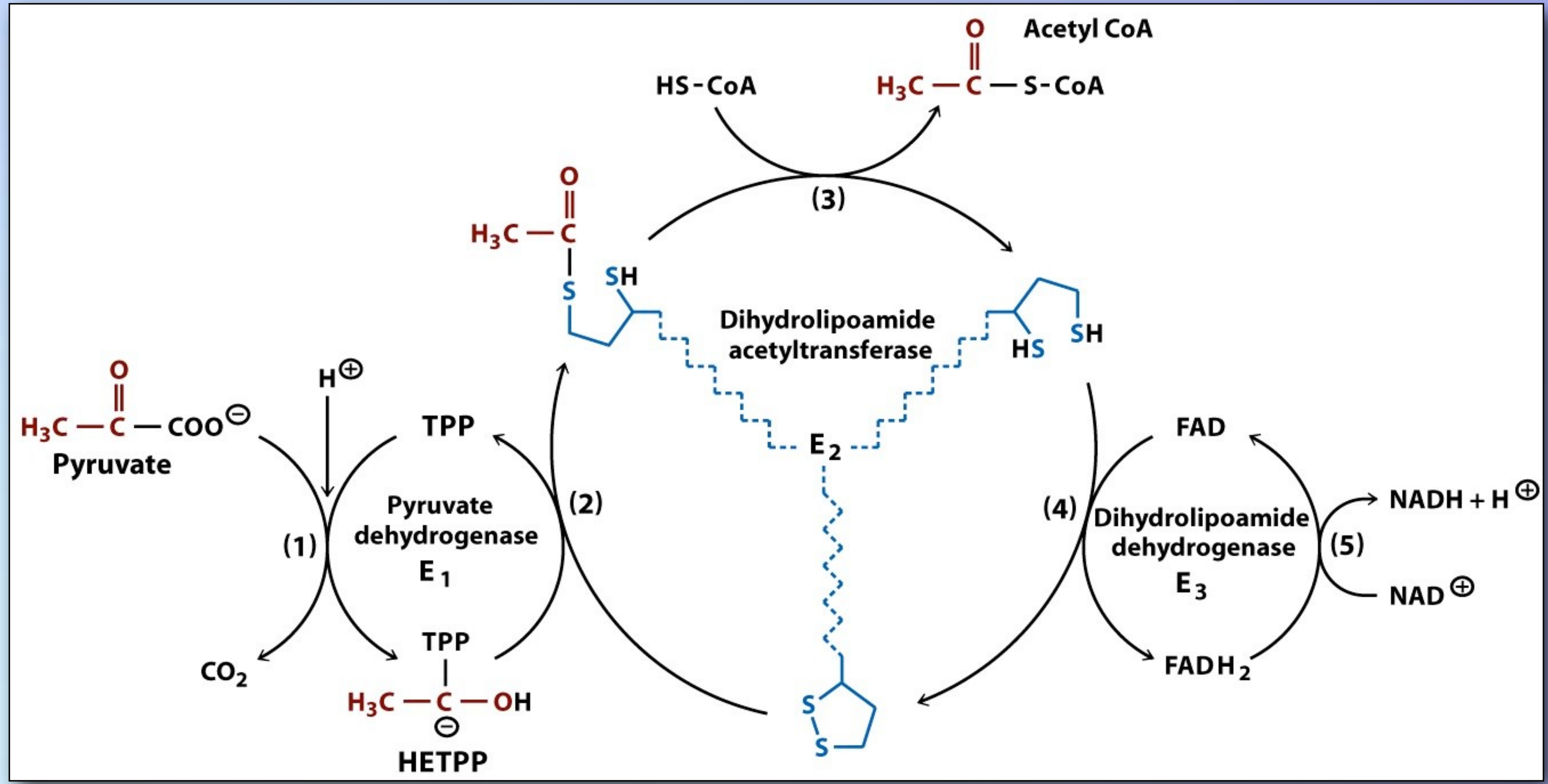

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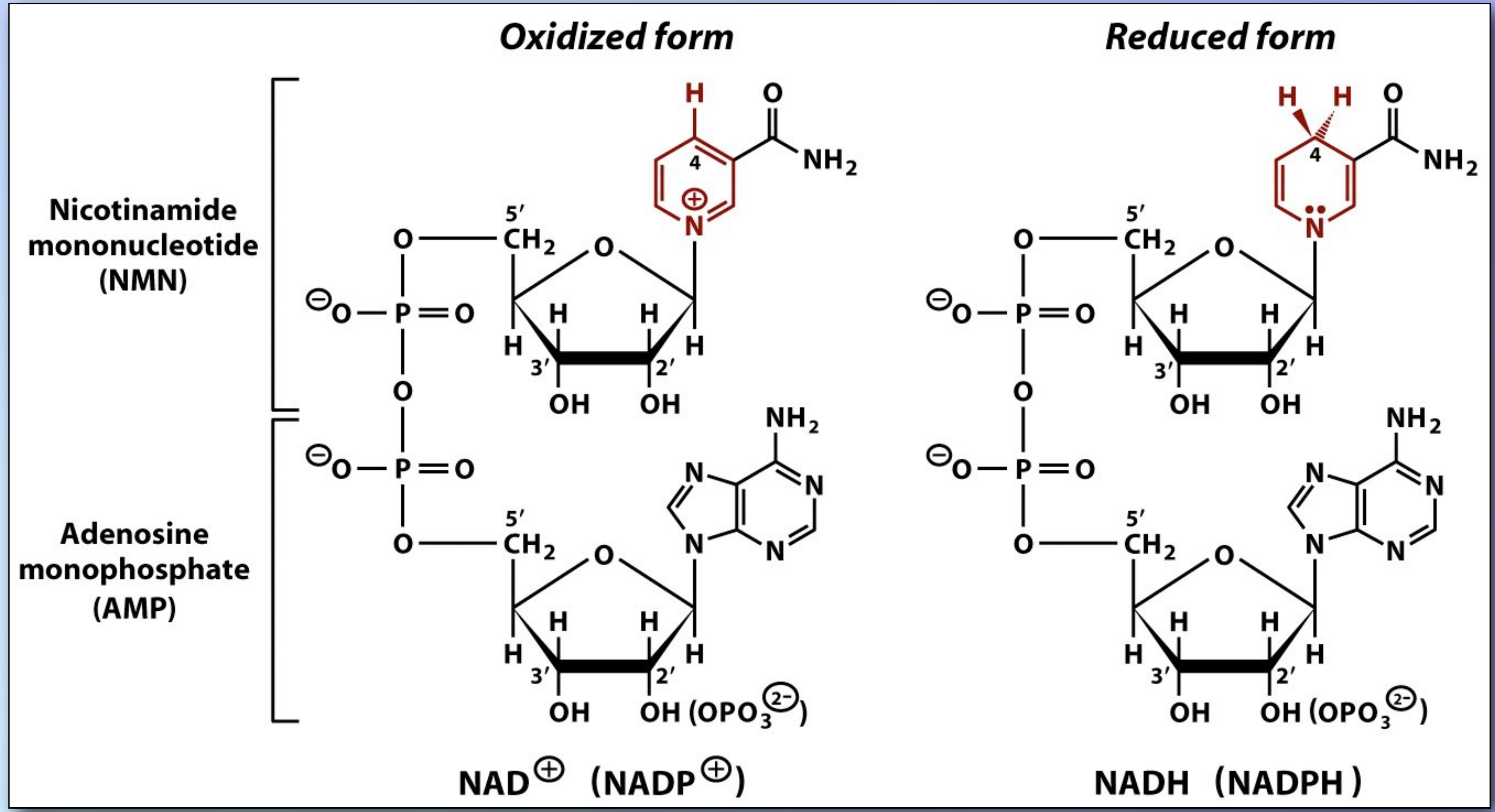

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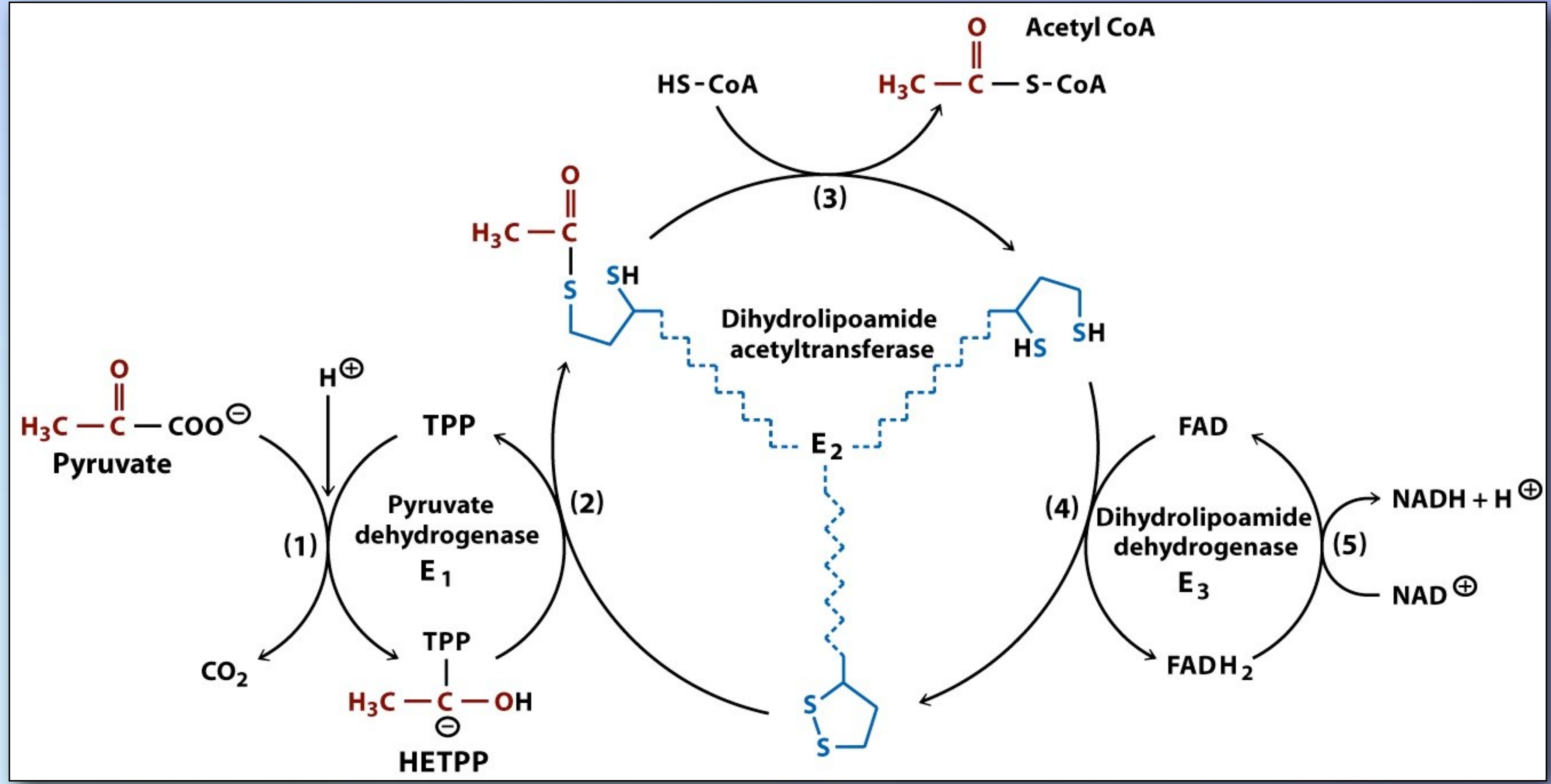

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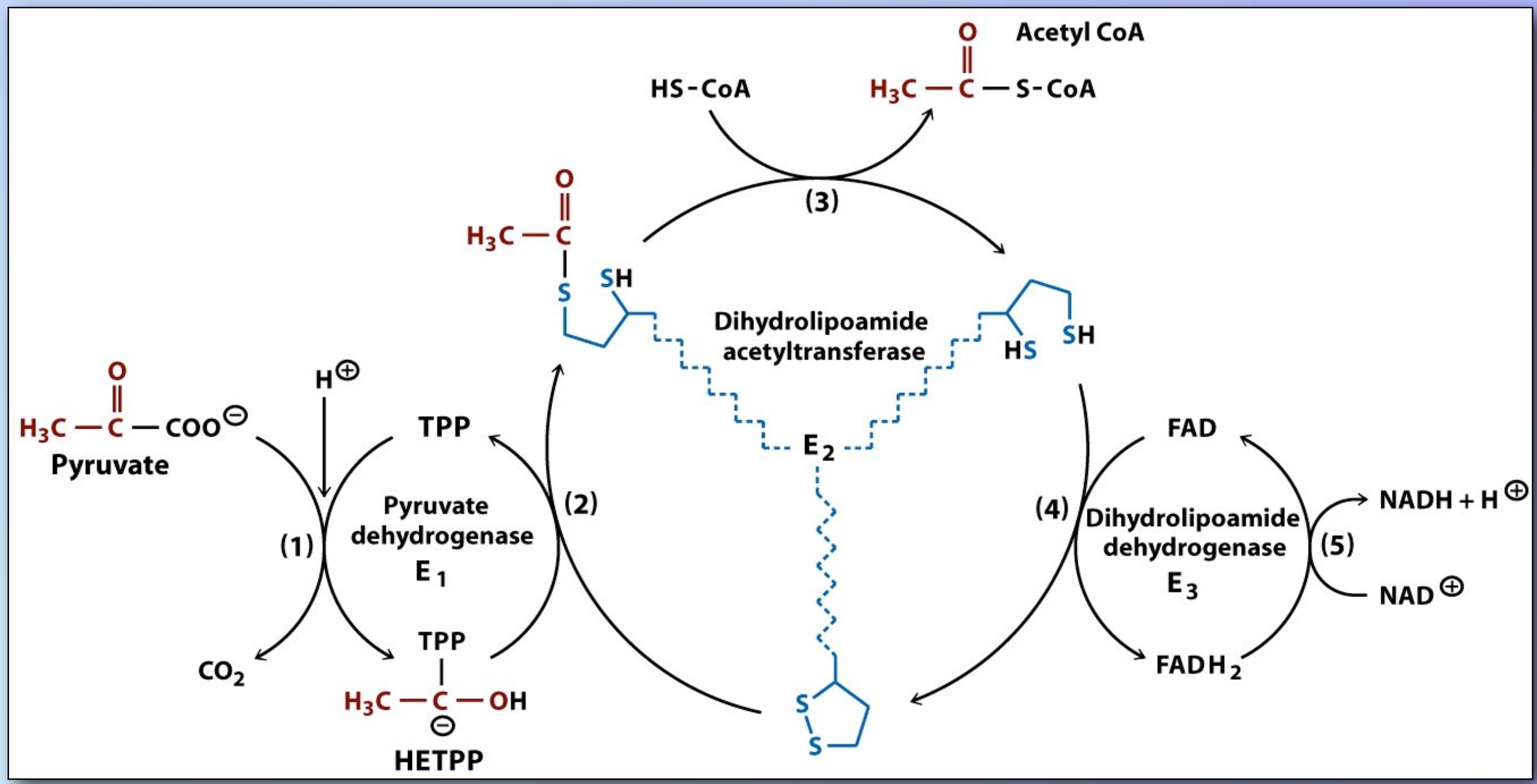

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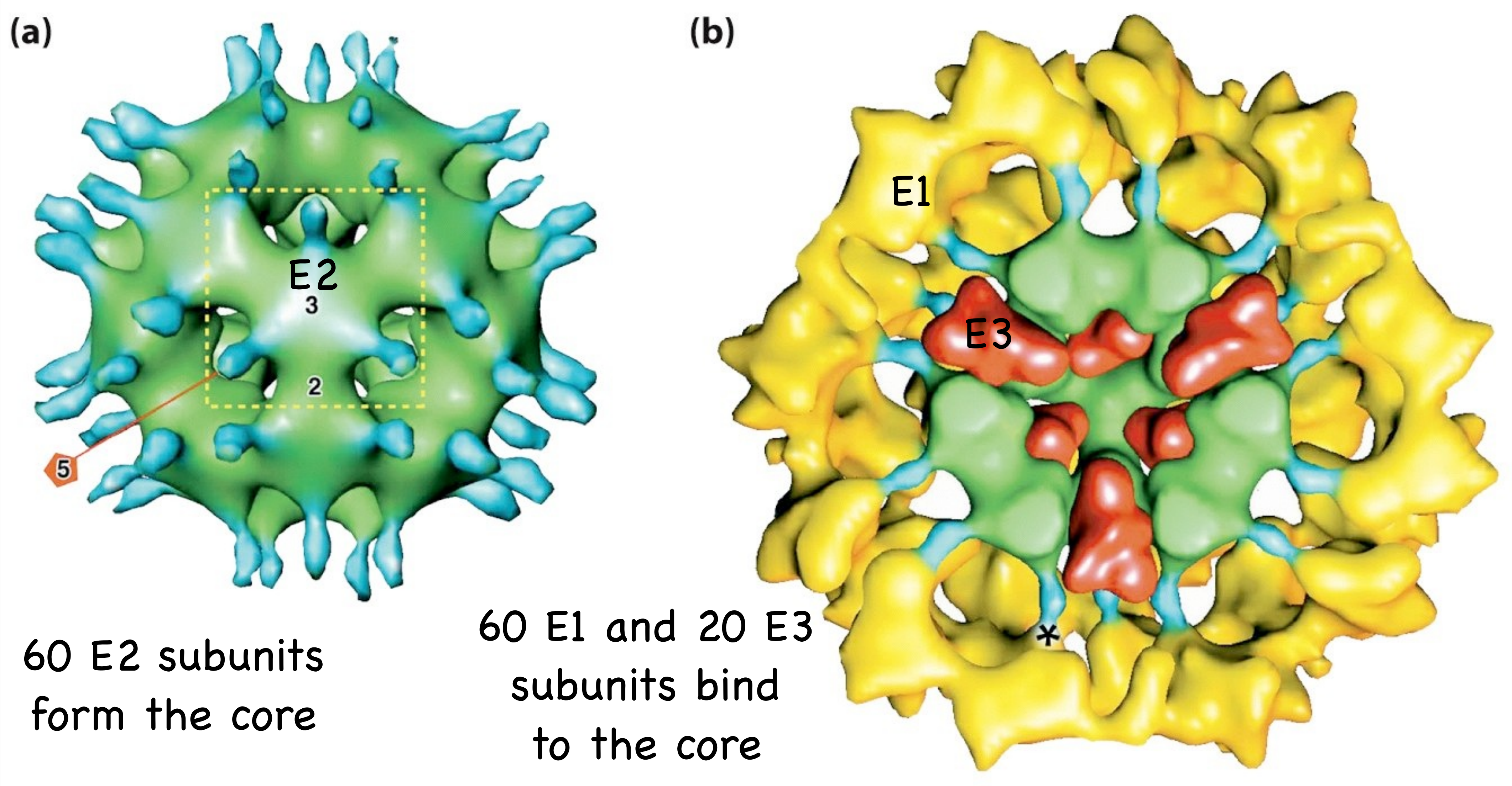

60 E2 subunits form the core

60 E1 and 20 E3 subunits bind to the core

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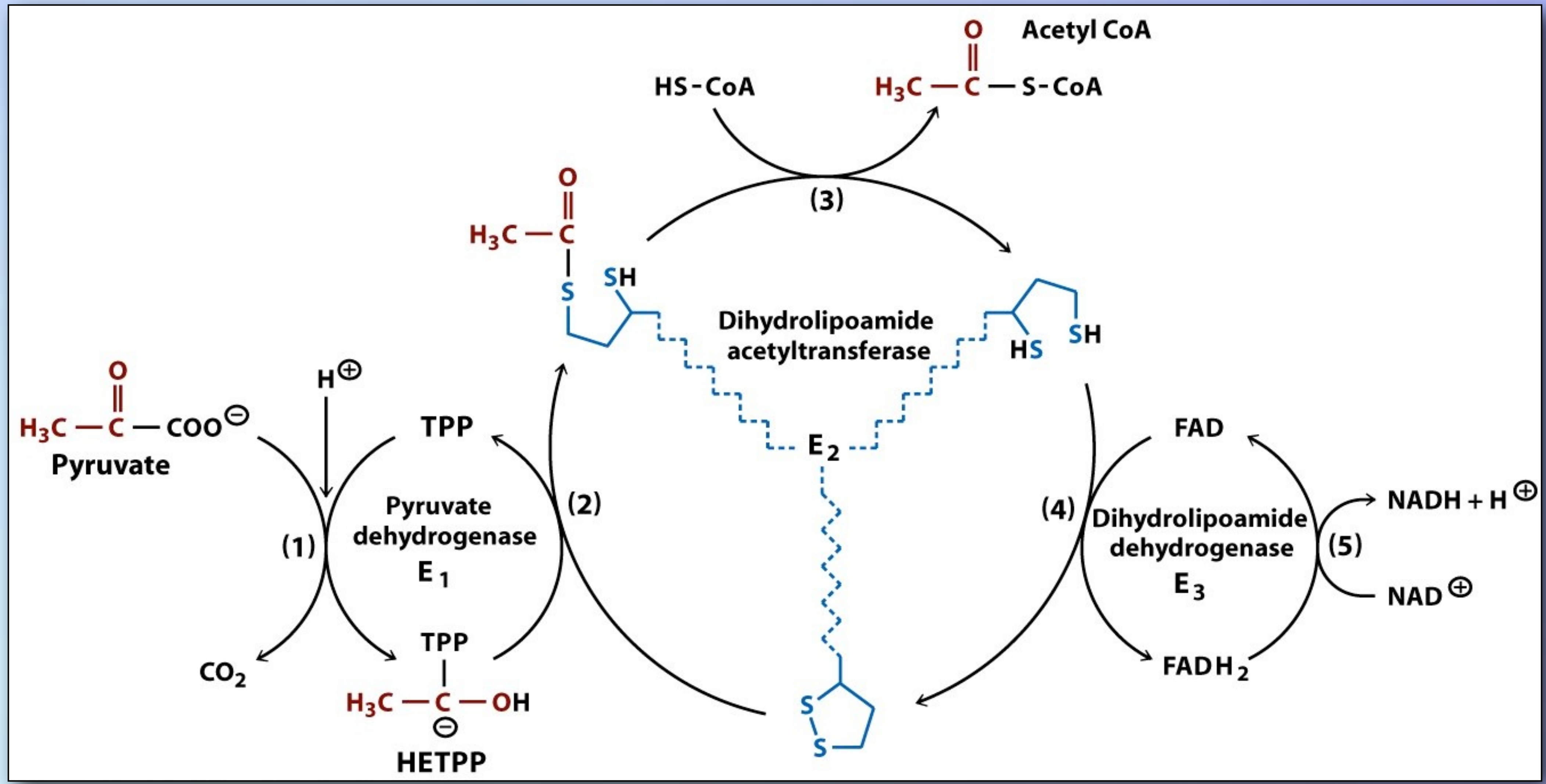

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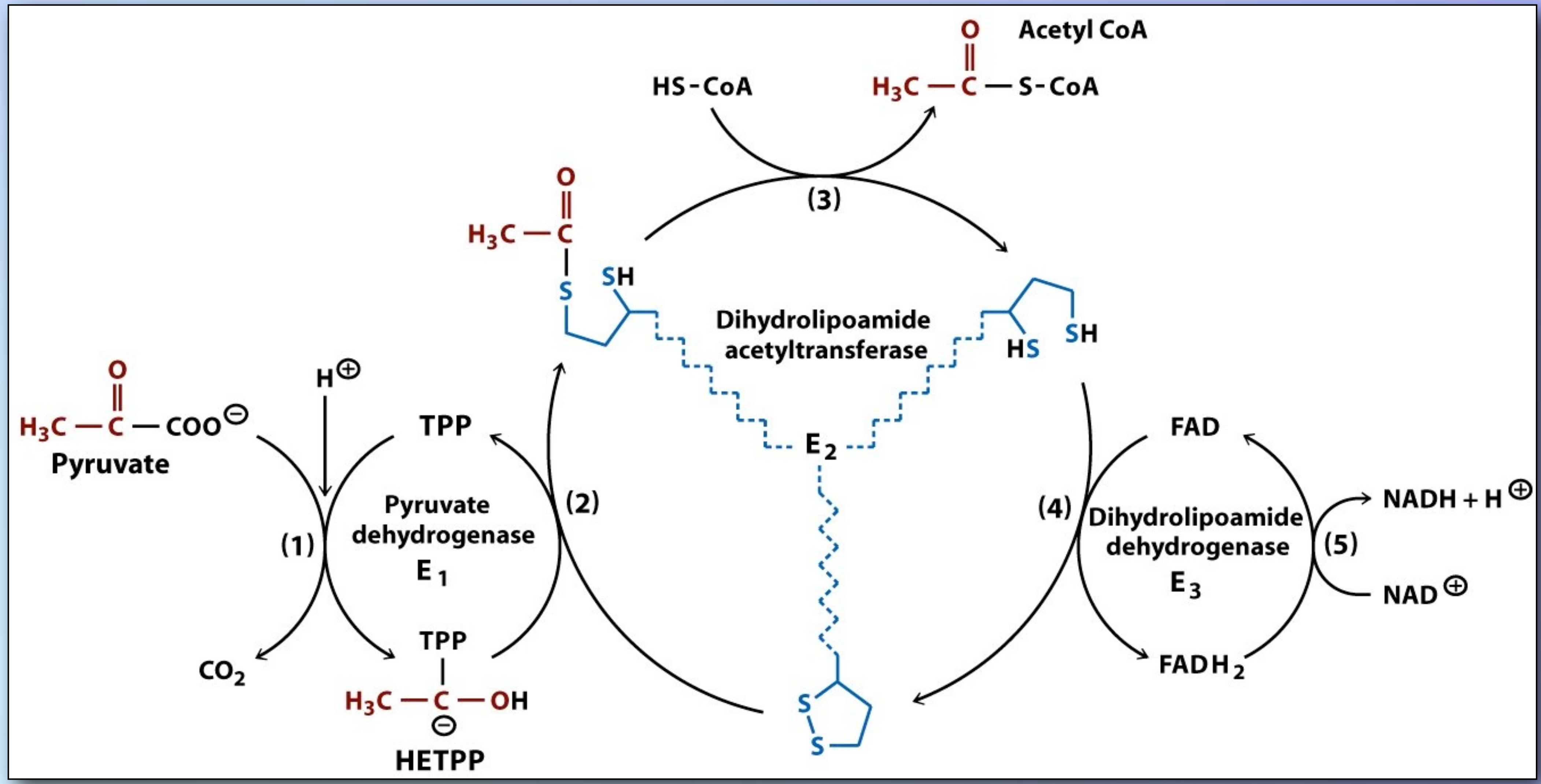

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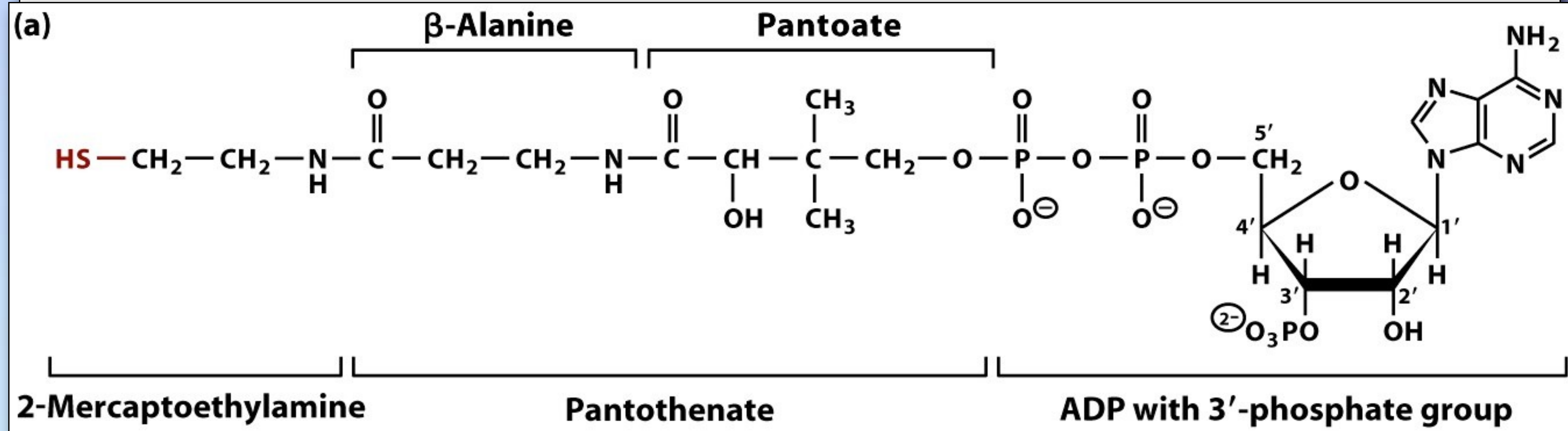

Coenzyme A

Conversion of Pyruvate to Acetyl CoA

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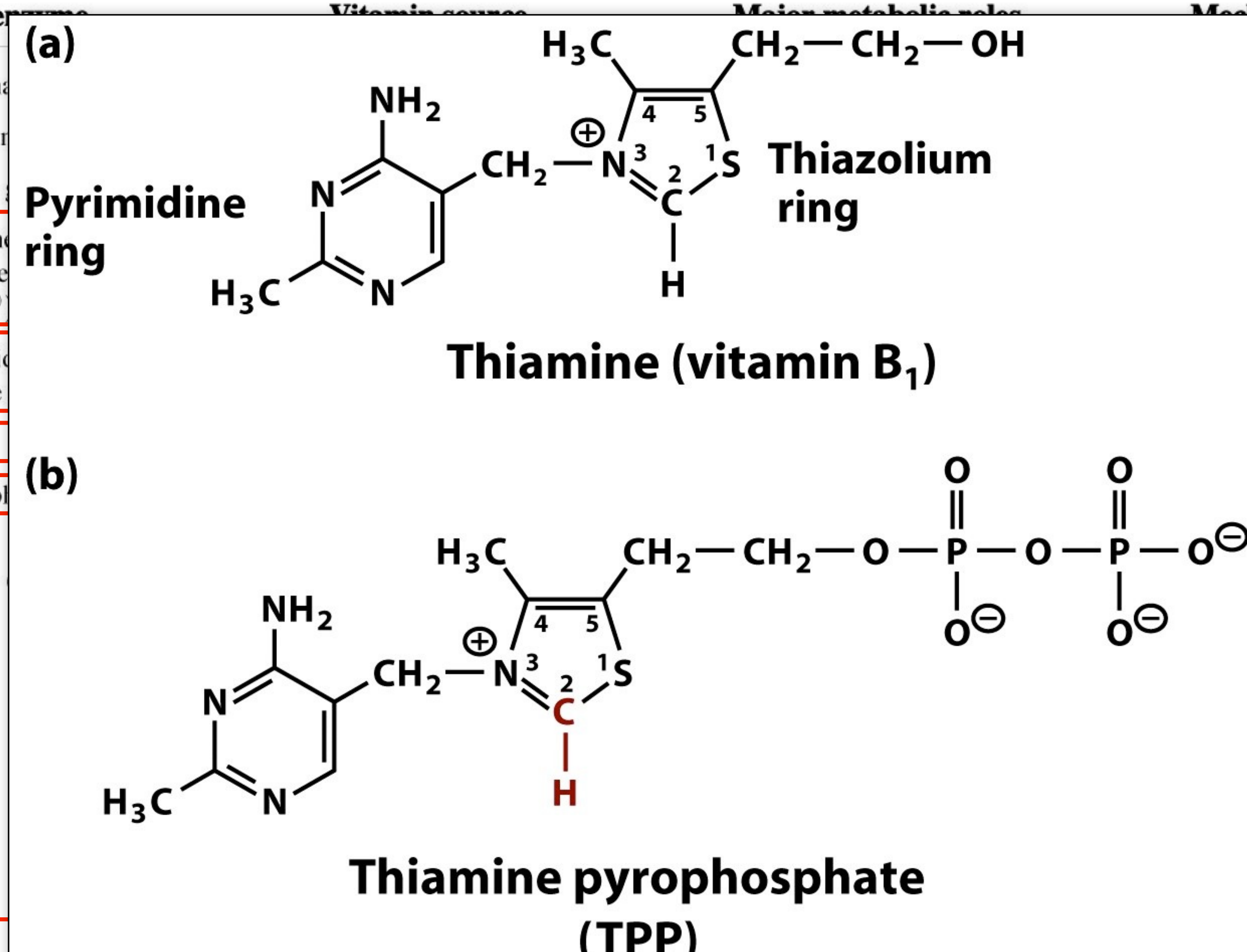

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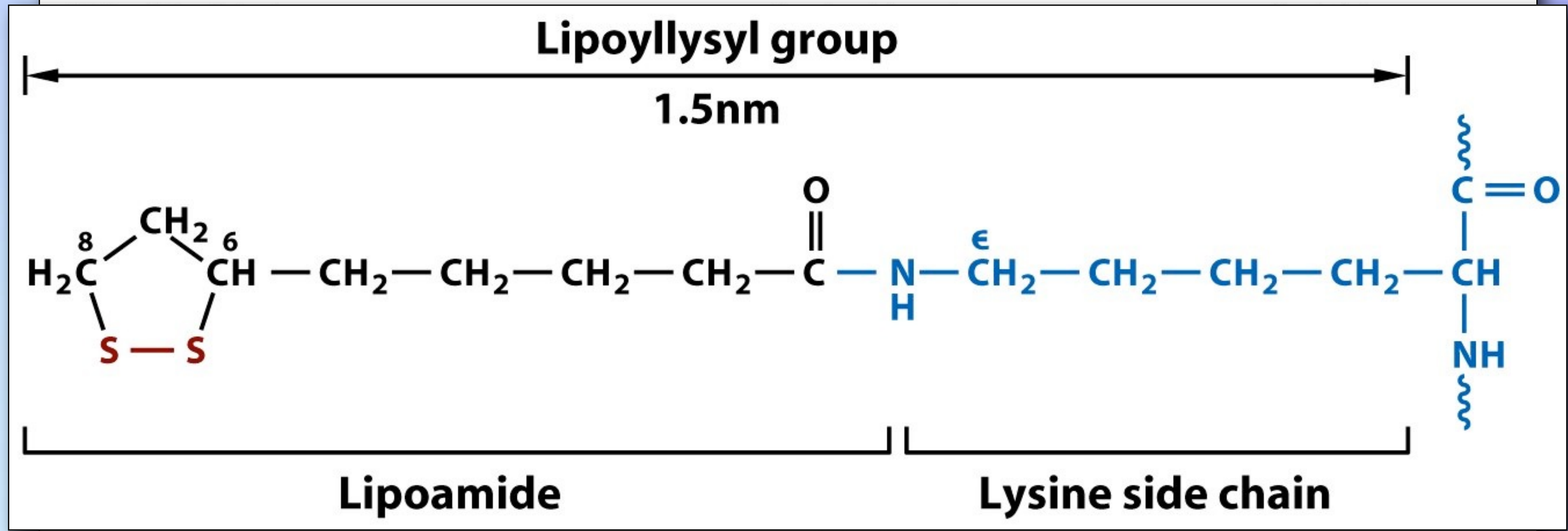
Retinal	Vitamin A	Vision	Prosthetic group
Vitamin K	Vitamin K	Carboxylation of some glutamate residues	Prosthetic group
Ubiquinone (Q)	—	Lipid-soluble electron carrier	Cosubstrate



Conversion of Pyruvate to Acetyl CoA

TABLE 7.2 Major coenzymes

Coenzyme	Vitamin source	Major metabolic roles	Mechanistic role
Adenosine triphosphate (ATP)	—	Transfer of phosphoryl or nucleotidyl groups	Cosubstrate
S-Adenosylmethionine	—	Transfer of methyl groups	Cosubstrate
Uridine diphosphate glucose	—	Transfer of glycosyl groups	Cosubstrate
Nicotinamide adenine dinucleotide ($NAD^{\oplus}$) and nicotinamide adenine dinucleotide phosphate ($NADP^{\oplus}$)	Niacin	Oxidation-reduction reactions involving two-electron transfers	Cosubstrate
Flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD)	Riboflavin (B_2)	Oxidation-reduction reactions involving one- and two-electron transfers	Prosthetic group
Coenzyme A (CoA)	Pantothenate (B_3)	Transfer of acyl groups	Cosubstrate
Thiamine pyrophosphate (TPP)	Thiamine (B_1)	Transfer of two-carbon fragments containing a carbonyl group	Prosthetic group
Pyridoxal phosphate (PLP)	Pyridoxine (B_6)	Transfer of groups to and from amino acids	Prosthetic group
Biotin	Biotin	ATP-dependent carboxylation of substrates or carboxyl-group transfer between substrates	Prosthetic group
Tetrahydrofolate	Folate	Transfer of one-carbon substituents, especially formyl and hydroxymethyl groups; provides the methyl group for thymine in DNA	Cosubstrate
Adenosylcobalamin	Cobalamin (B_{12})	Intramolecular rearrangements	Prosthetic group
Methylcobalamin	Cobalamin (B_{12})	Transfer of methyl groups	Prosthetic group
Lipoamide	—	Oxidation of a hydroxyalkyl group from TPP and subsequent transfer as an acyl group	Prosthetic group
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Thiamine pyrophosphate (TPP)			Prosthetic group
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Adenosylcobalamin			Prosthetic group
Methylcobalamin			Prosthetic group
Lipoamide			Prosthetic group
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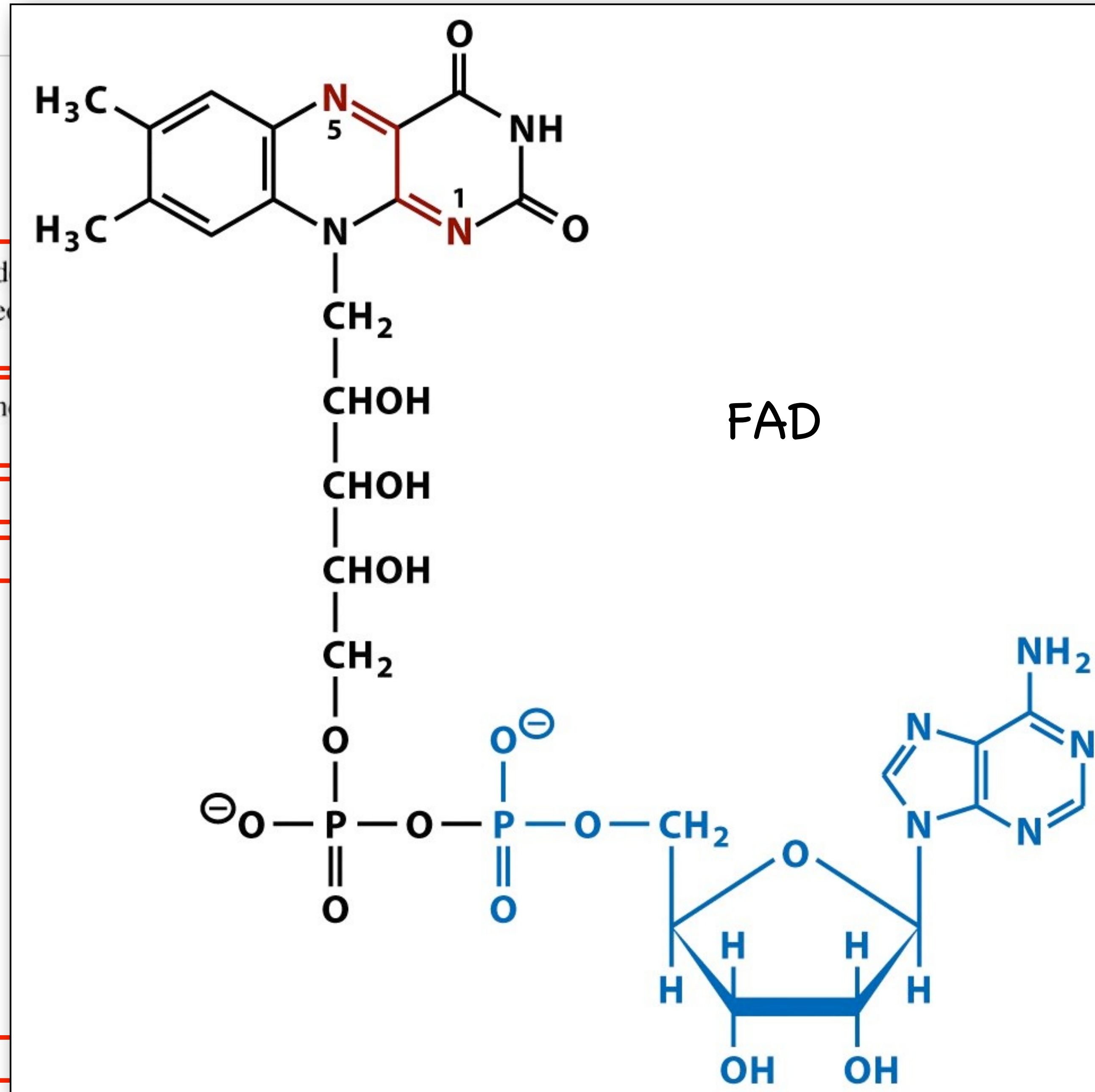

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Conversion of Pyruvate to Acetyl CoA

TABLE 7.2 Major coenzymes

Coenzyme	Vitamin source	Major metabolic roles	Mechanistic role
Ad			
S-A			
Uri			
Ni an ph			
Fla ade			
Co			
Th			
Py			
Bi			
Te			
Ad			
Me			
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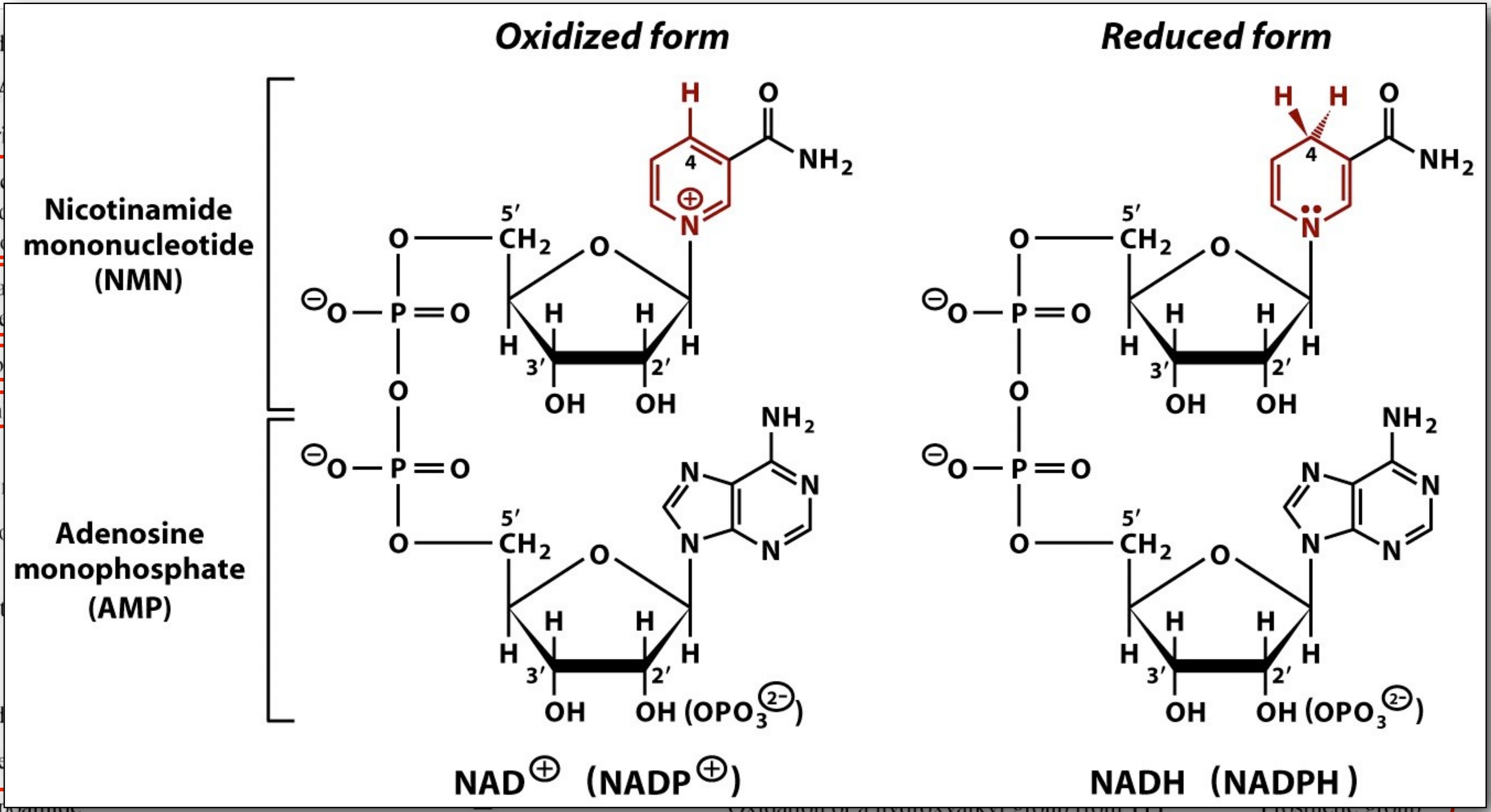

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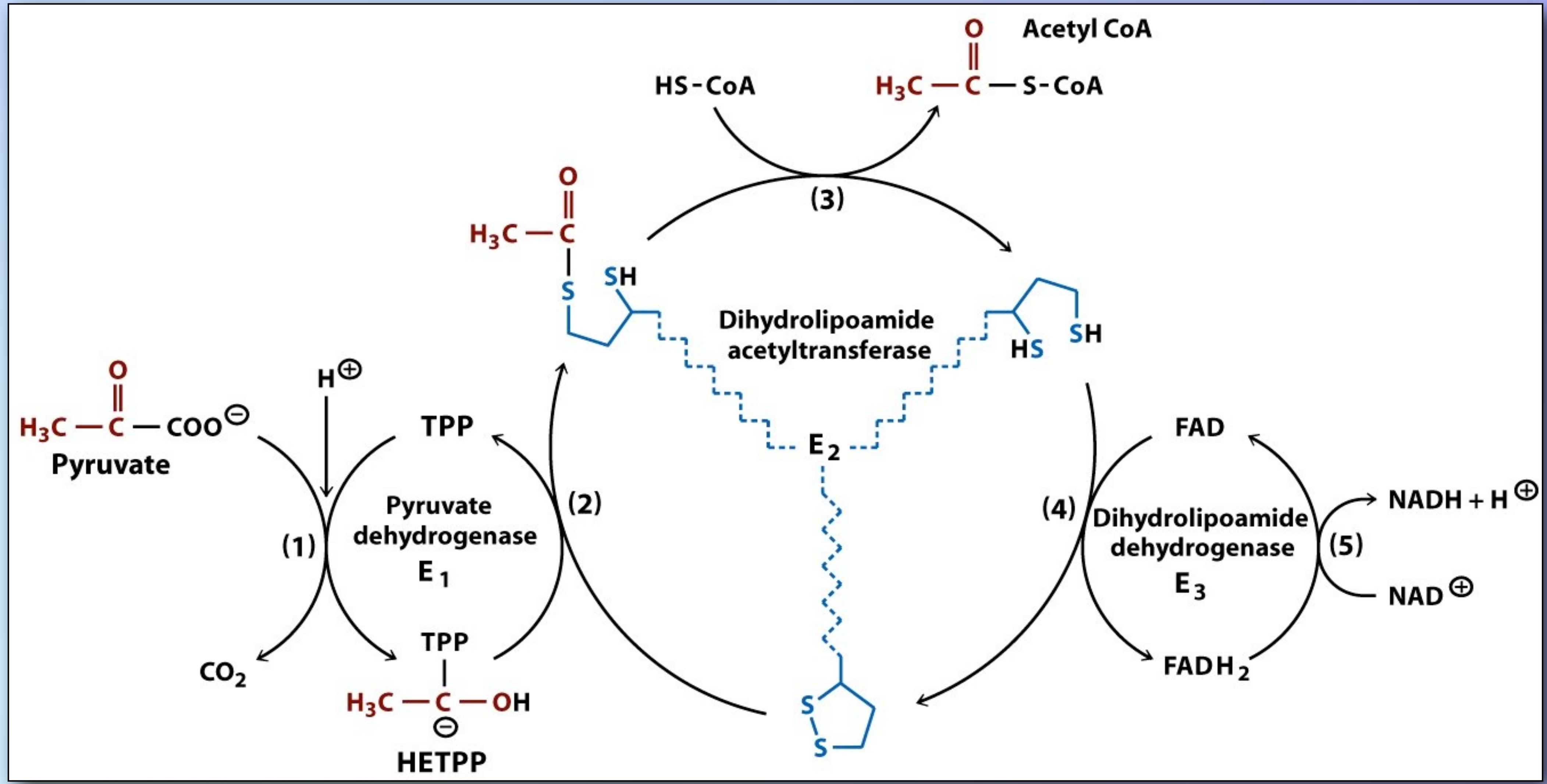
Conversion of Pyruvate to Acetyl CoA

- Pyruvate Dehydrogenase



The Citric Acid Cycle

- Catabolic Mode

TABLE 13.1 The enzymatic reactions of the citric acid cycle.

Reaction	Enzyme
1. Acetyl CoA + Oxaloacetate + $H_2O \longrightarrow$ Citrate + HS-CoA + $H^{\oplus}$	Citrate synthase
2. Citrate $\rightleftharpoons$ Isocitrate	Aconitase (Aconitate hydratase)
3. Isocitrate + $NAD^{\oplus} \longrightarrow$ α-Ketoglutarate + NADH + CO_2	Isocitrate dehydrogenase
4. α-Ketoglutarate + HS-CoA + $NAD^{\oplus} \longrightarrow$ Succinyl CoA + NADH + CO_2	α-Ketoglutarate dehydrogenase complex
5. Succinyl CoA + GDP (or ADP) + P_i $\rightleftharpoons$ Succinate + GTP(or ATP) + HS-CoA	Succinyl-CoA synthetase
6. Succinate + Q $\rightleftharpoons$ Fumarate + QH_2	Succinate dehydrogenase complex
7. Fumarate + H_2O $\rightleftharpoons$ L-Malate	Fumarase (Fumarate hydratase)
8. L-Malate + $NAD^{\oplus}$ $\rightleftharpoons$ Oxaloacetate + NADH + $H^{\oplus}$	Malate dehydrogenase

Net equation:

Acetyl CoA + 3 $NAD^{\oplus}$ + Q + GDP (or ADP) + P_i + 2 $H_2O \longrightarrow$ HS-CoA + 3 NADH + QH_2 + GTP (or ATP) + 2 CO_2 + 2 $H^{\oplus}$

The Ci

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TABLE 13.1 The enzym	
Reaction	
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3. Isocitrate + $NAD^{\oplus}$ $\longrightarrow$ α	ehydrogenase
4. α-Ketoglutarate + HS-CoA	arate dehydrogenase complex
5. Succinyl CoA + GDP (or A	oA synthetase
6. Succinate + Q $\rightleftharpoons$ Fuma	lehydrogenase complex
7. Fumarate + H_2O $\rightleftharpoons$ L-	(Fumarate hydratase)
8. L-Malate + $NAD^{\oplus}$ $\rightleftharpoons$	ydrogenase
Net equation:	
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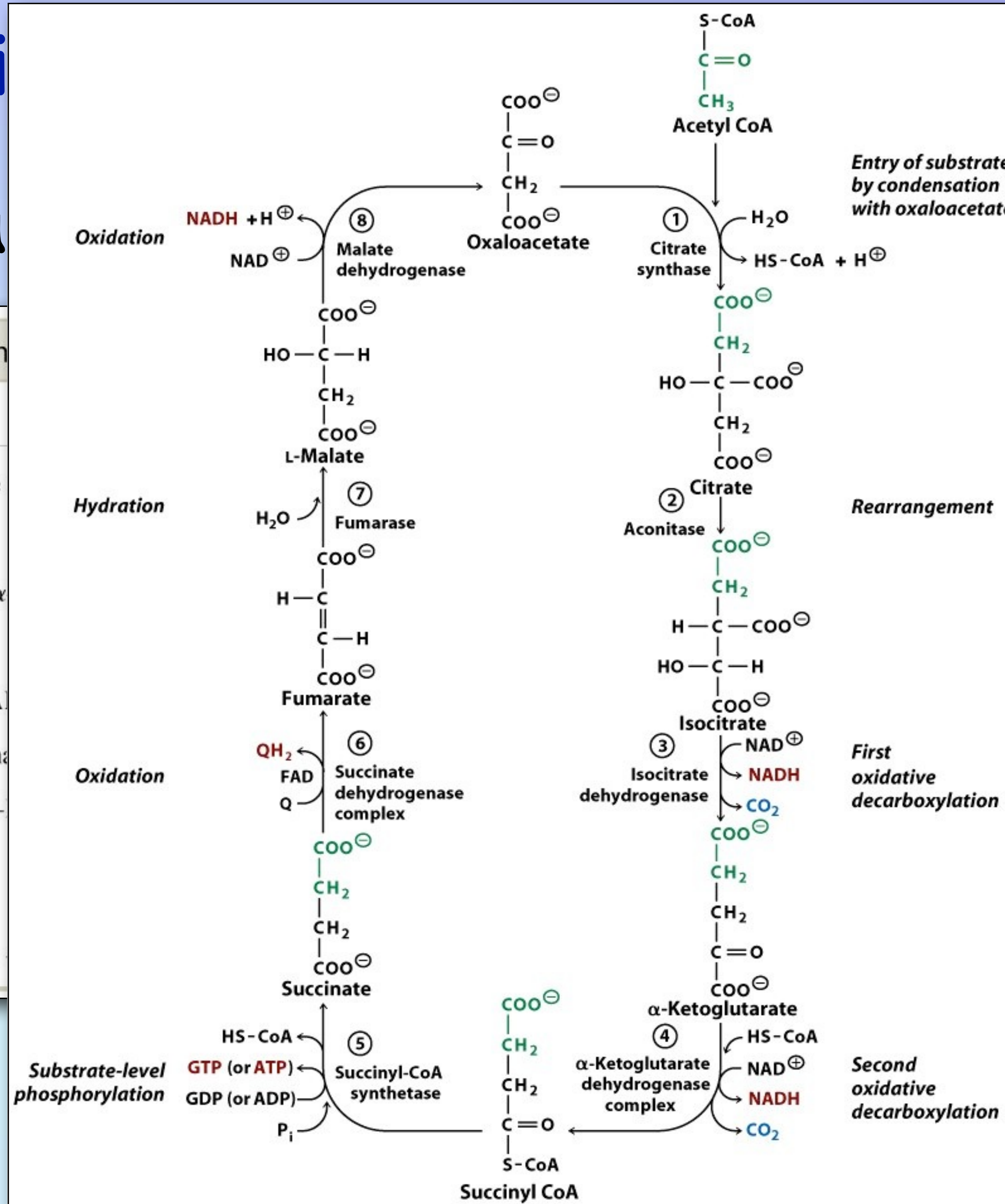

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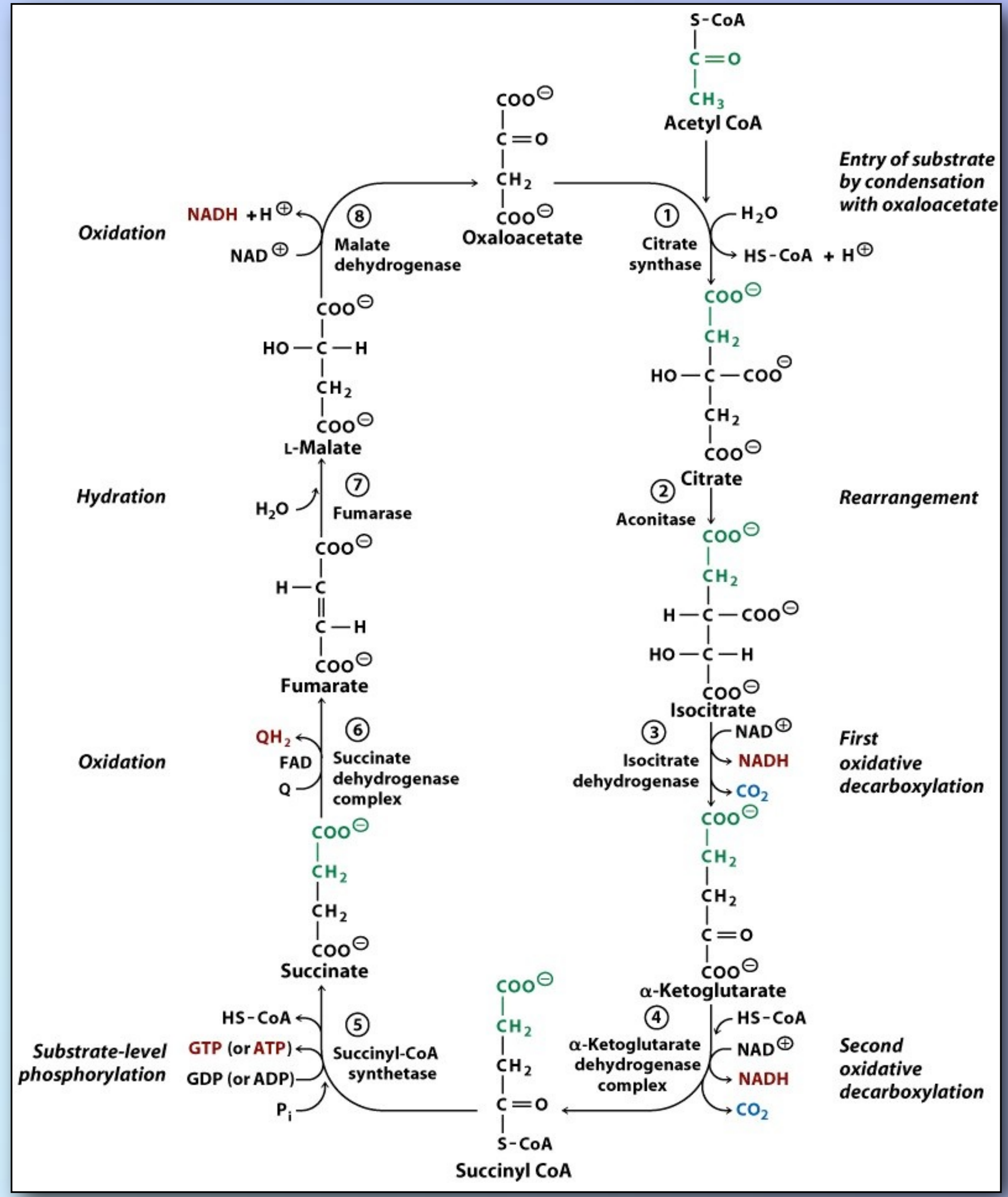
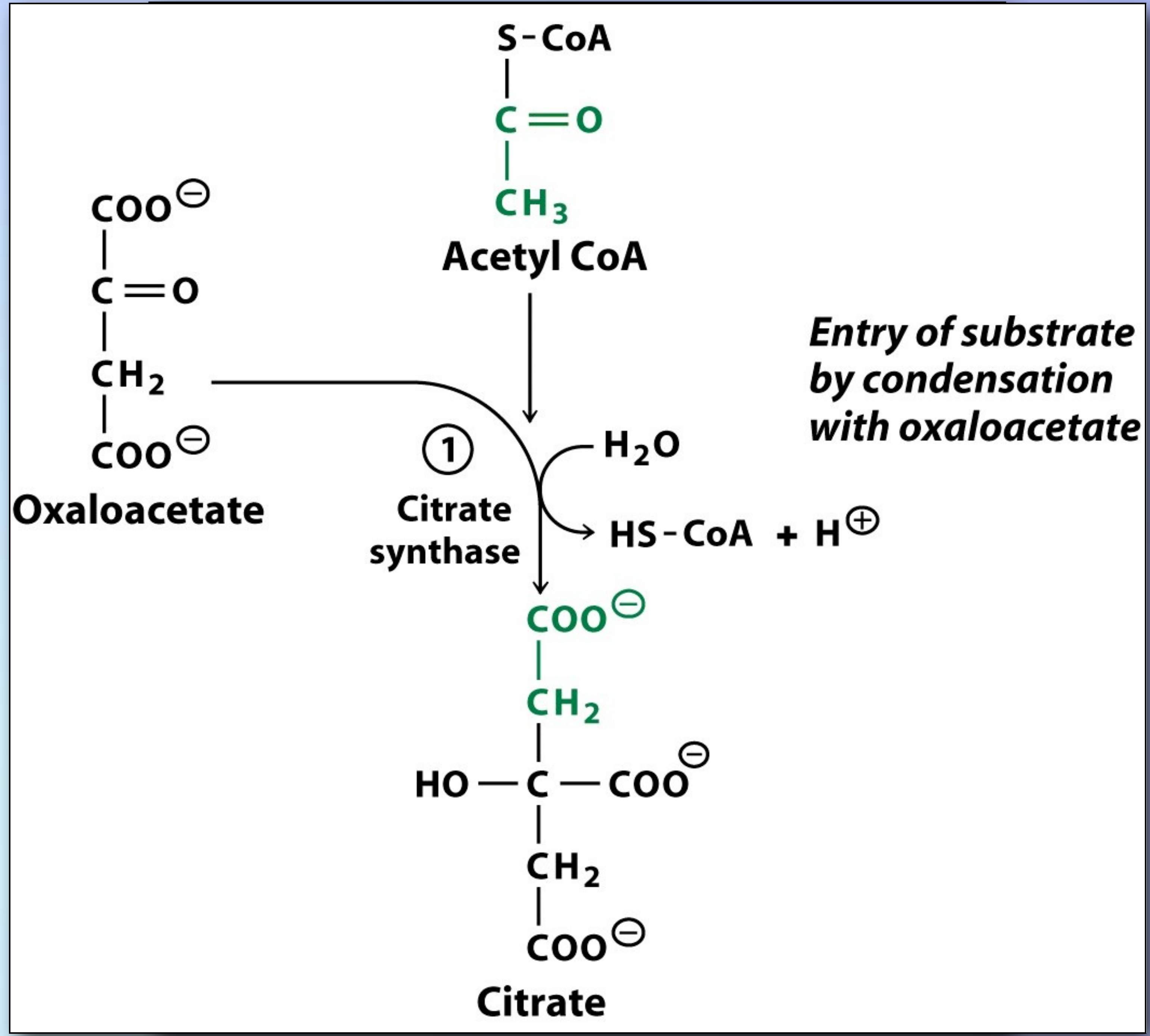
The Citric Acid Cycle

- Catabolic Mode



The Citric Acid Cycle

- Catabolic Mode



The Citric Acid Cycle

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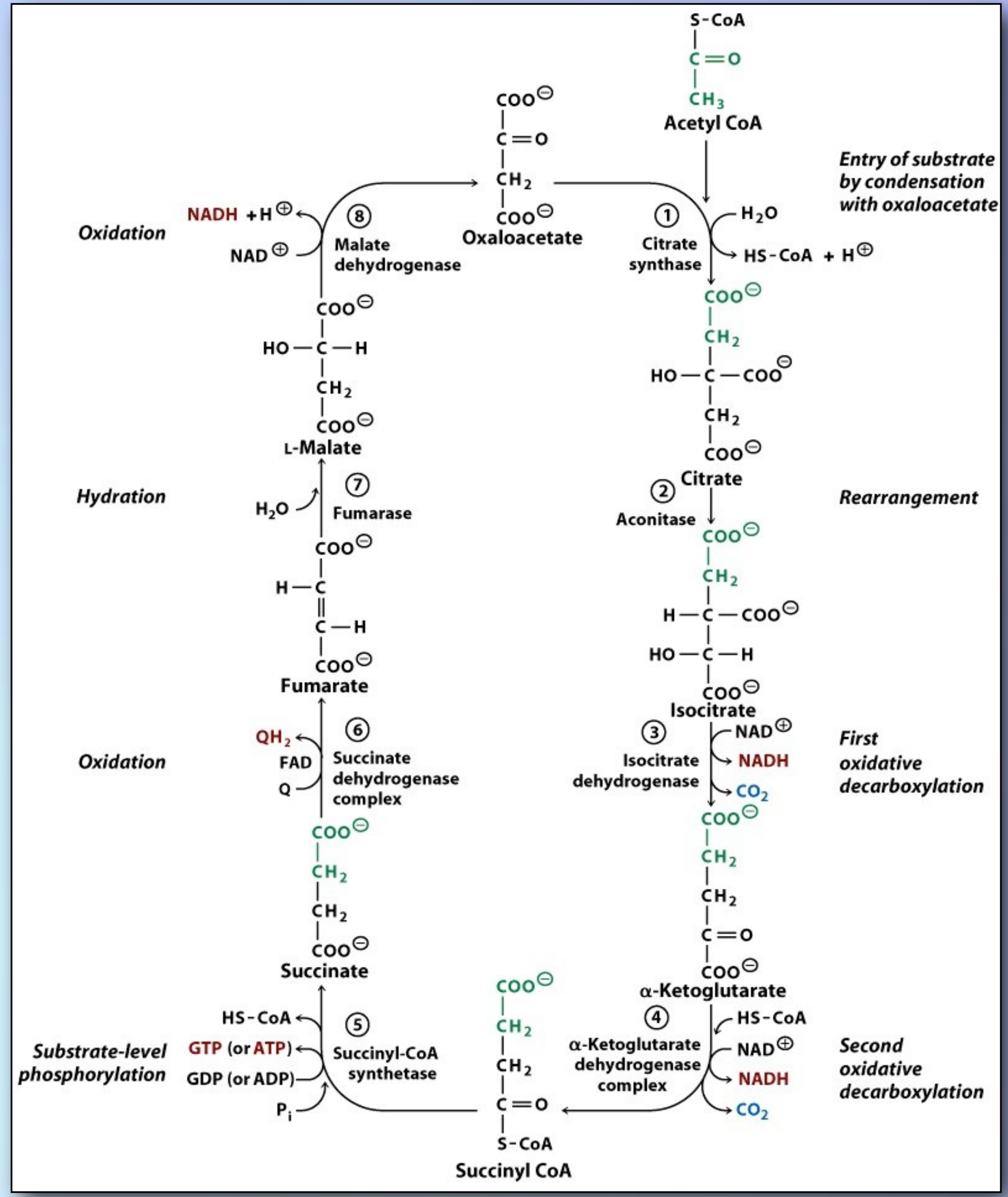

The Citric Acid Cycle

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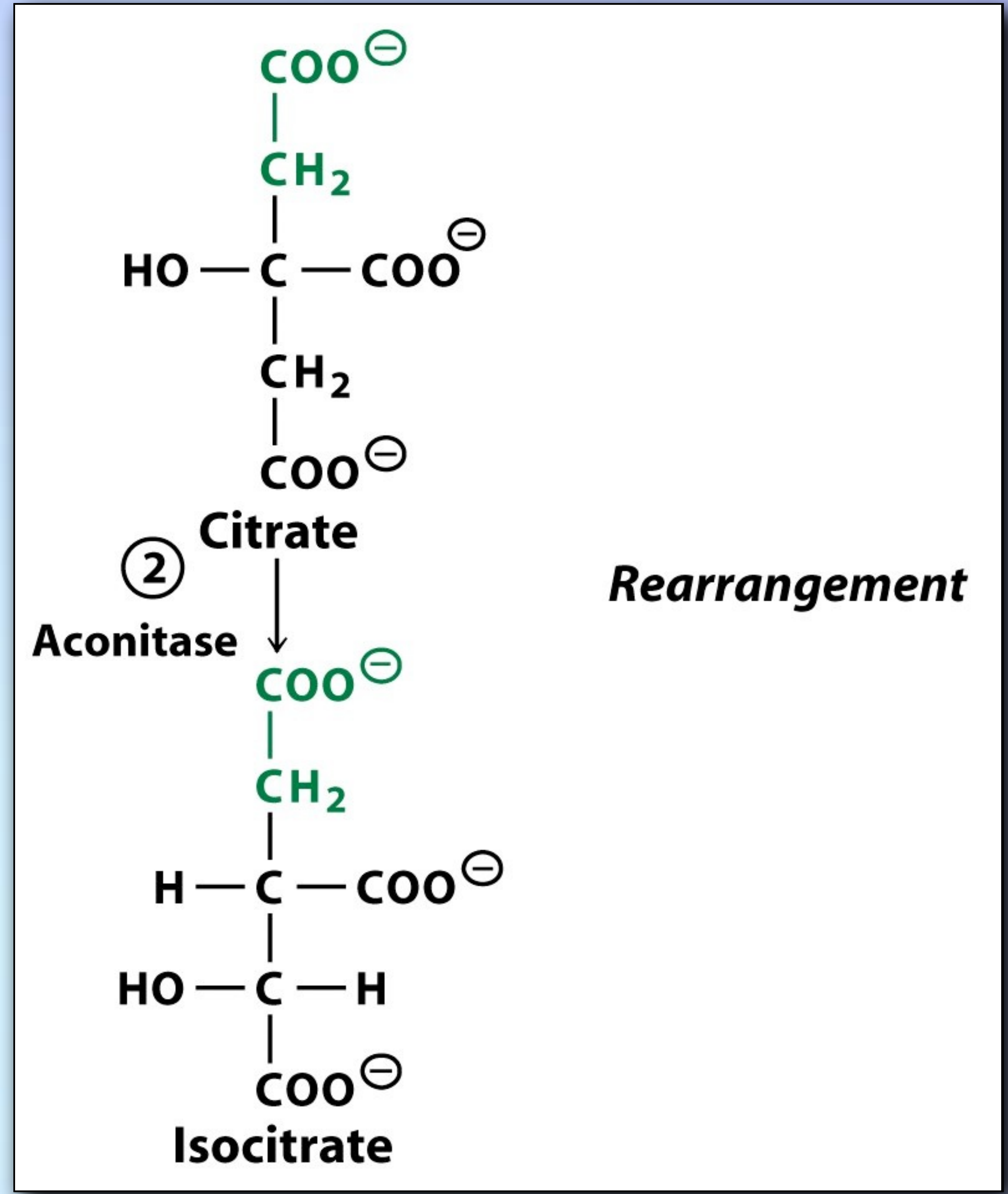

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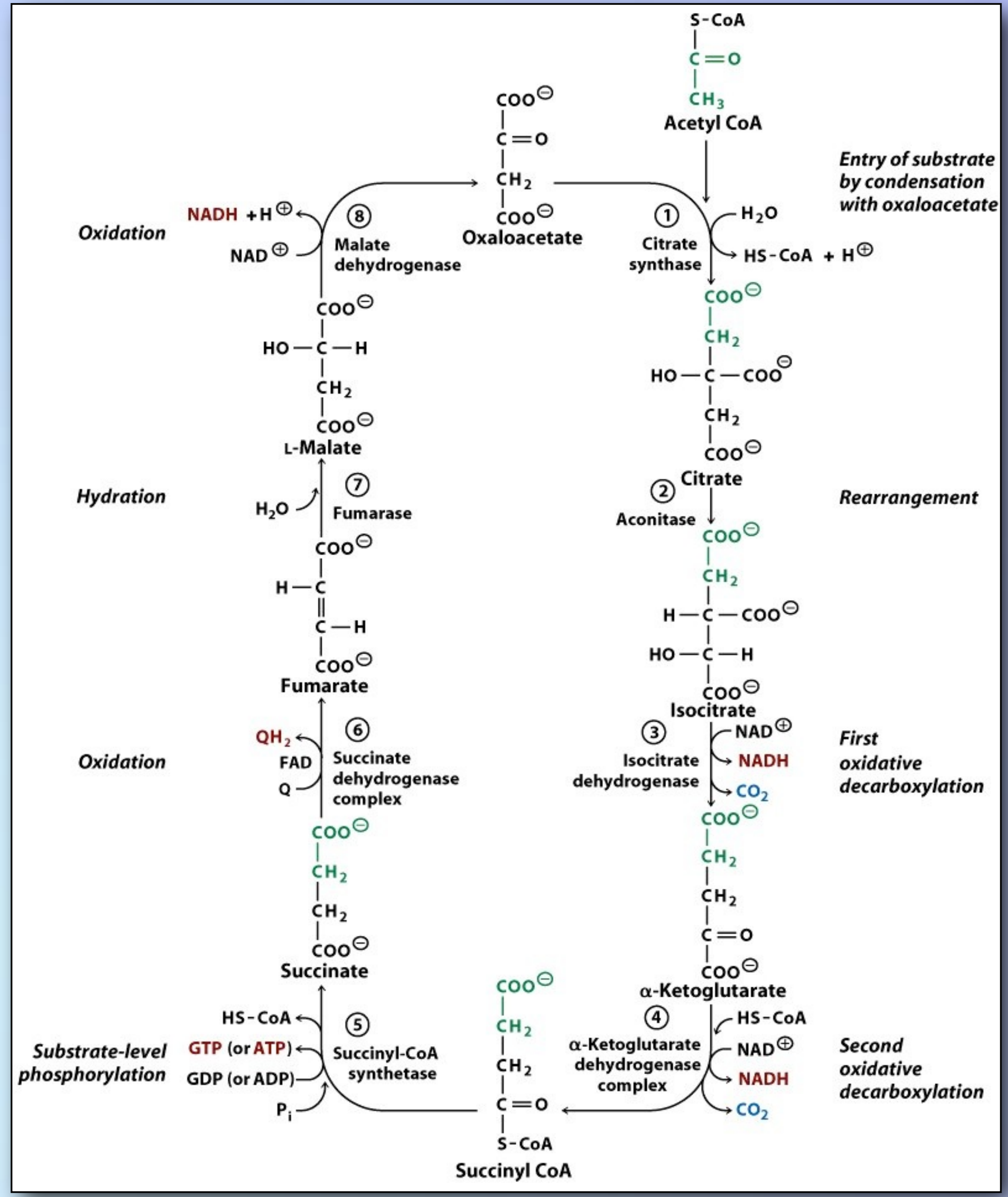

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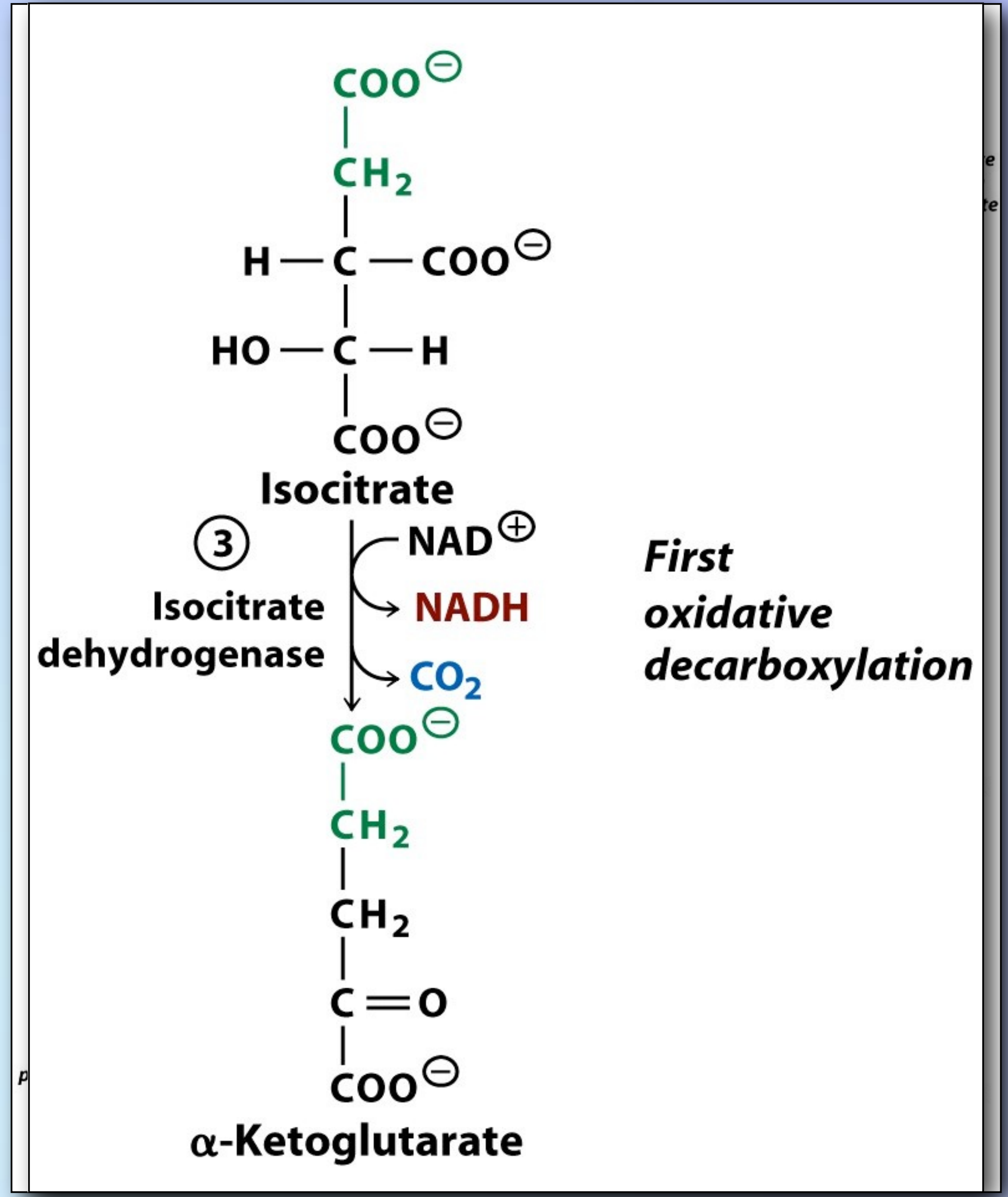

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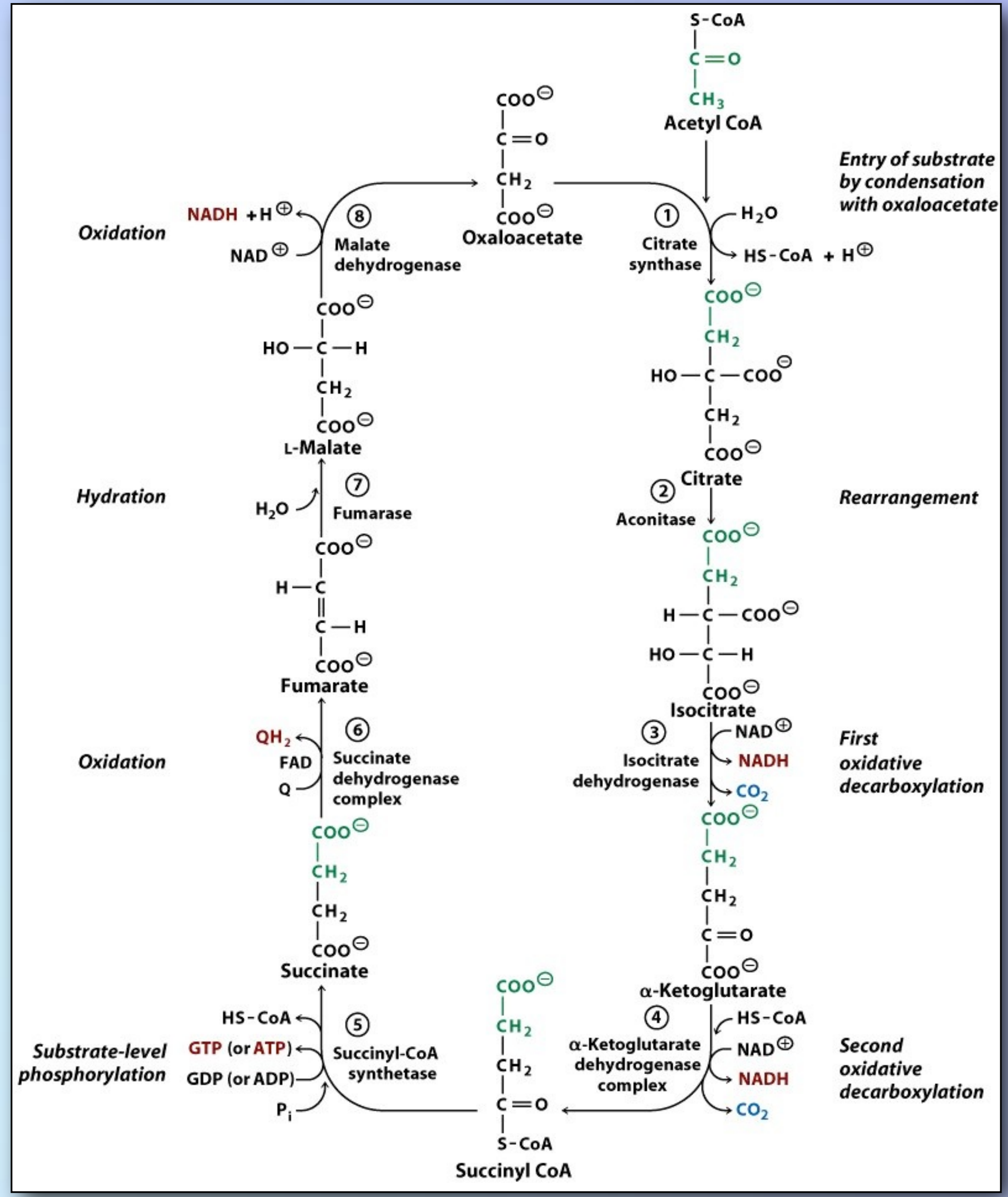

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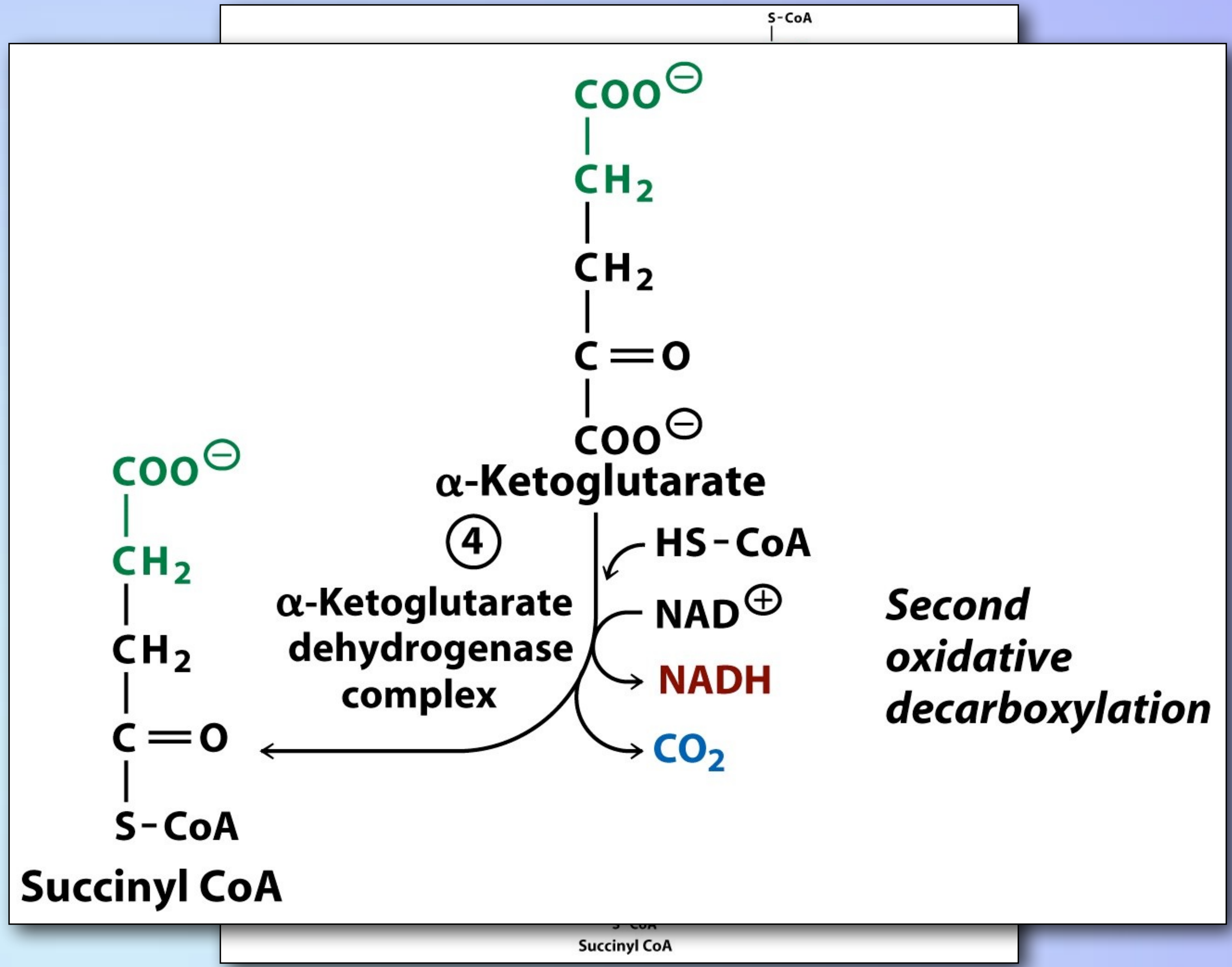

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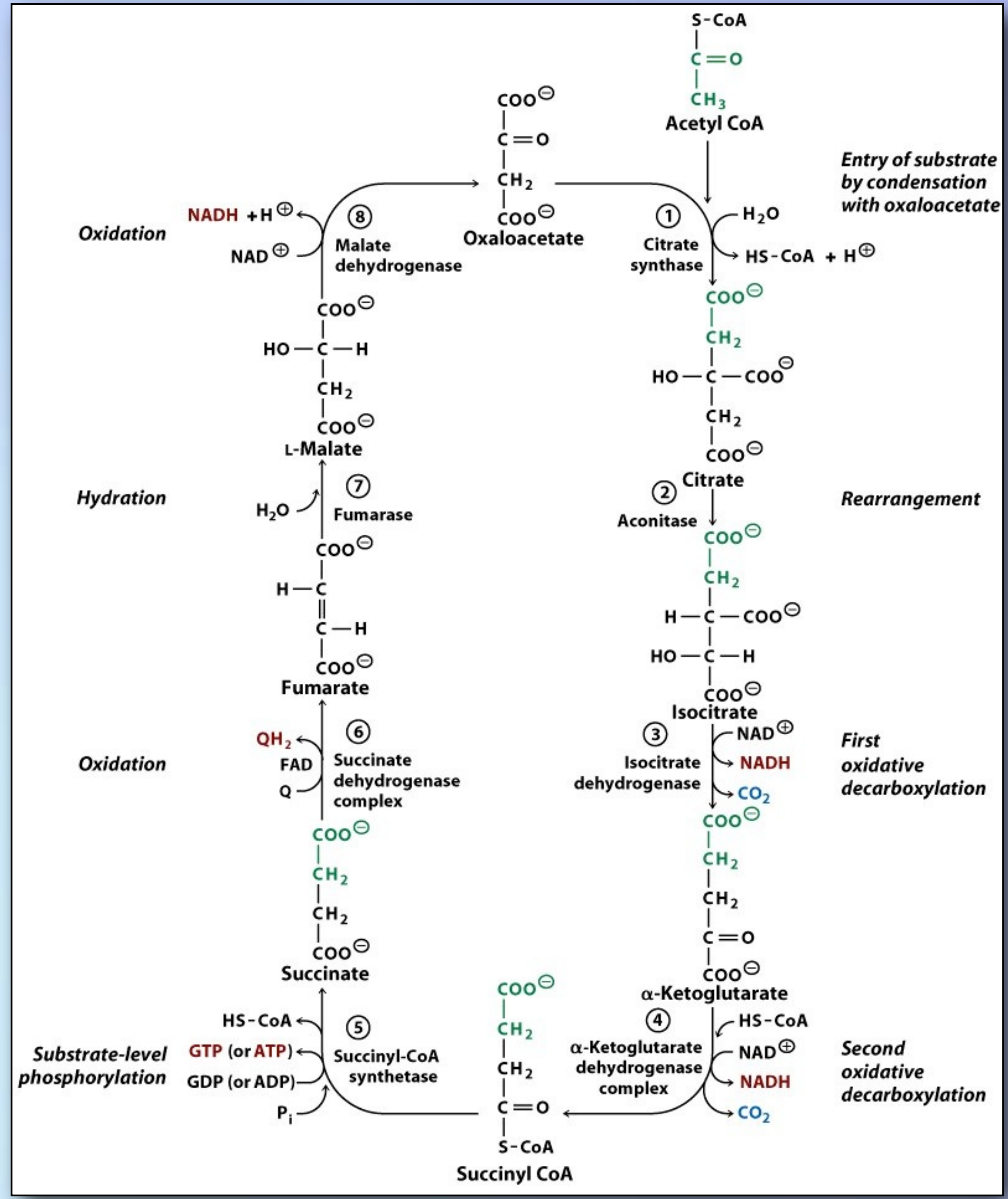

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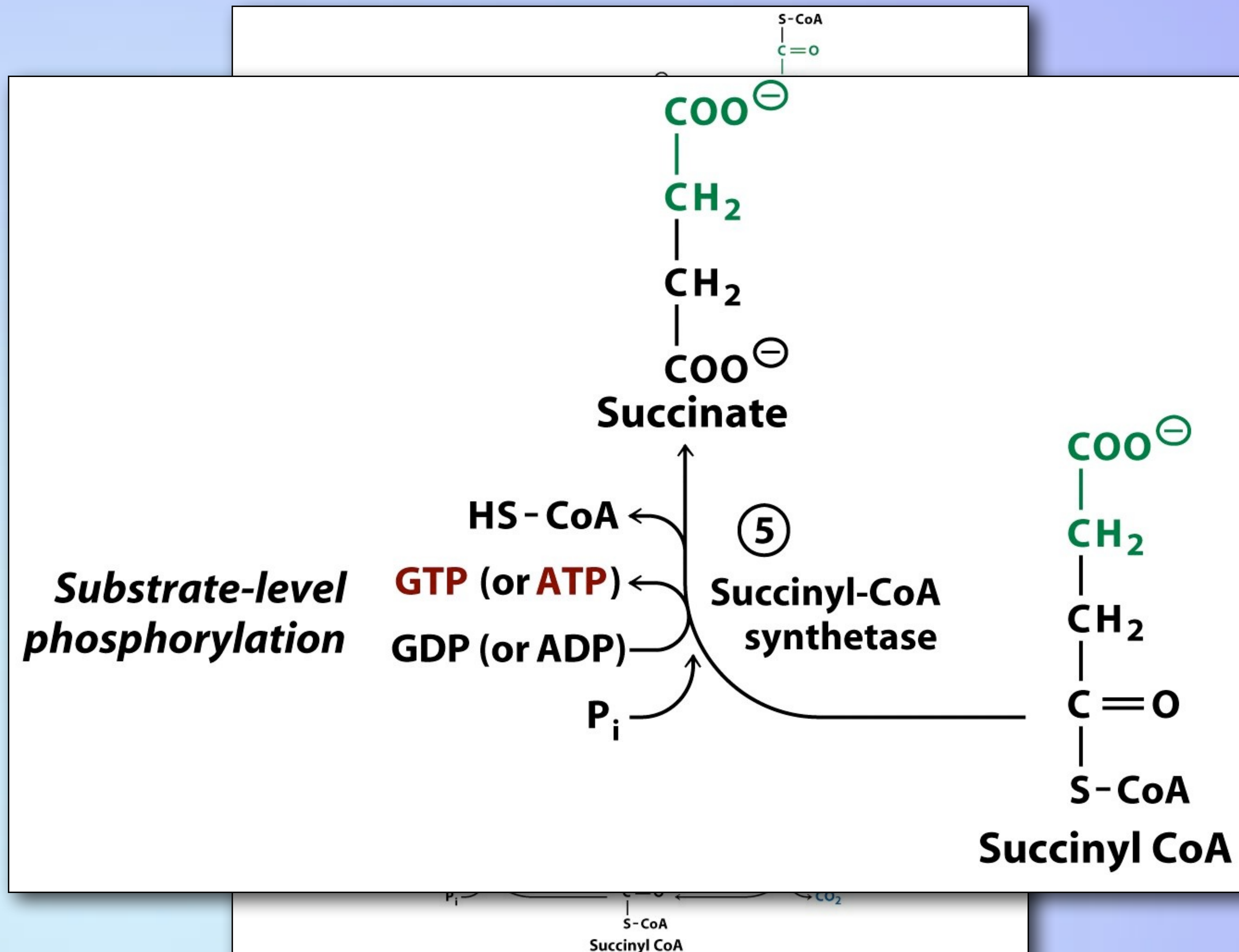

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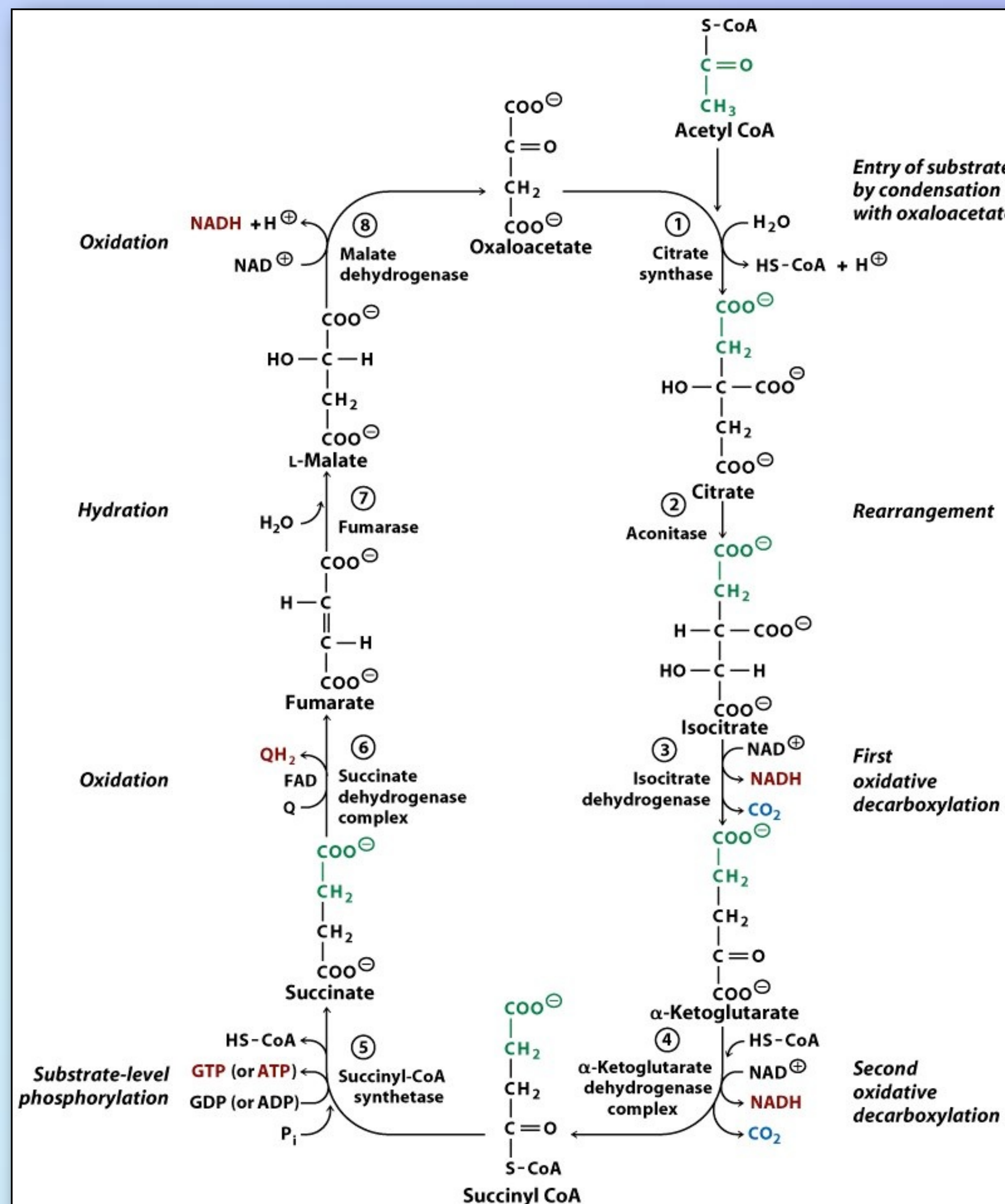

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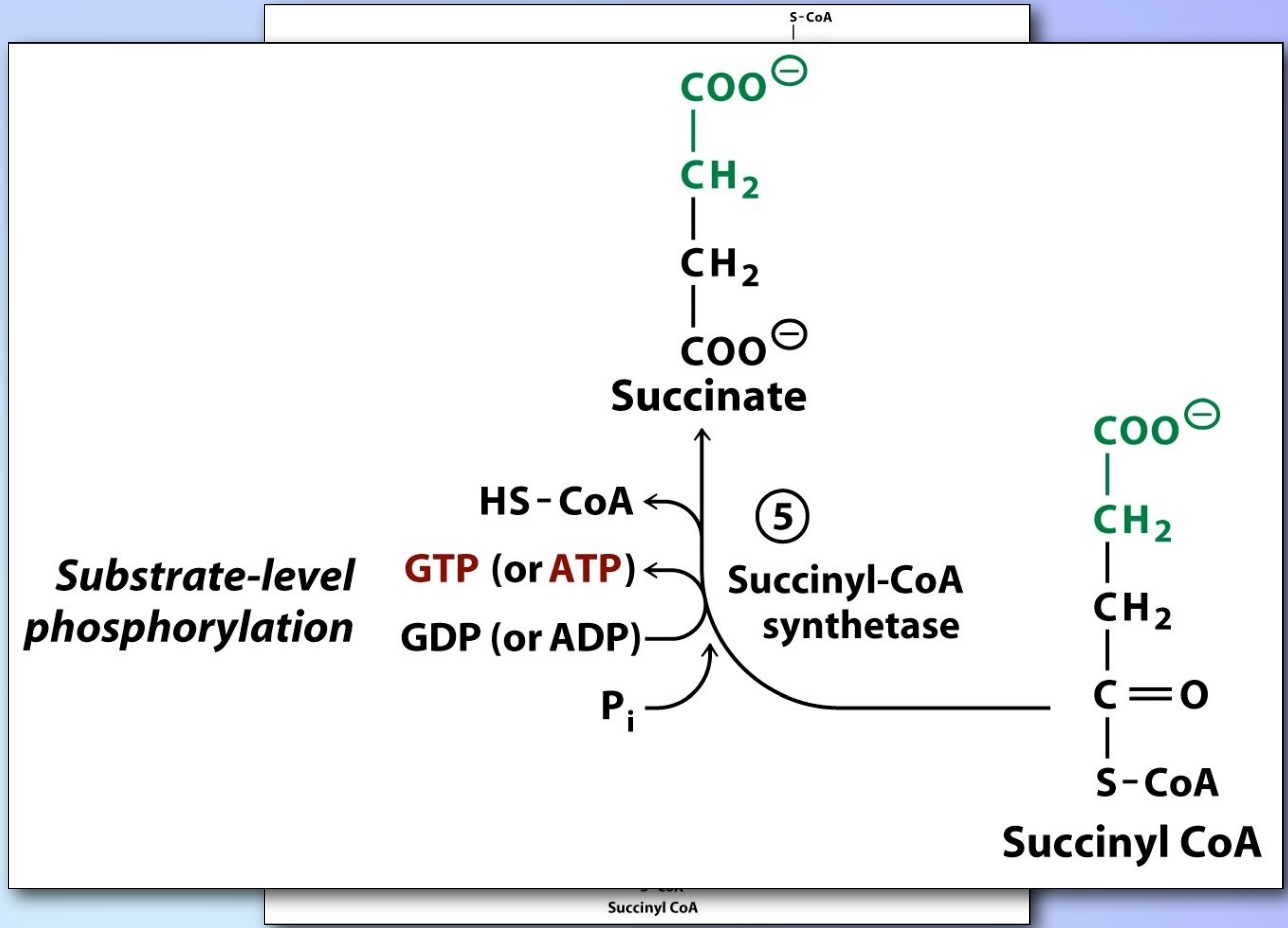

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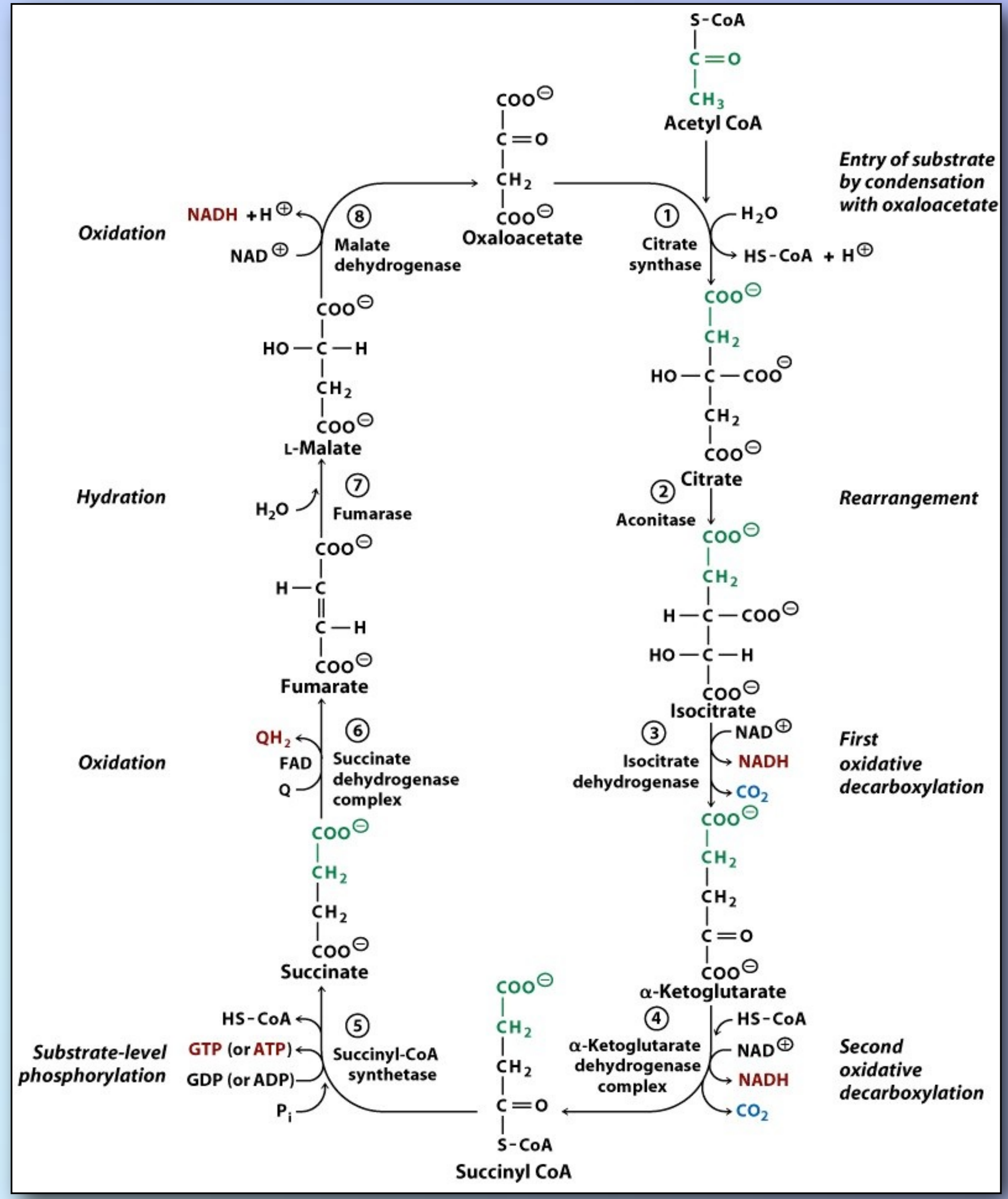

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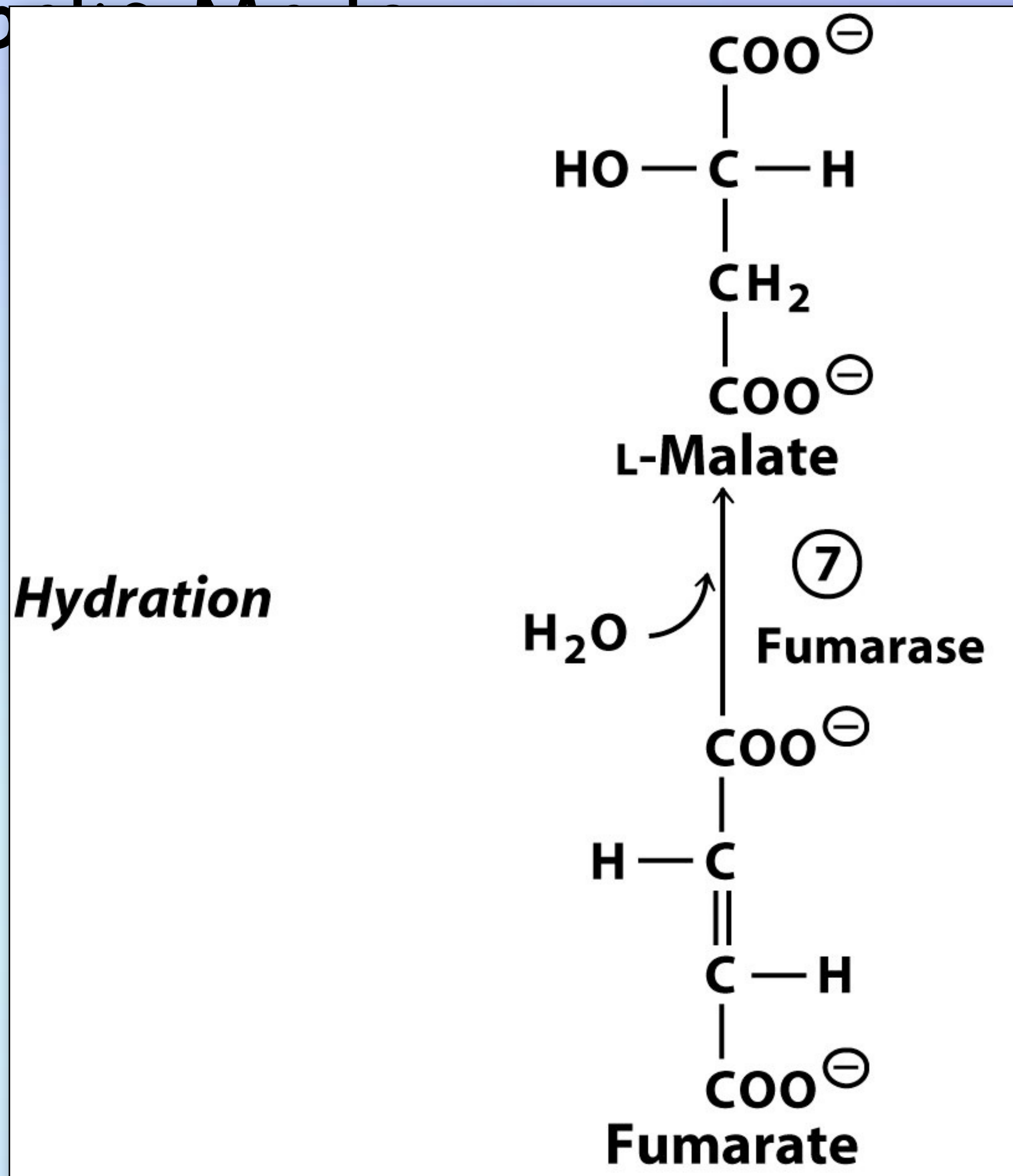

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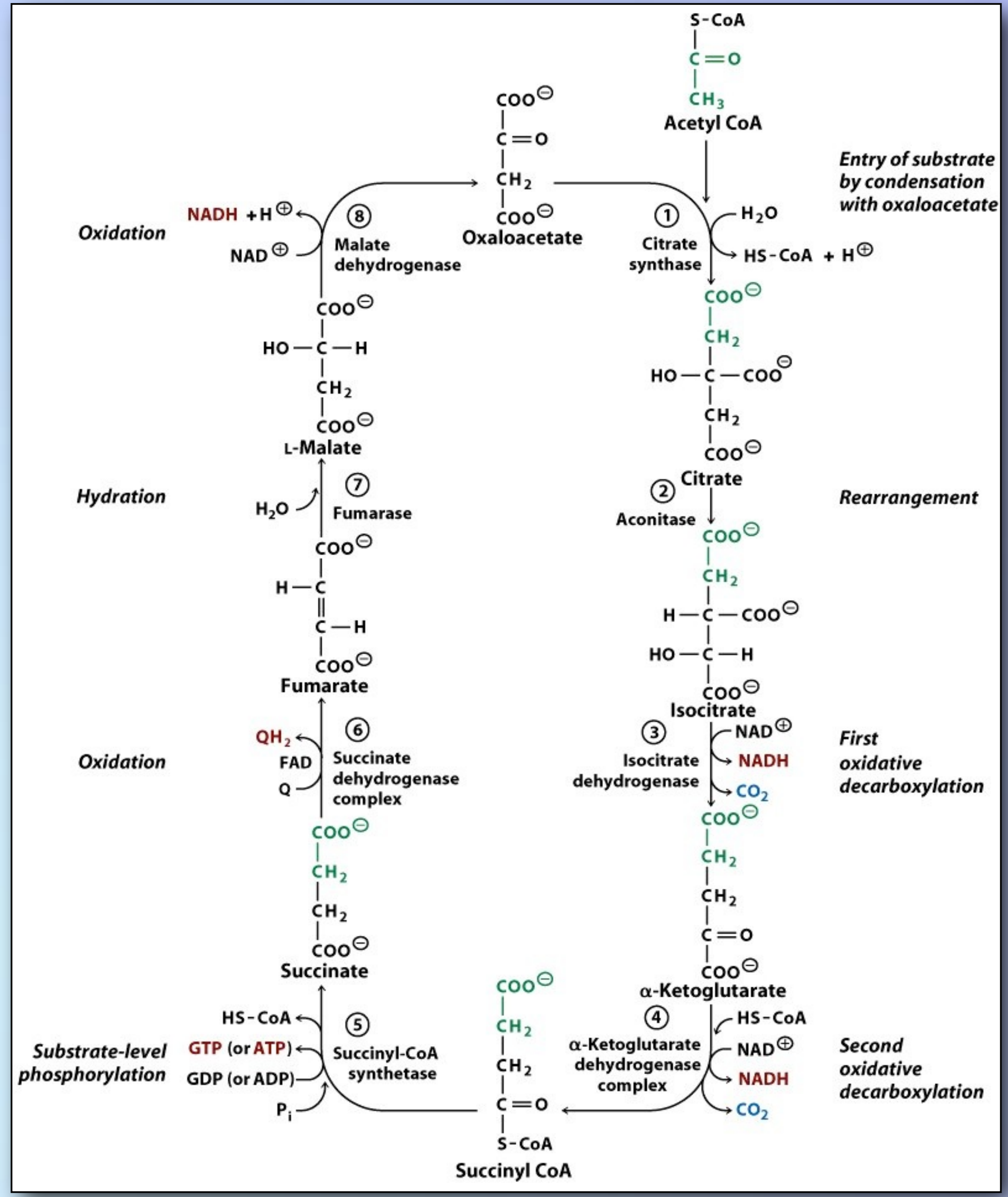

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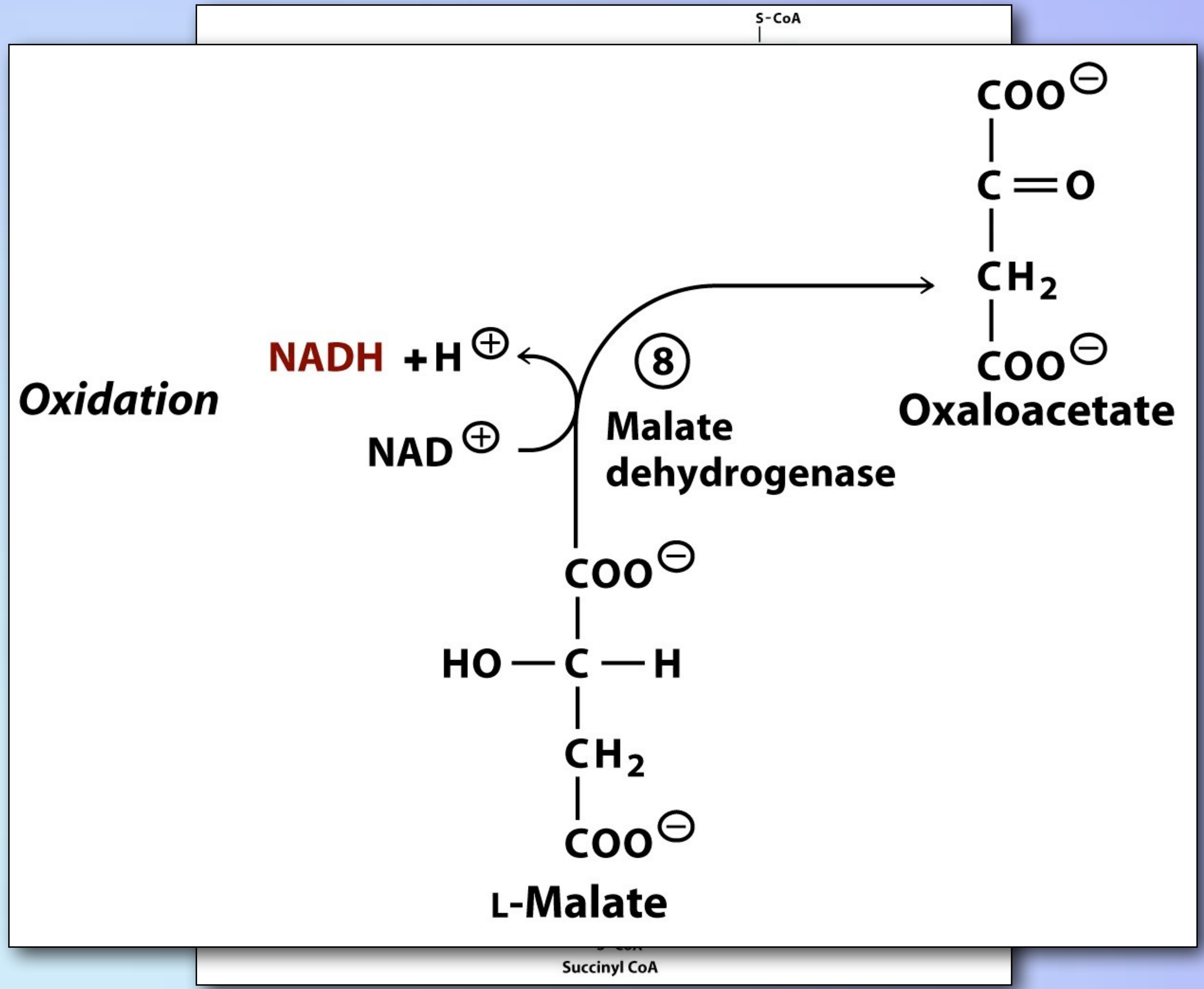

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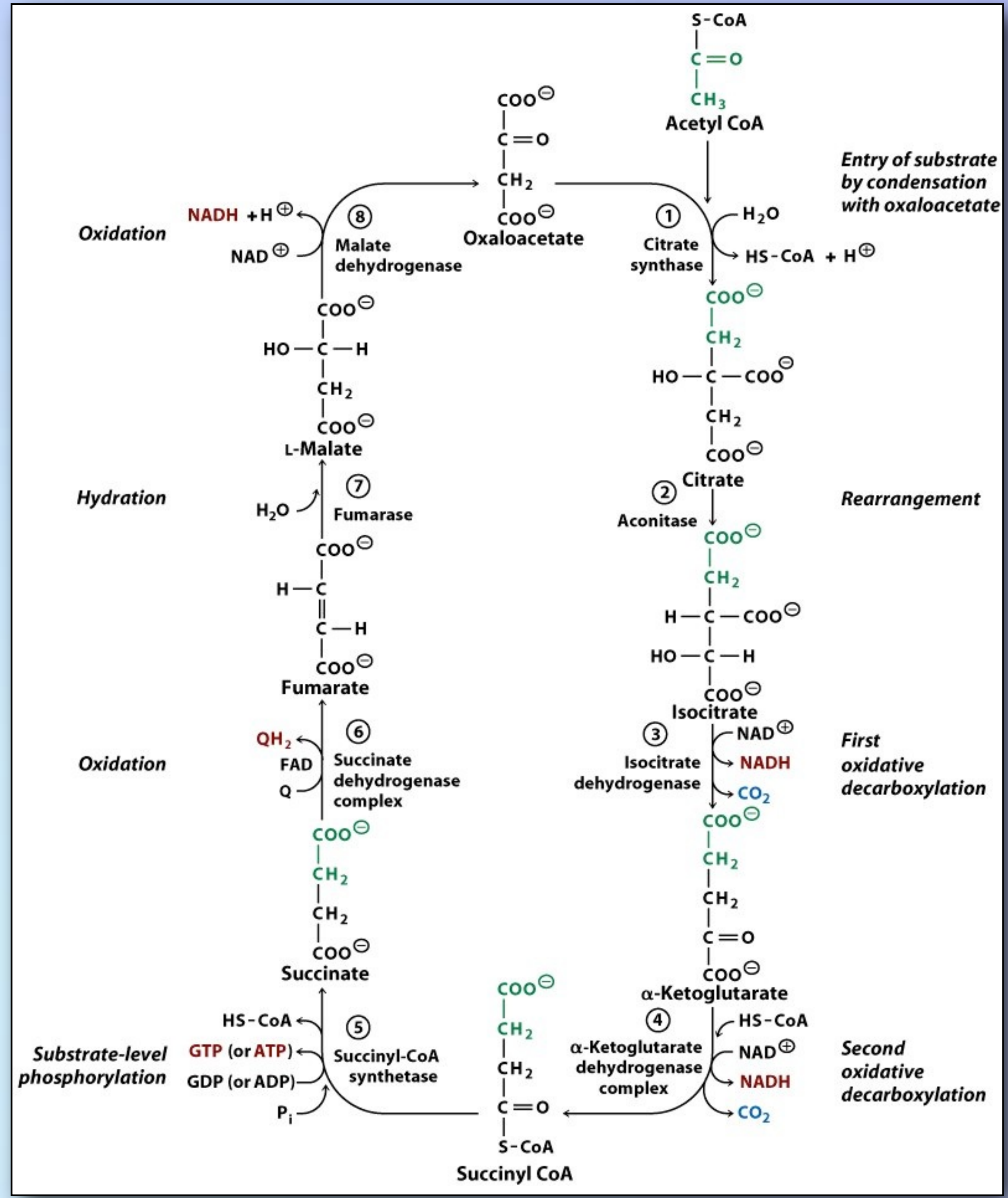

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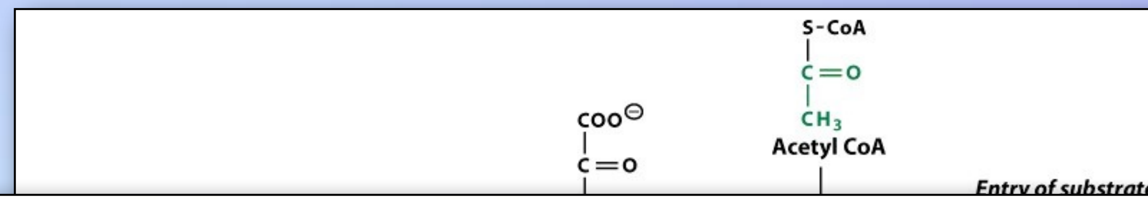

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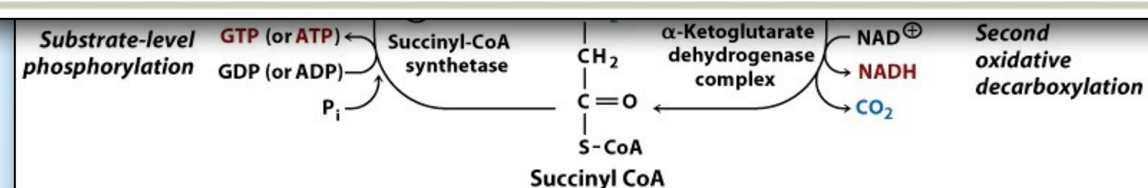
Net equation:

$$\text{Acetyl CoA} + 3\,NAD^{\oplus} + Q + \text{GDP (or ADP)} + P_i + 2\,H_2O \longrightarrow \text{HS-CoA} + 3\,NADH + QH_2 + \text{GTP (or ATP)} + 2\,CO_2 + 2\,H^{\oplus}$$



Chem 352 - Lecture 8
Carbohydrate Metabolism
Part III: Citric Acid Cycle
14. April, 2014

Question for the Day: One of the observations that led Hans Krebs to discover the citric acid cycle, was that dicarboxylic acids, such as fumarate and succinate, had a catalytic effect on the oxidation of glucose to CO_2 and H_2O by muscle tissue. Explain this observation.

The Citric Acid Cycle

- What you should know about each reaction in the citric acid cycle
  - The structures and names of each intermediates
  - The structures and names of the subtrates and products.
  - The names of the enzymes.
  - One interesting aspect each reaction in the cycle.

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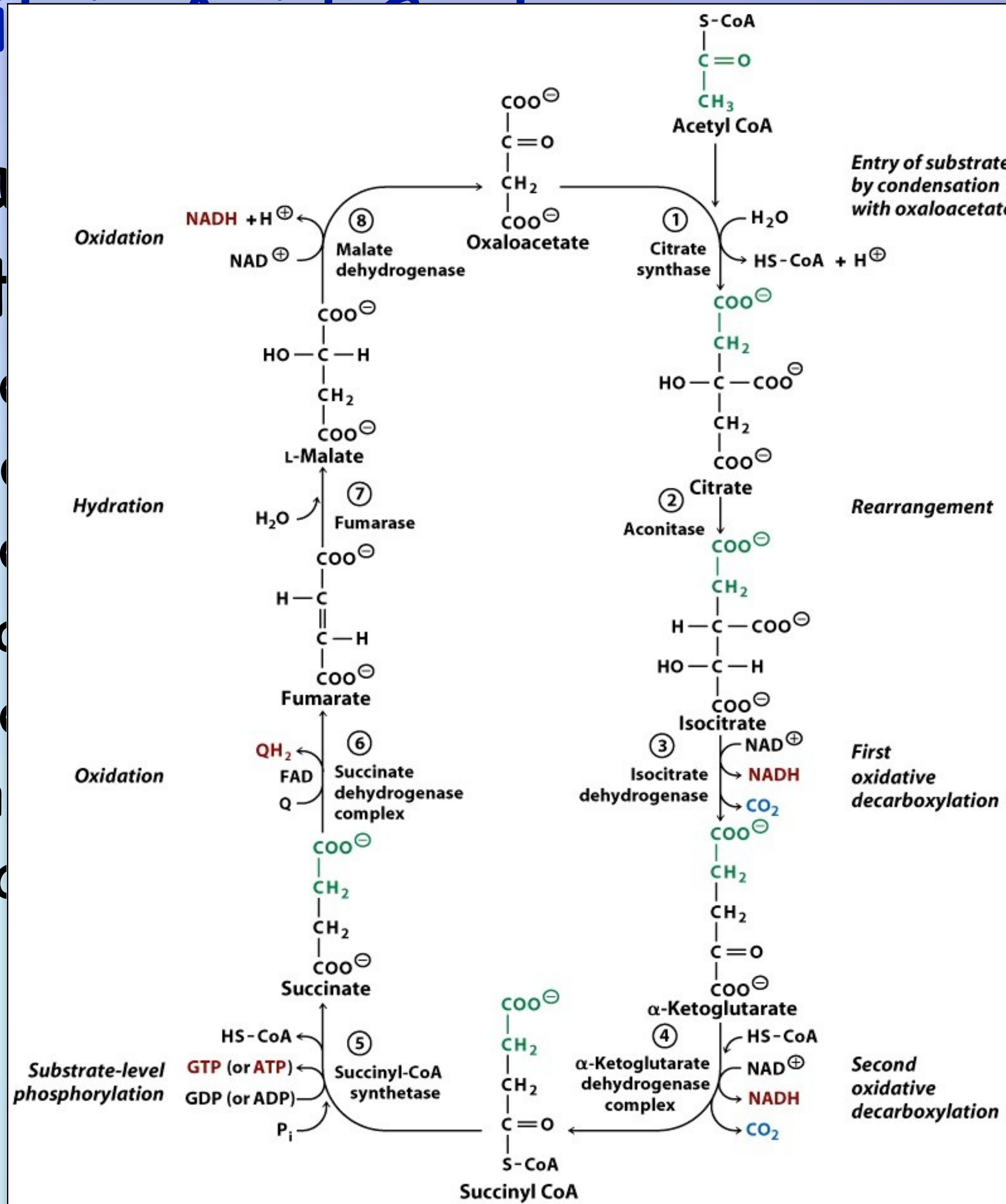

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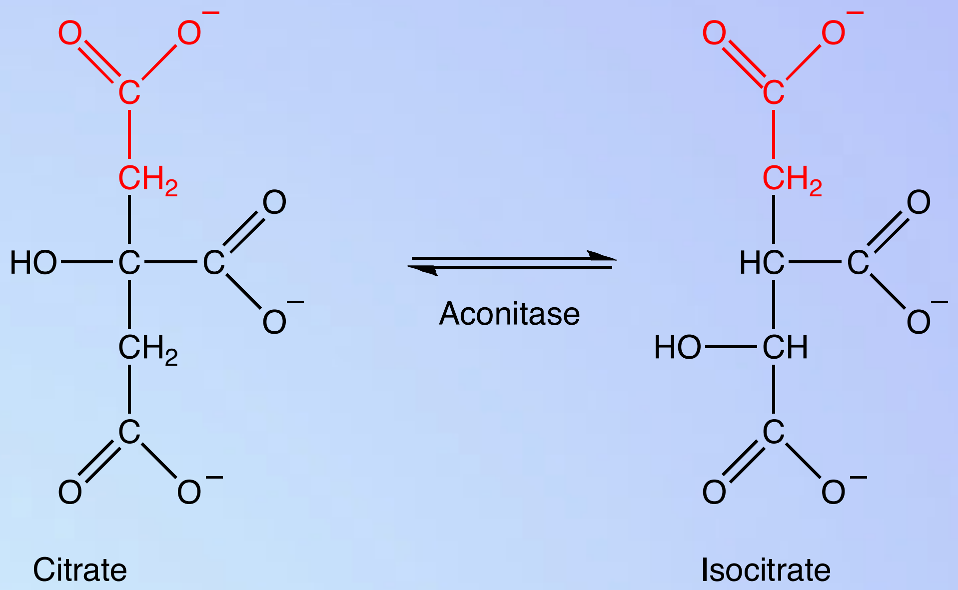
The Citric Acid Cycle

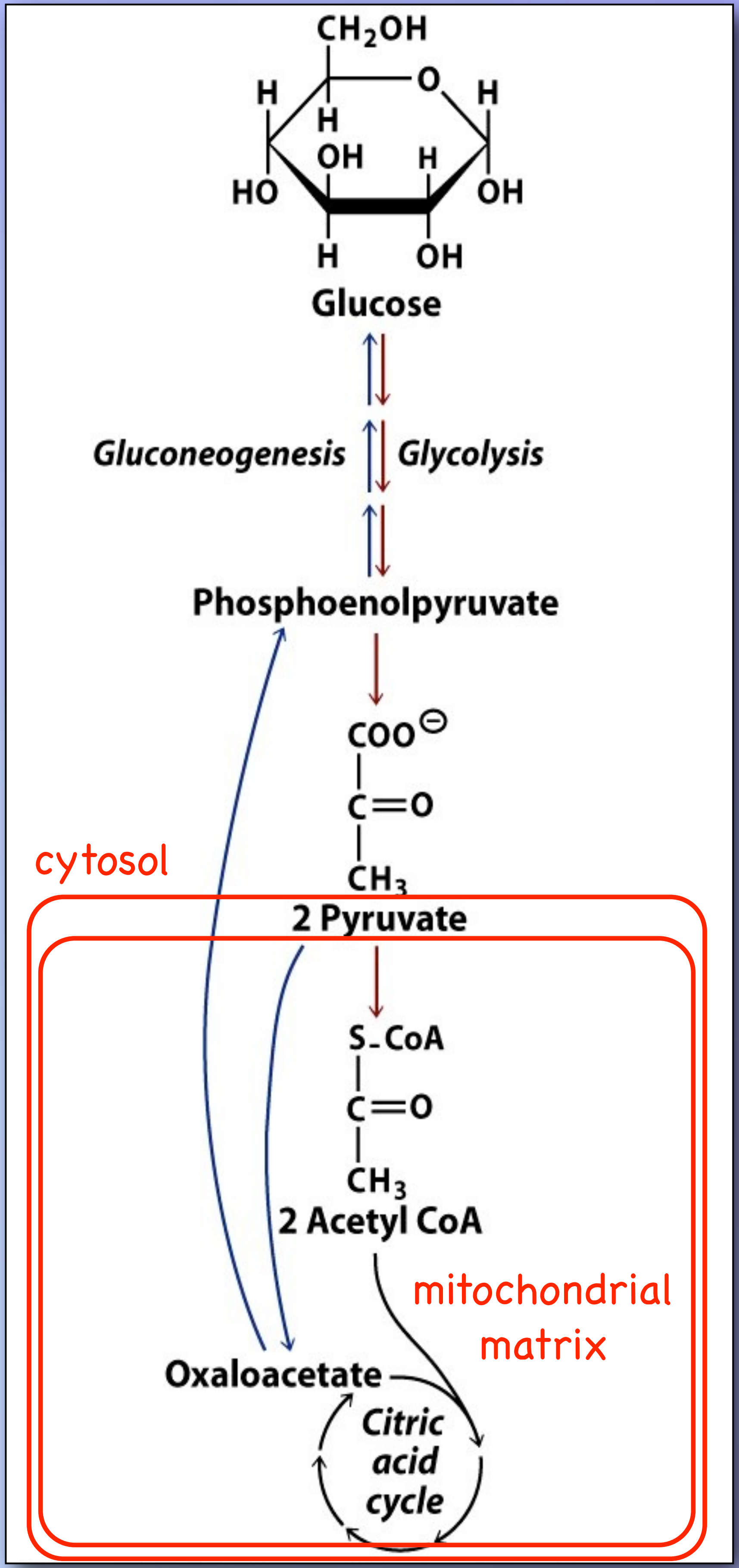
- For example, the **Aconitase** reaction



- Class: Isomerase
- Interesting features of the reaction:
  - The -OH is moved towards the carbon that came from the oxaloacetate used in the citrate synthase reaction.
  - Of the 4 possible stereoisomers of isocitrate, only one is produced (2R,3S)

The Citric Acid Cycle

- In mammals, the pyruvate dehydrogenase reaction and the citric acid cycle take place in the mitochondrial matrix.



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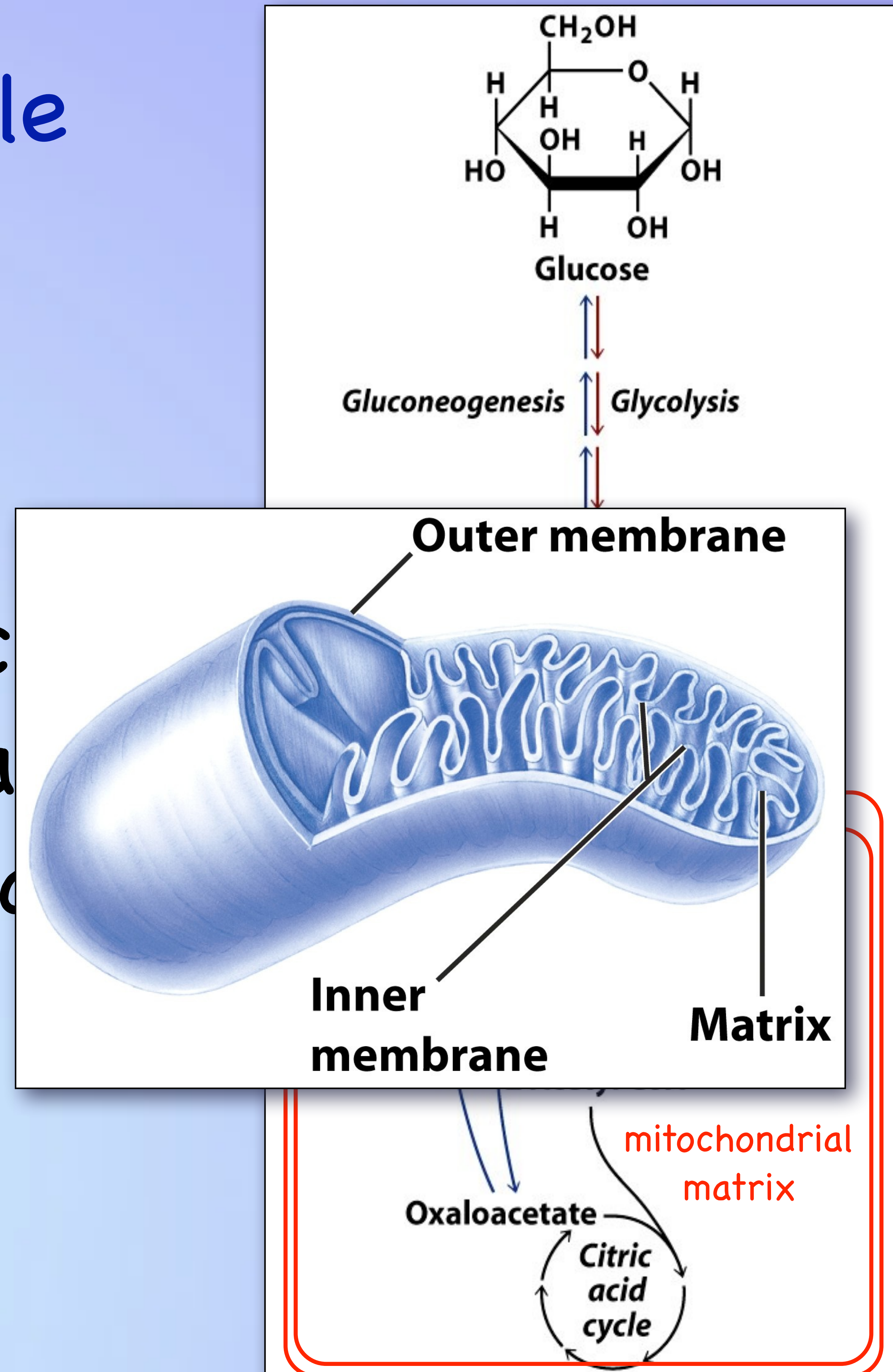
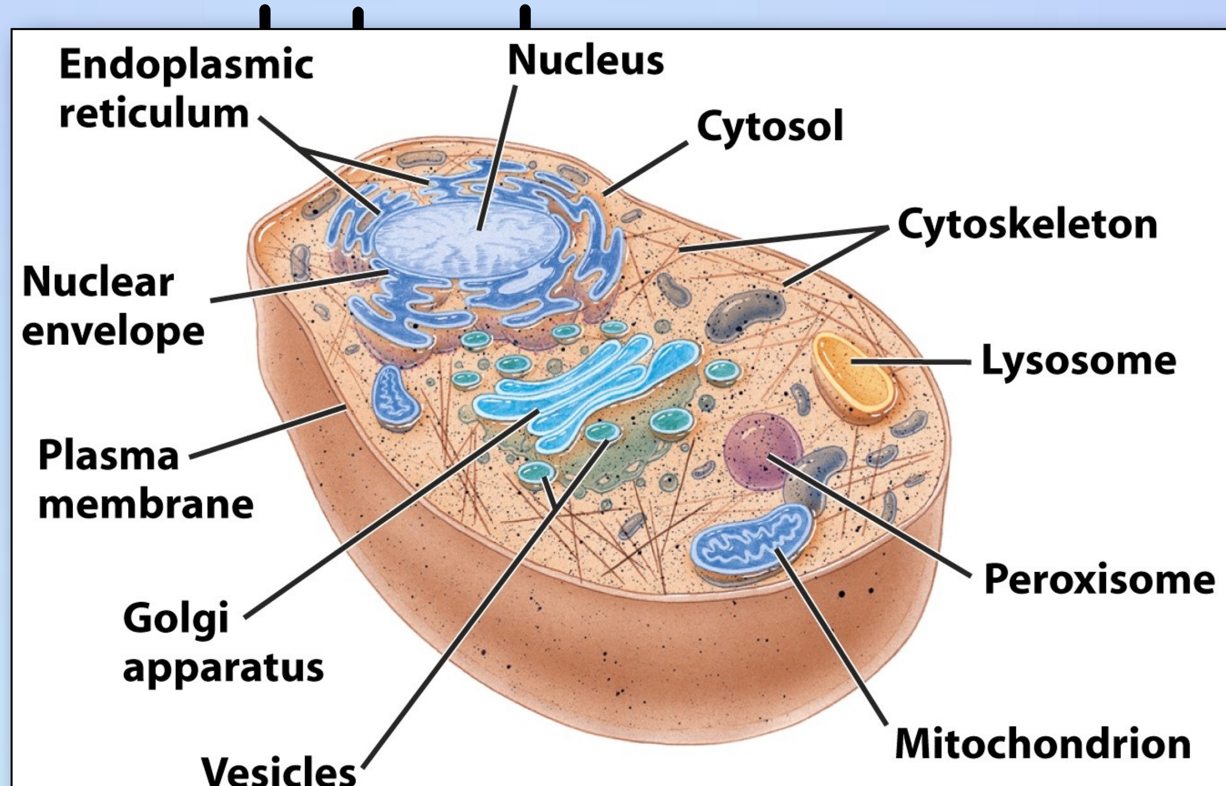


The Citric Acid Cycle

- In mammals, the pyruvate



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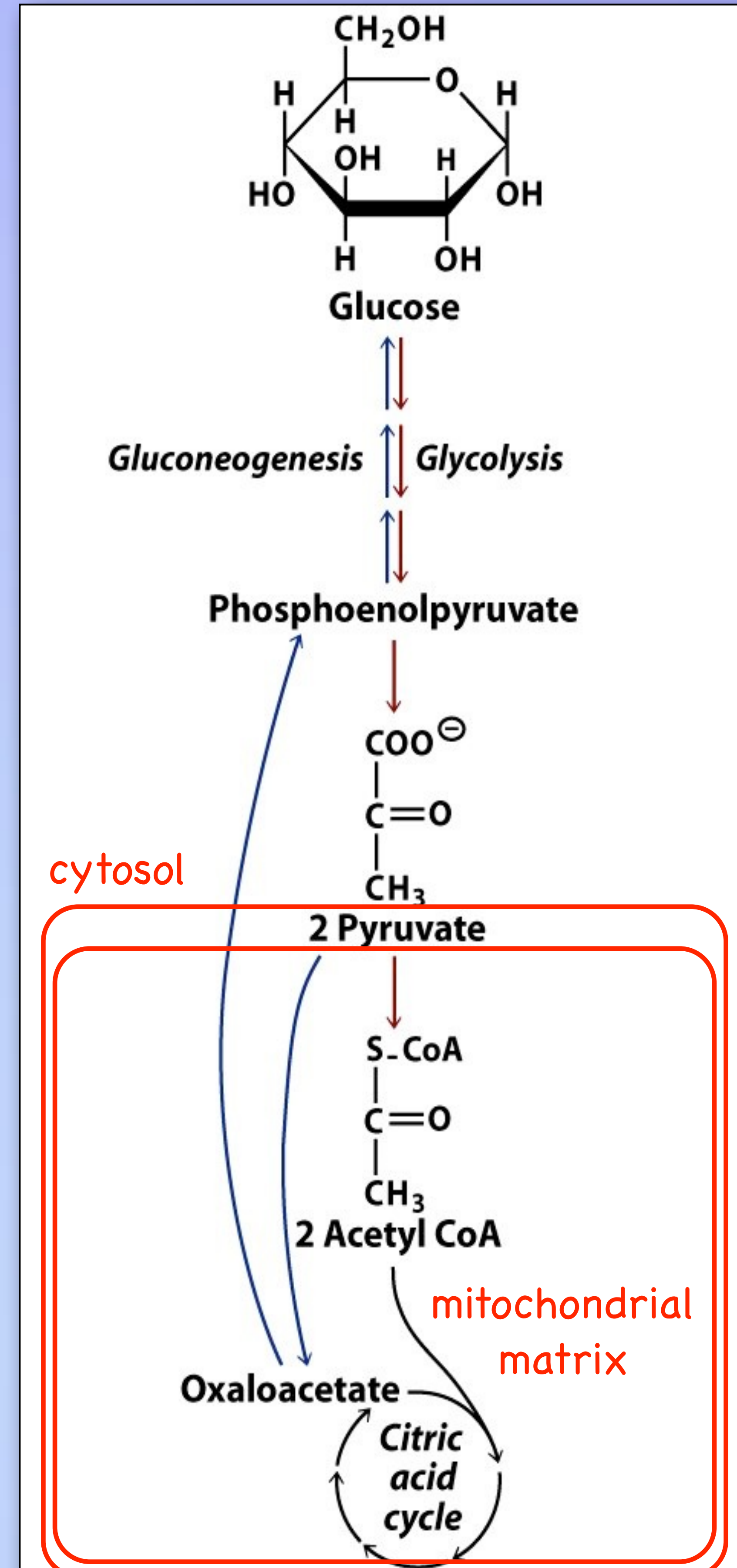

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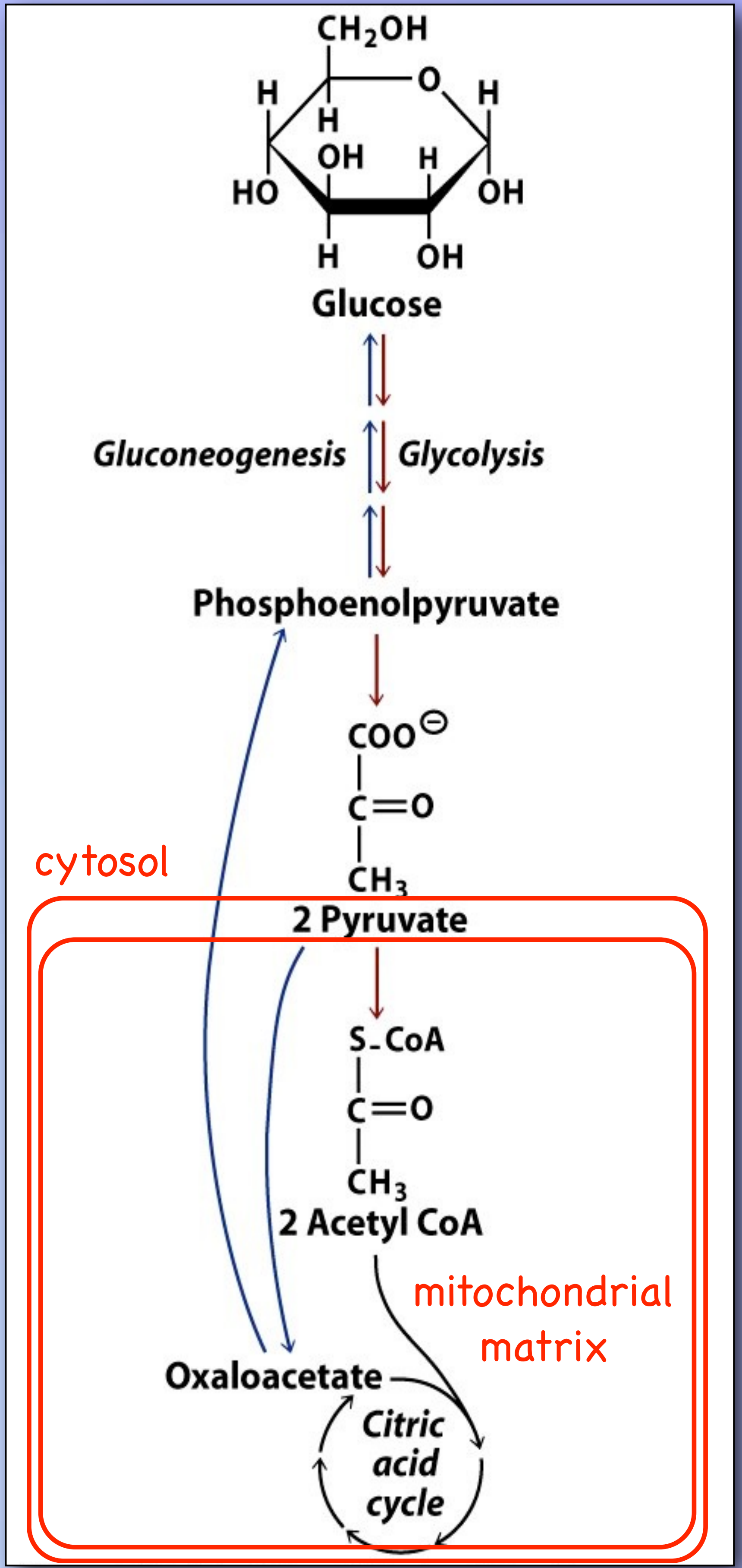
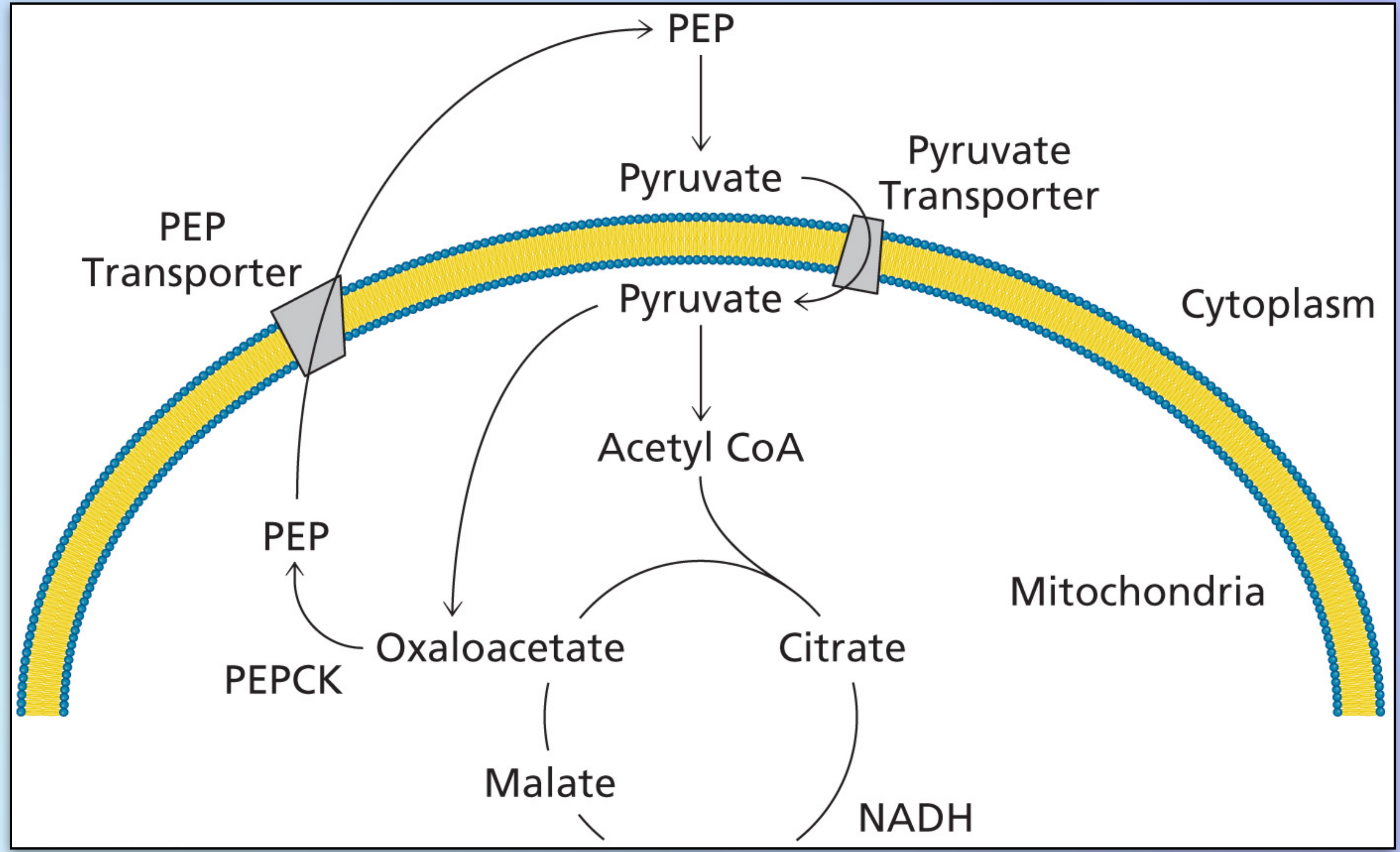


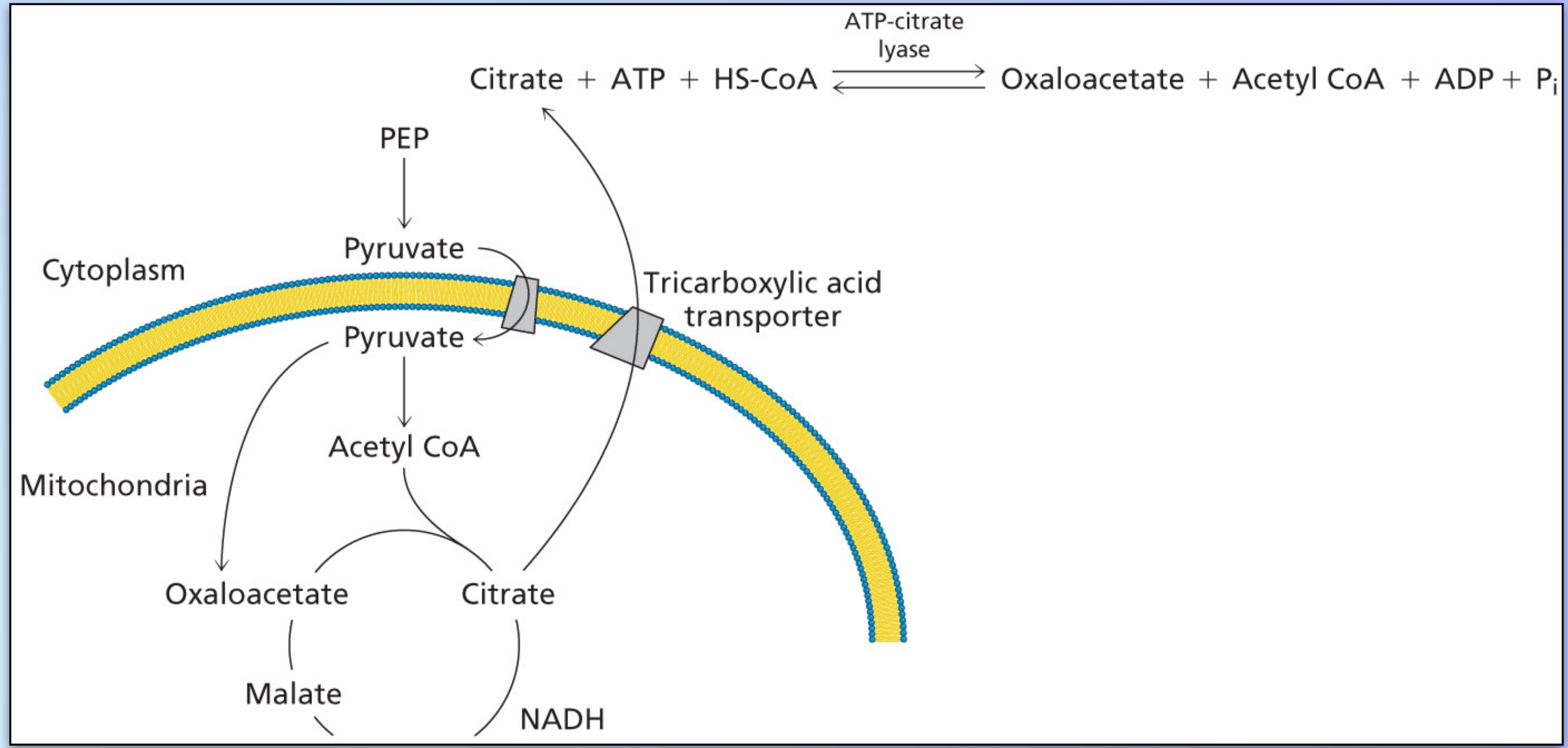
The Citric Acid Cycle

- Transporters are used to move pyruvate through the inner mitochondrial membrane and into the matrix.



The Citric Acid Cycle

- When Acetyl CoA is require in the cytoplasm for fatty acid synthesis, it is transported out as citrate.



The Citric Acid Cycle

- For gluconeogenesis, and alternative to transporting PEP out of the matrix is to transport oxaloacetate out as malate.

The Citric Acid Cycle

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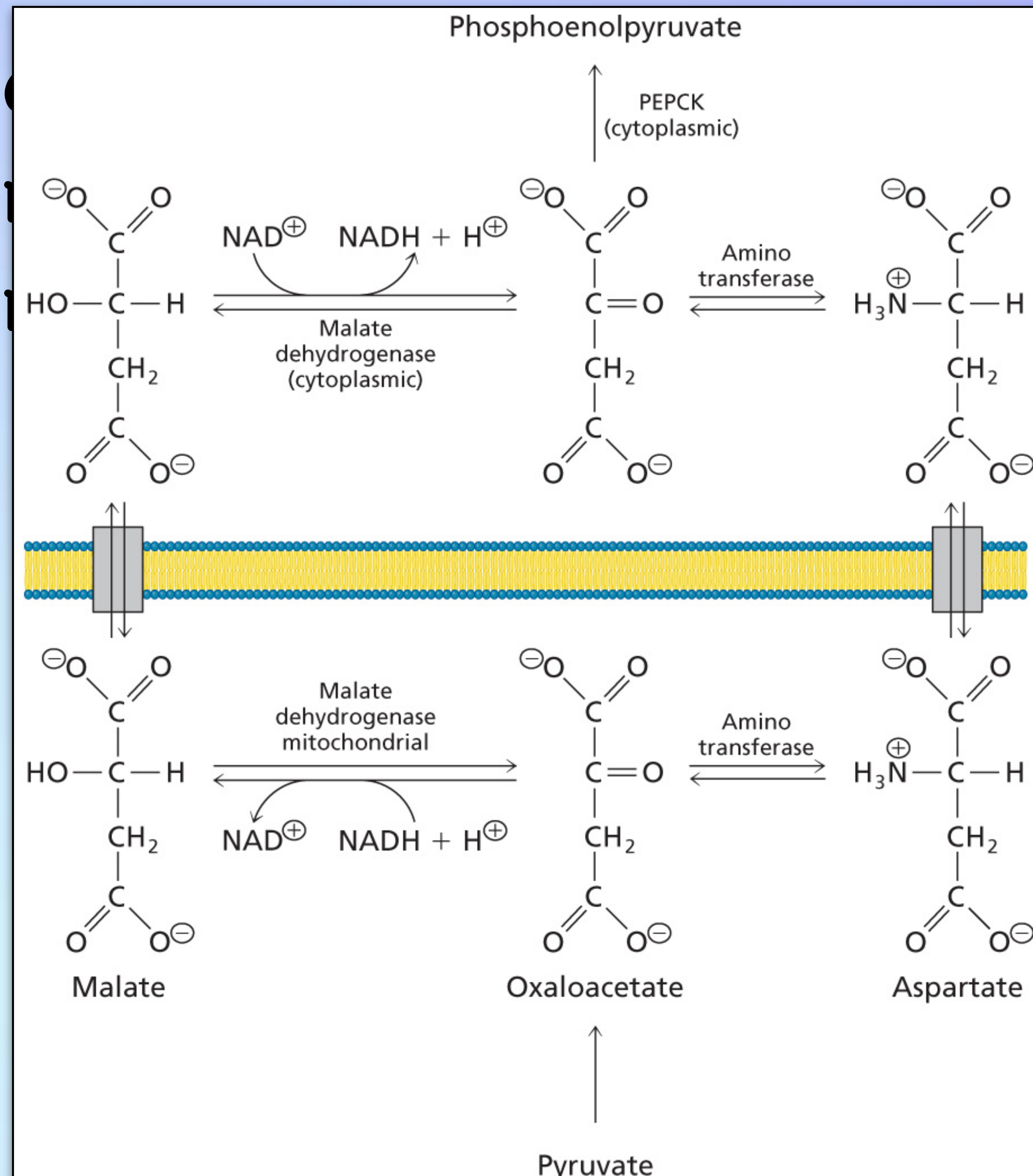

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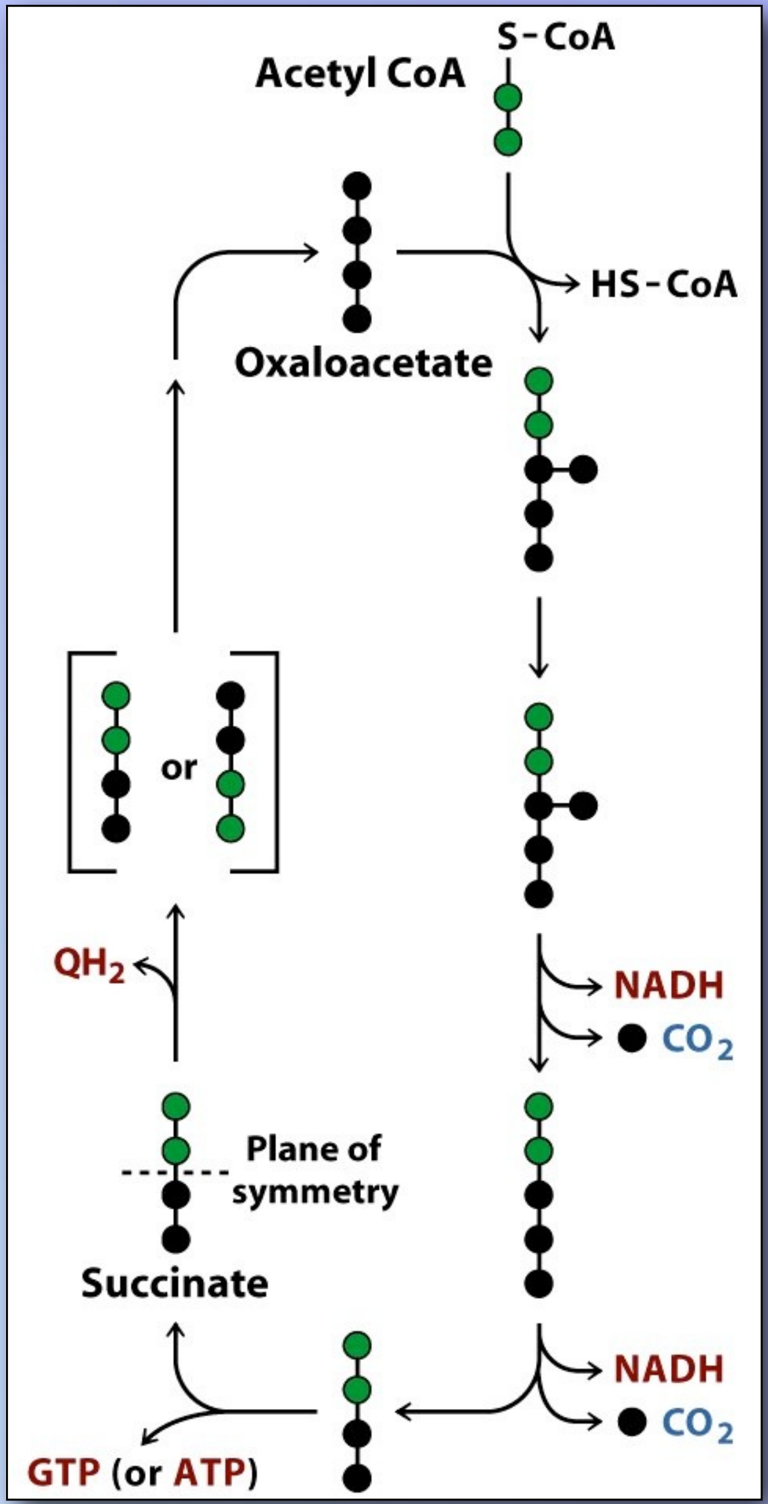
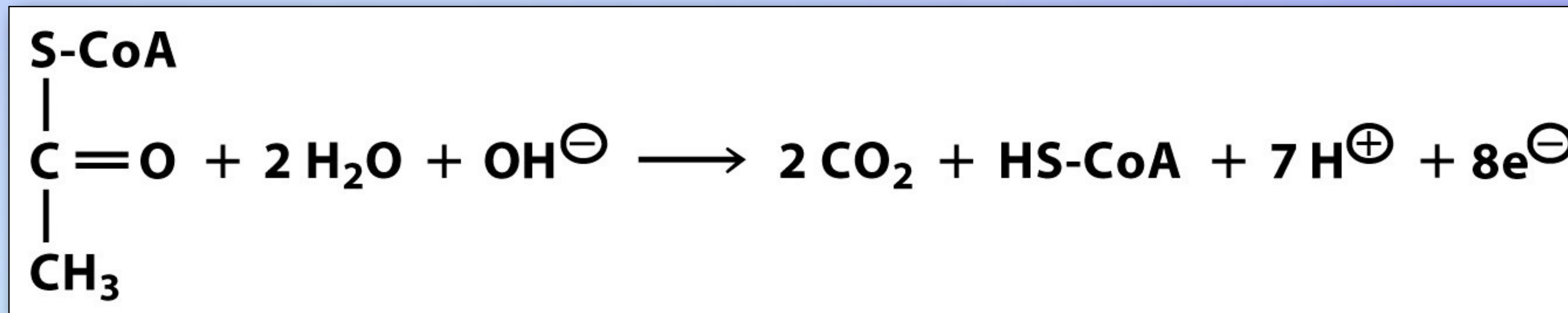
The Citric Acid Cycle

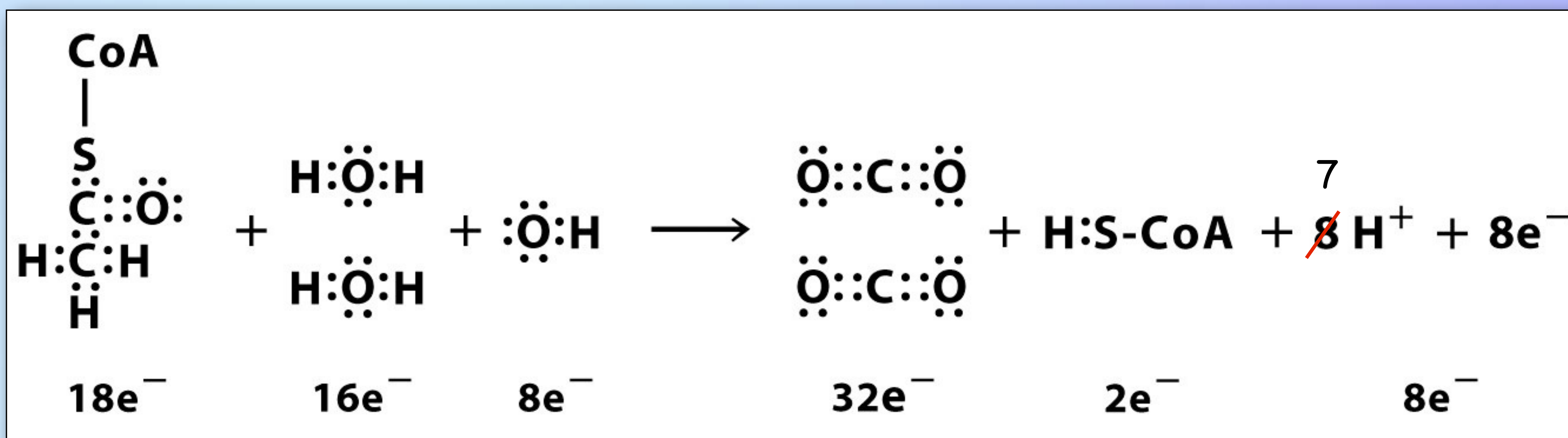
- Catabolic Mode
  - None of CO_2 released in the first round comes directly from the acetyl group.



The Citric Acid Cycle

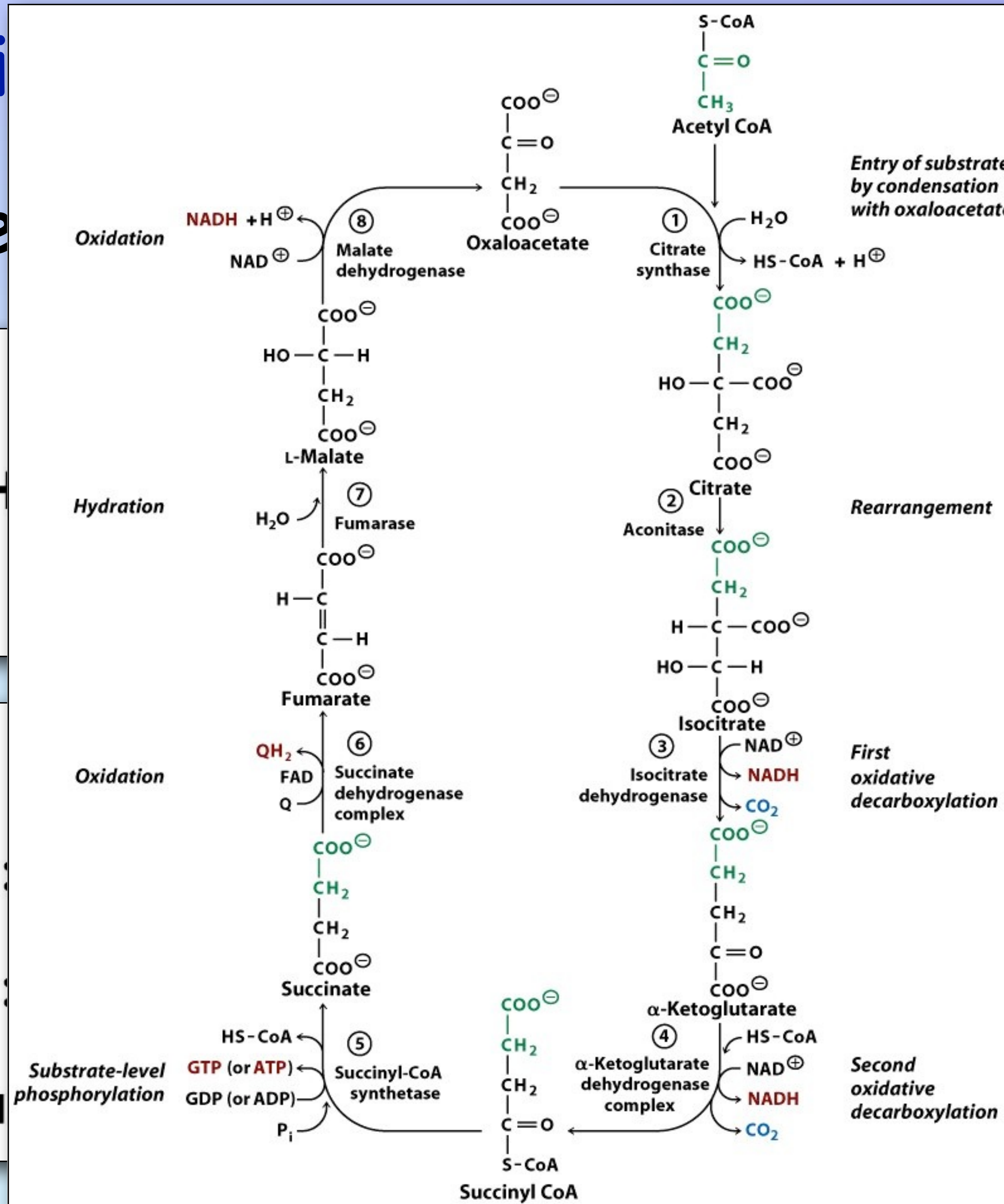
- Where do the electrons come from?





The Ci

- Whe ... from?



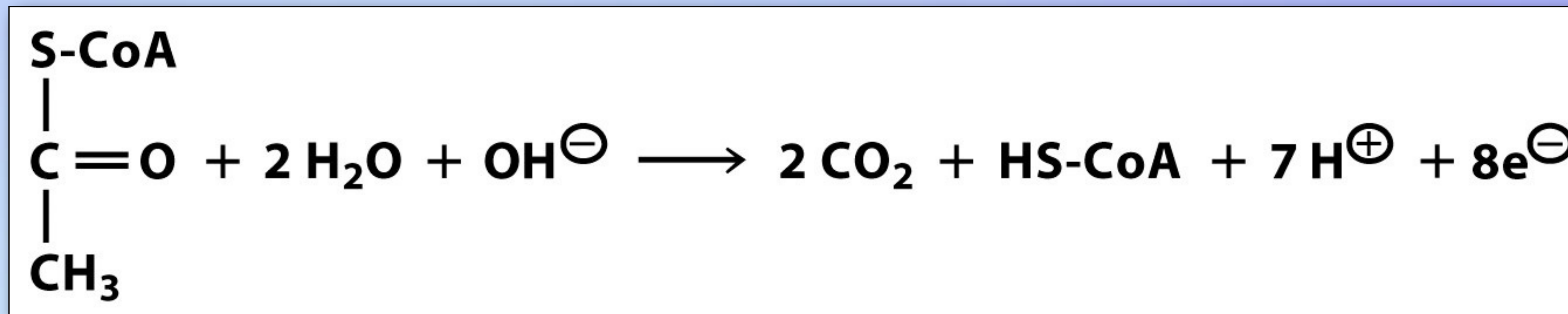
S-CoA | C=O | CH3 + 2 H ... H⊕ + 8e⊖

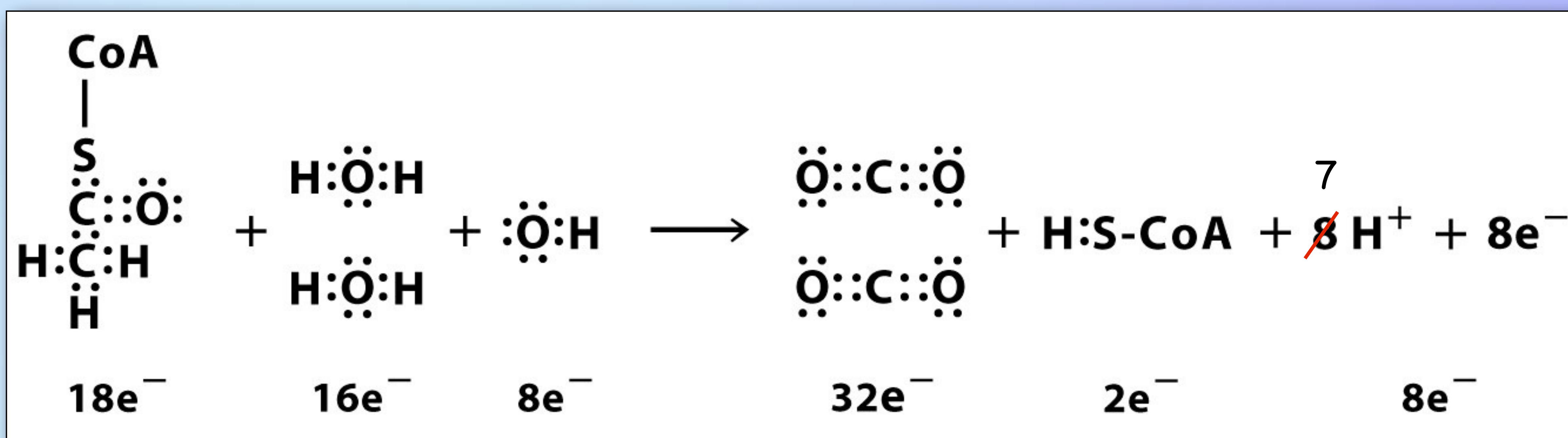
CoA | S | C::O: | H:C:H | H + H: H: ... ~~8~~ 7 H+ + 8e−

18e− 1 ... 8e−

The Citric Acid Cycle

- Where do the electrons come from?



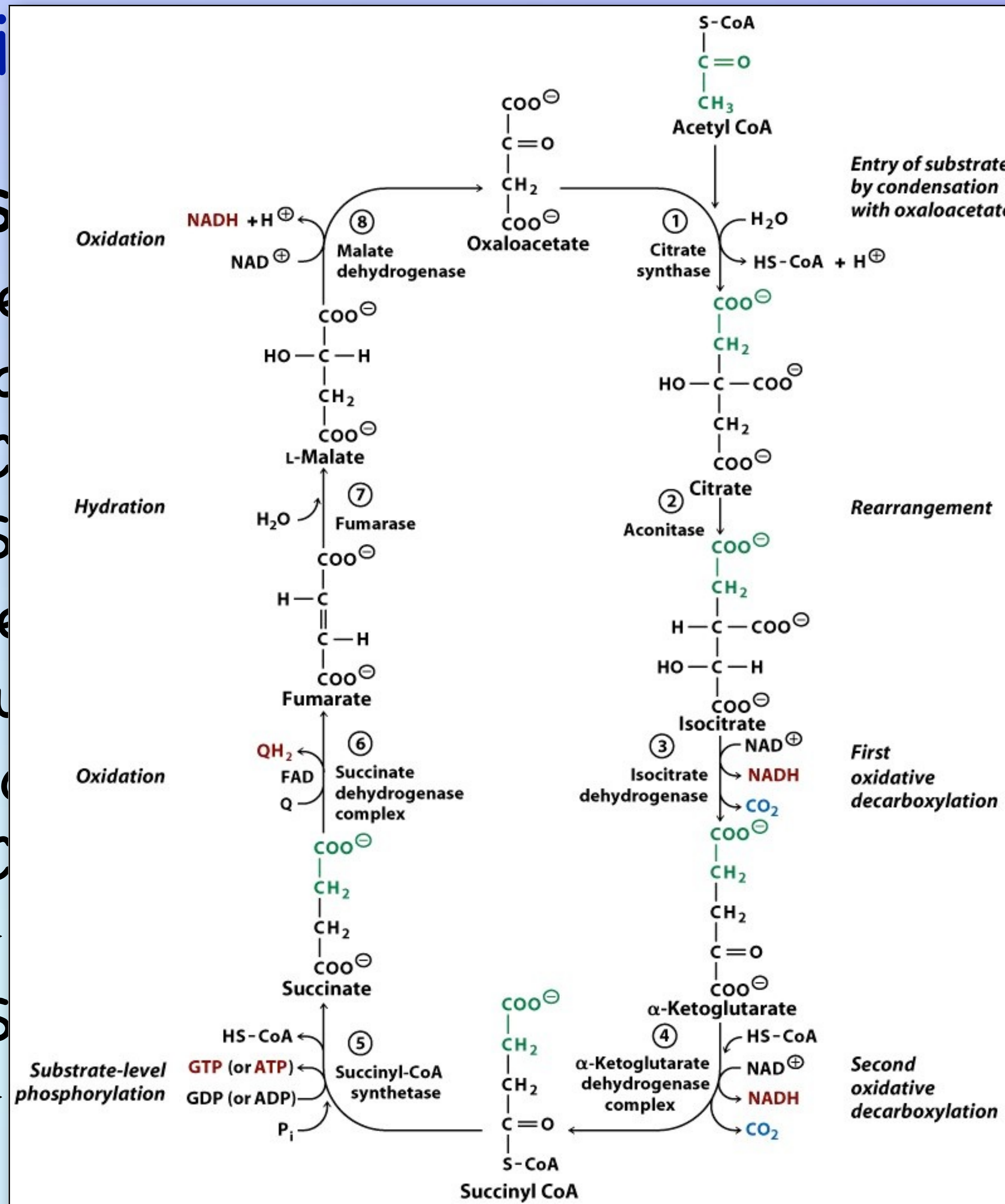


The Citric Acid Cycle

- Substrate level phosphorylation.
  - There are two reactions that involve the hydrolysis of a "high energy" thioester bond.
    - Citrate synthase
    - Succinyl-CoA synthetase
  - The high negative free energy (≈ -31 kJ/mol) is used for two different purposes in these two reactions.
    - Citrate synthase
      - Drives cycle in the clockwise direction.
    - Succinyl-CoA synthetase
      - Coupled to the synthesis of GTP (ATP)

The Ci

- •Subs
  - ✦ The … the hyc … r bond.
    - ‣ C
    - ‣ S
  - ✦ The … kJ/mol) is u … these two
    - ‣ C
      - ✦ … ction.
    - ‣ S
      - ✦ … ATP)



The Ci

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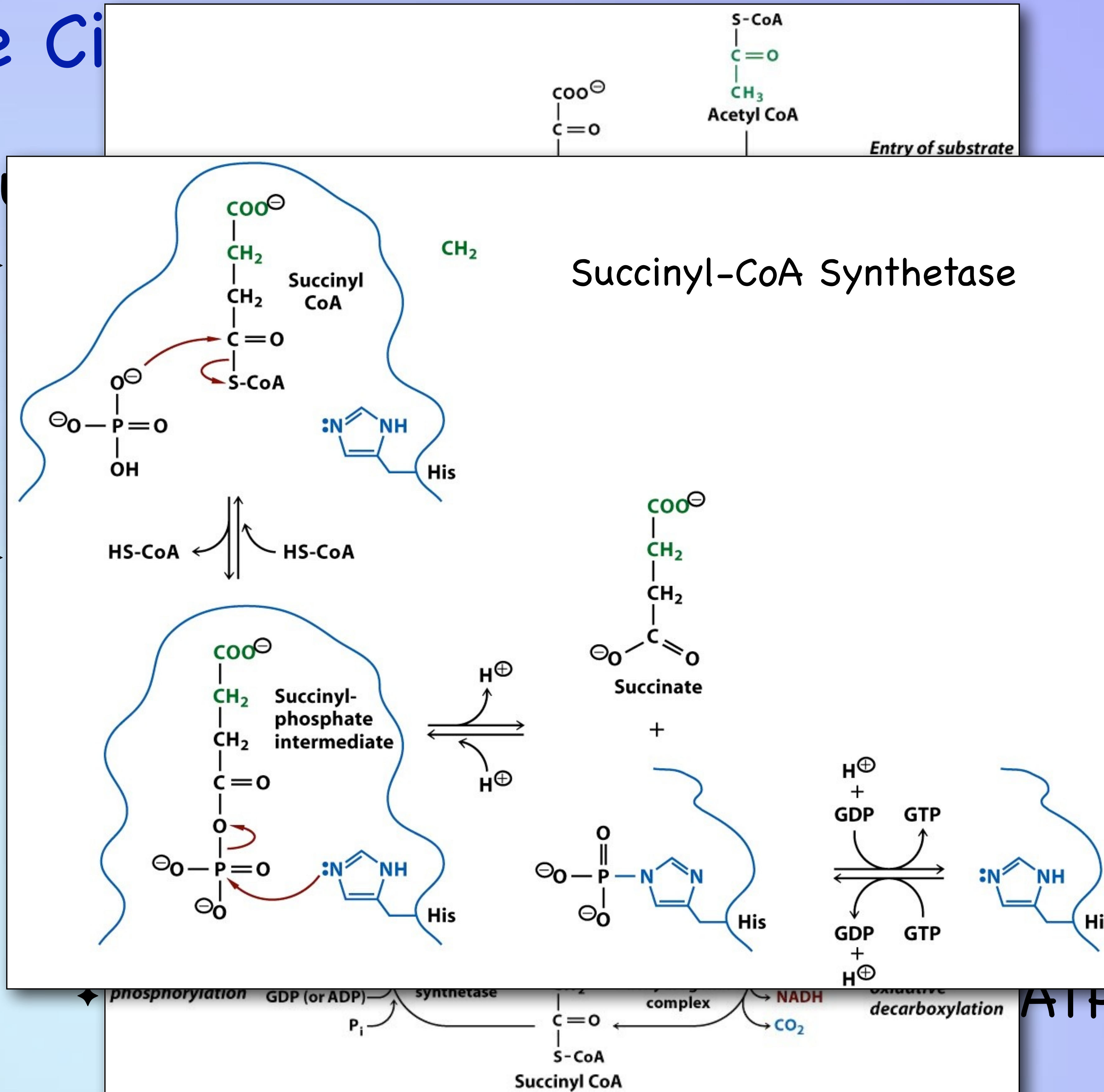

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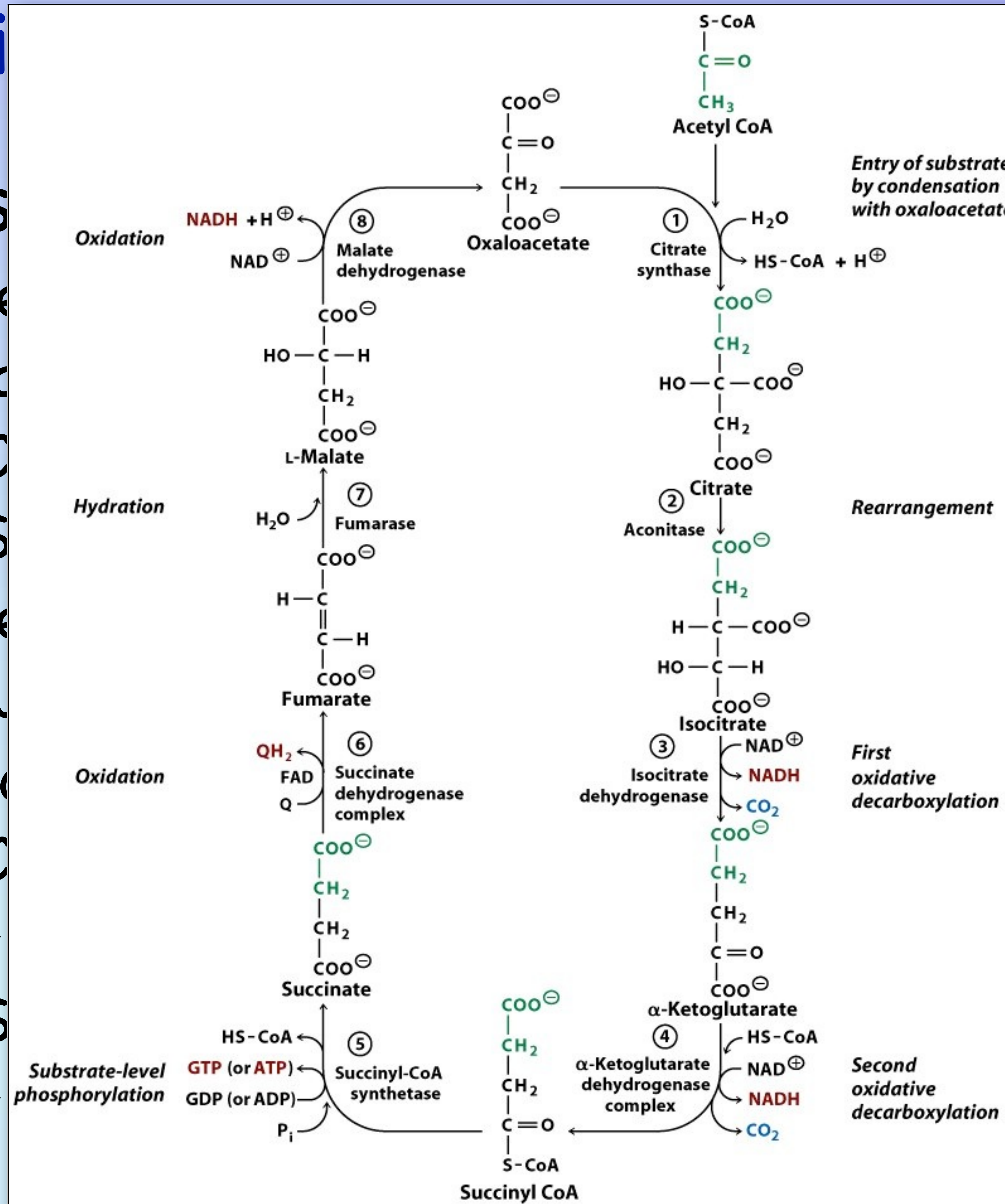

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The Citric Acid Cycle

- Reduced nucleotides are used in oxidative phosphorylation to make ATP.
  - ATP's produced per Acetyl-CoA

Reaction	Energy-yielding product	ATP equivalents
Isocitrate dehydrogenase	NADH	2.5
α-Ketoglutarate dehydrogenase complex	NADH	2.5
Succinyl-CoA synthetase	GTP or ATP	1.0
Succinate dehydrogenase complex	QH_2	1.5
Malate dehydrogenase	NADH	2.5
Total		10.0

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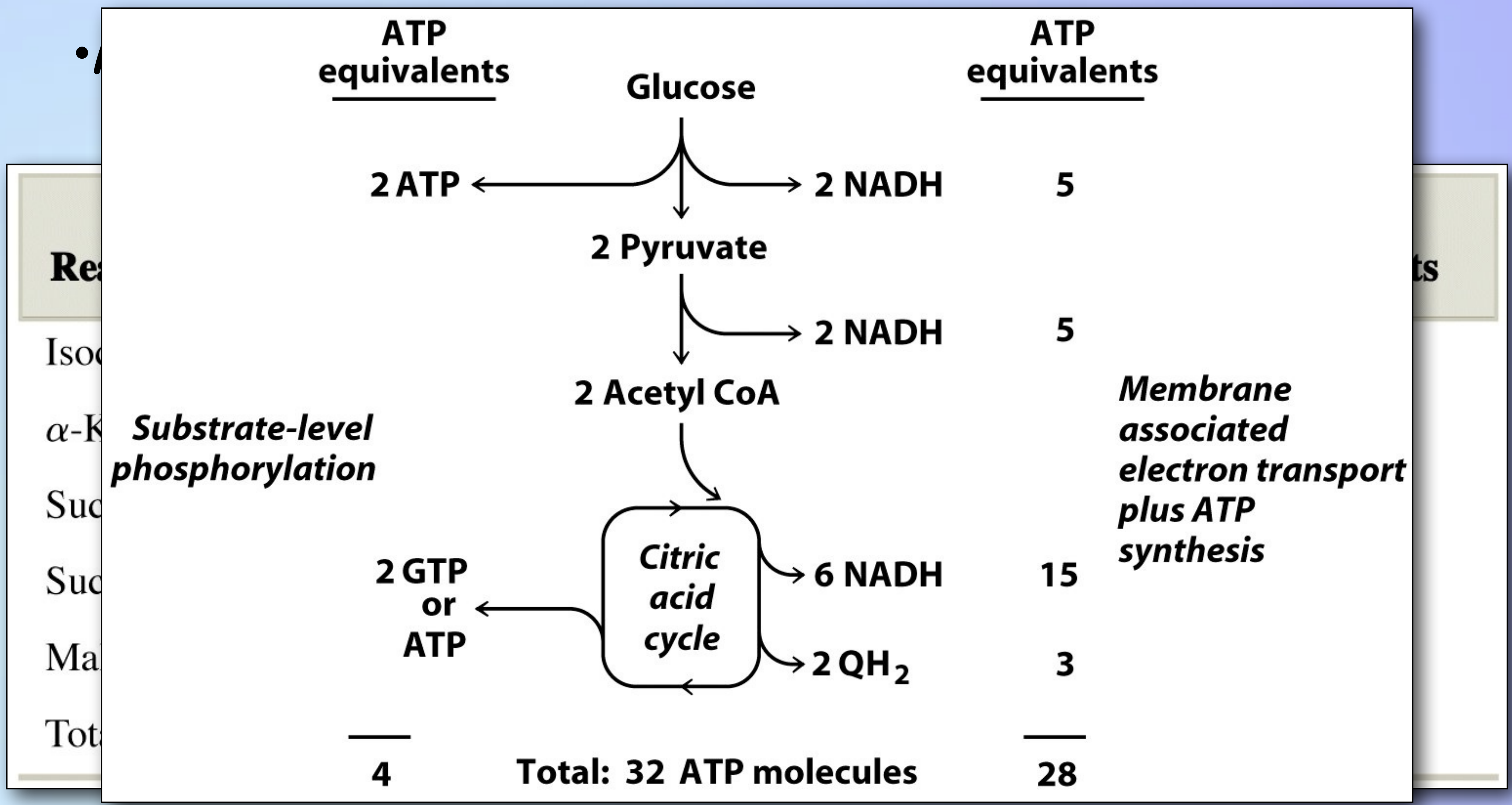

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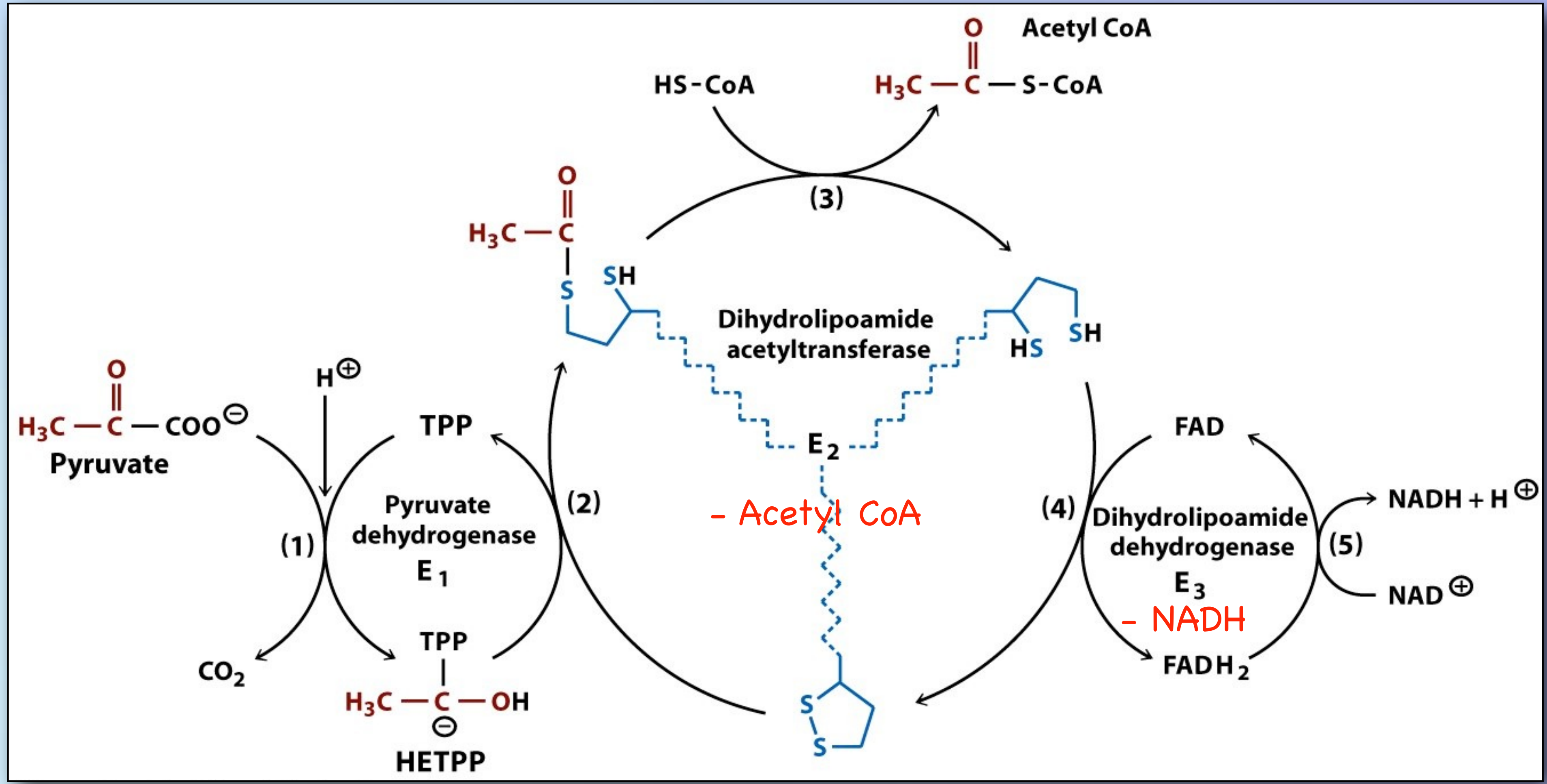
Succinate dehydrogenase complex	QH_2	1.5
Malate dehydrogenase	NADH	2.5
Total		10.0

Regulation of the The Citric Acid Cycle

- Like glycolysis and gluconeogenesis, the citric acid cycle is closely regulated to meet the catabolic and anabolic needs of the cell and the organism.

Regulation of the The Citric Acid Cycle

- The flow of Acetyl-CoA into the cycle is regulated by the pyruvate dehydrogenase complex



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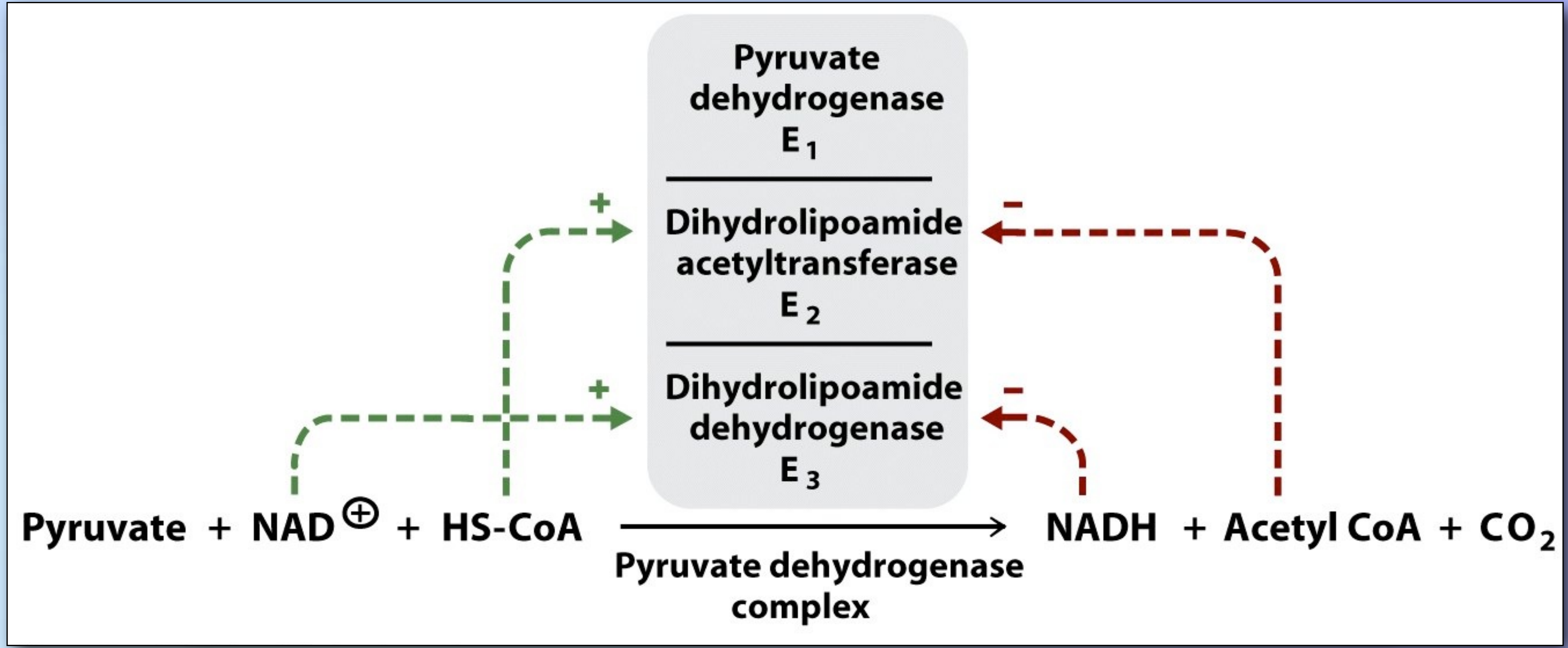

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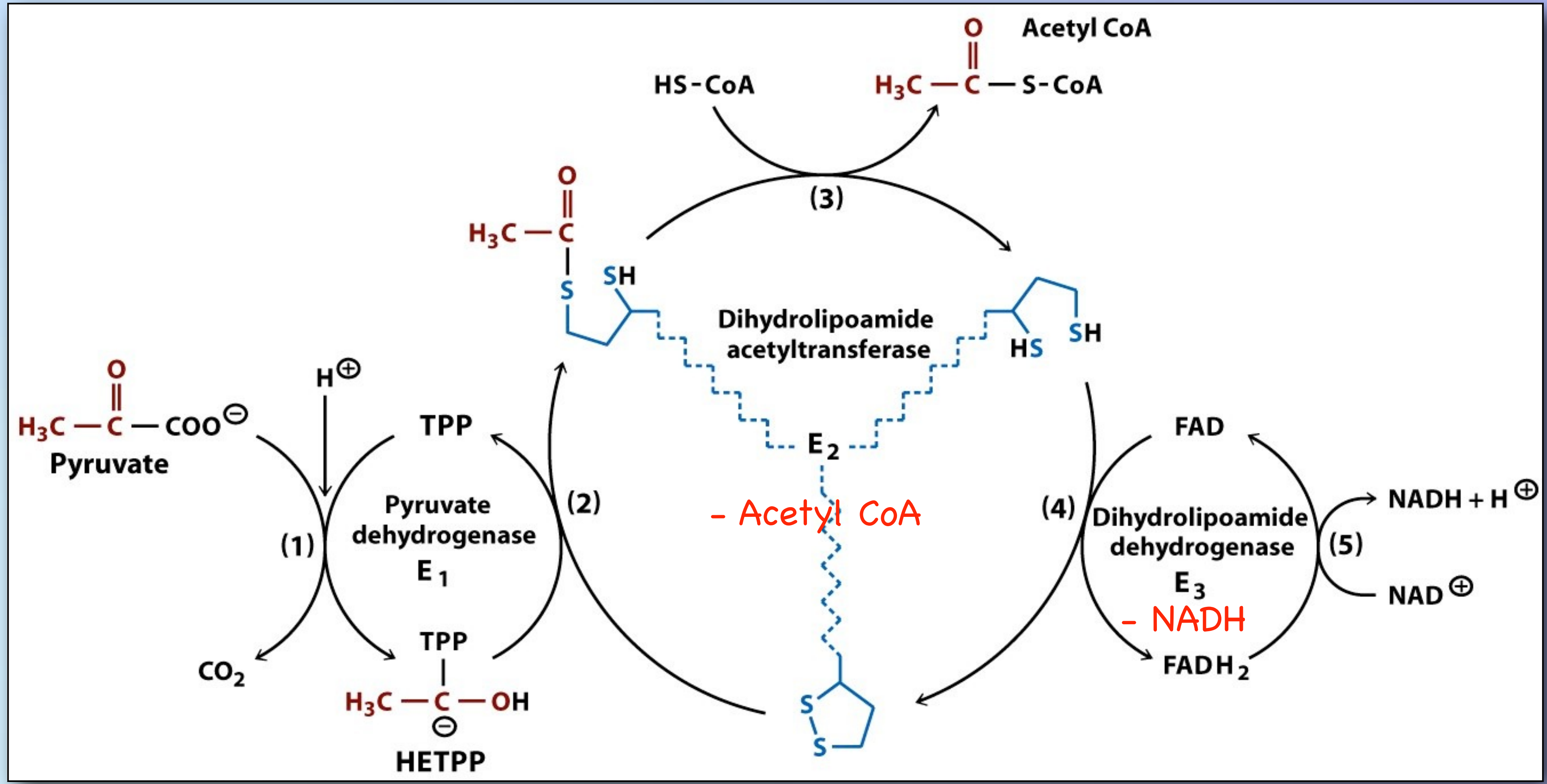
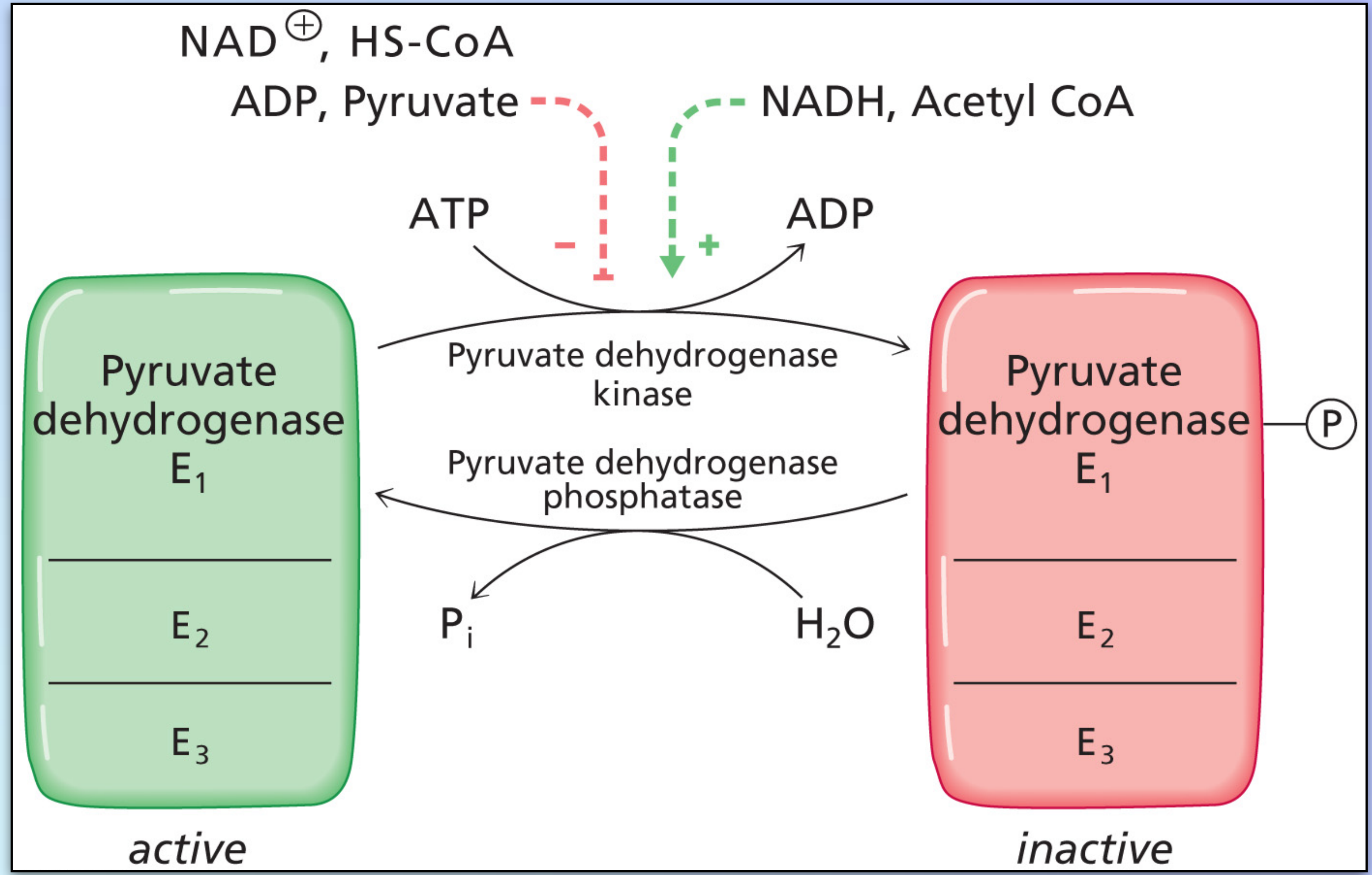


Regulation of the The Citric Acid Cycle

- Mammalian pyruvate dehydrogenase is also covalently regulated



Regulation of the The Citric Acid Cycle

- Three reactions in the citric acid cycle are also allosterically regulated
  - Citrate synthase
    - + α-Ketoglutarate (bacteria)
    - - NADH (bacteria)

Regulation of the The Citric Acid Cycle

- Three reactions in the citric acid cycle are allosterically regulated
  - Isocitrate dehydrogenase
    - + Ca^{2+} (mammals)
    - + ADP (mammals)
    - - NADH (mammals)

Regulation of the The Citric Acid Cycle

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  - Isocitrate dehydrogenase
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    - + ADP (mammals)
    - - NADH (mammals)

Ca^{2+} is a secondary messenger, whose levels are hormonally controlled in the mitochondria

Regulation of the The Citric Acid Cycle

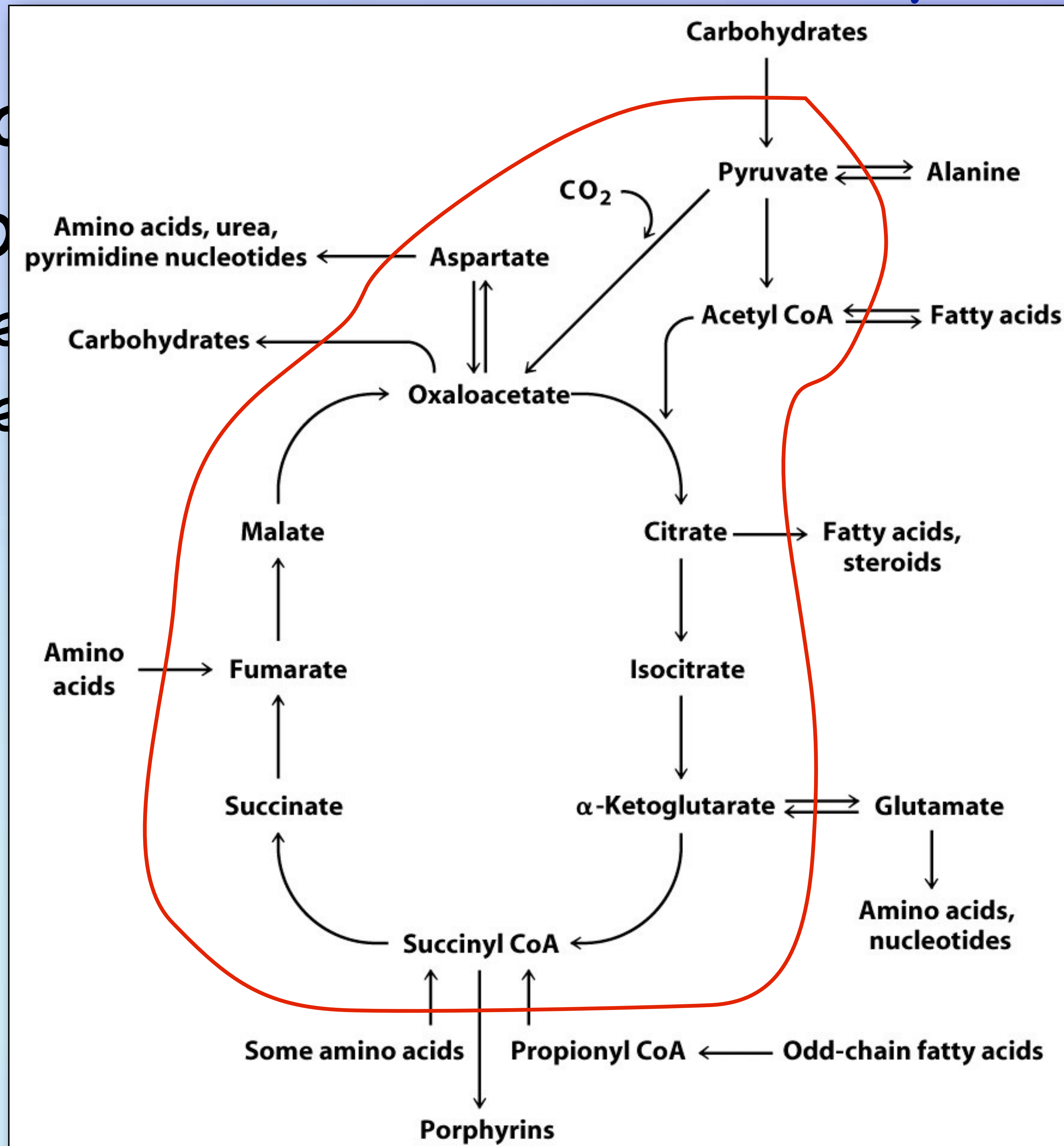
- Three reactions in the citric acid cycle are allosterically regulated
  - α-Ketoglutarate dehydrogenase
    - Unlike pyruvate dehydrogenase, it is not regulated by phosphorylation
    - + Ca^{2+} (Bind to E_1 and lower K_M)
    - - Succinyl-CoA
    - - NADH

Other Roles for Citric Acid Cycle

- Besides serving as intermediates in the oxidation of acetyl groups to CO_2,
  - the citric acid cycle intermediates are also the starting and ending points for a number of other anabolic and catabolic pathways.

Other Roles for Citric Acid Cycle

•Besi s in the o o CO_2,
- the e also the number of ays.



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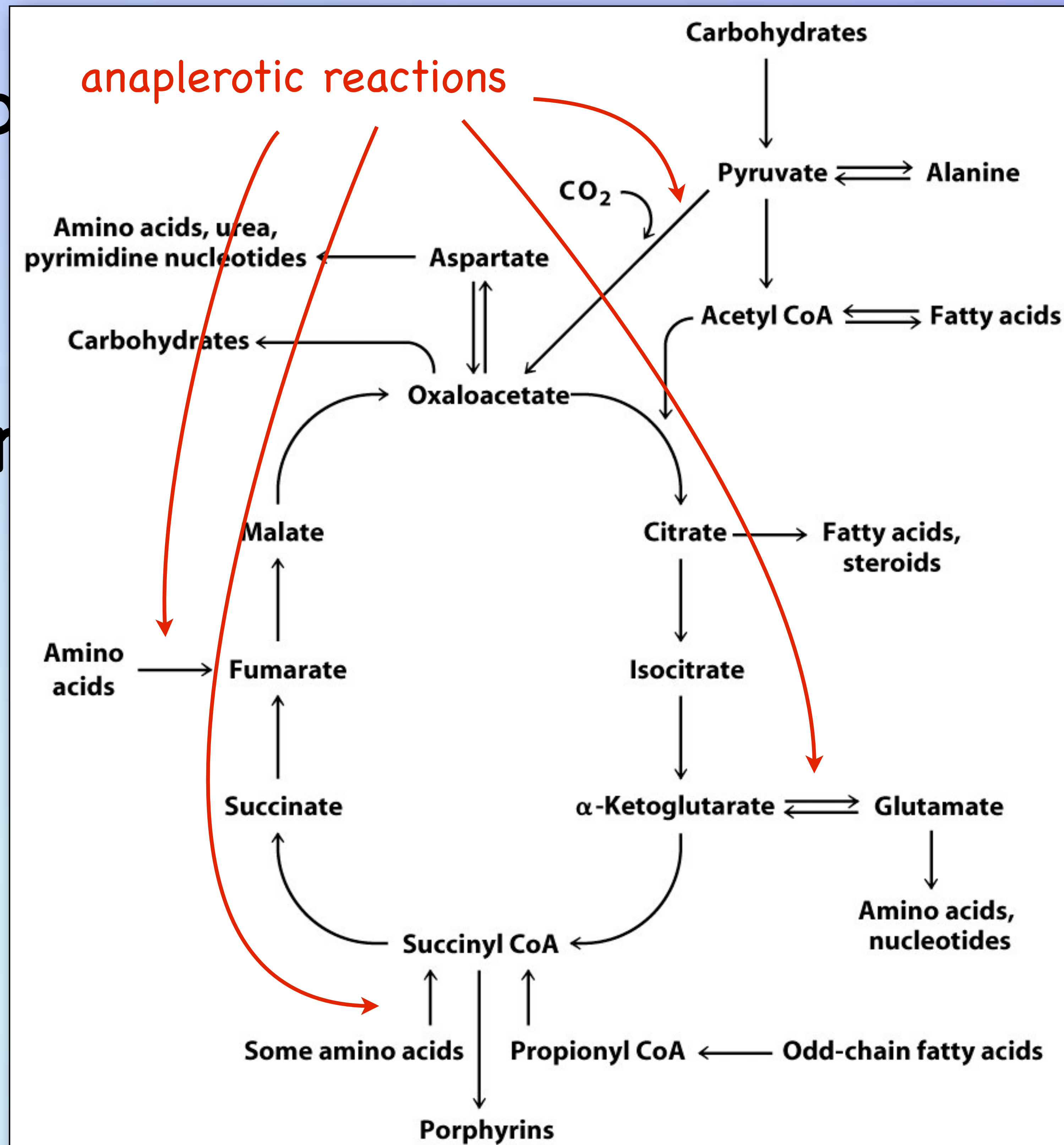
Other Roles for Citric Acid Cycle

- Anaplerotic reactions ("filling up") feed material into the citric acid cycle as citric acid cycle intermediates.

Other Roles for Citric Acid Cycle

•Anap ... o”)
feed ... d
cycle
interr



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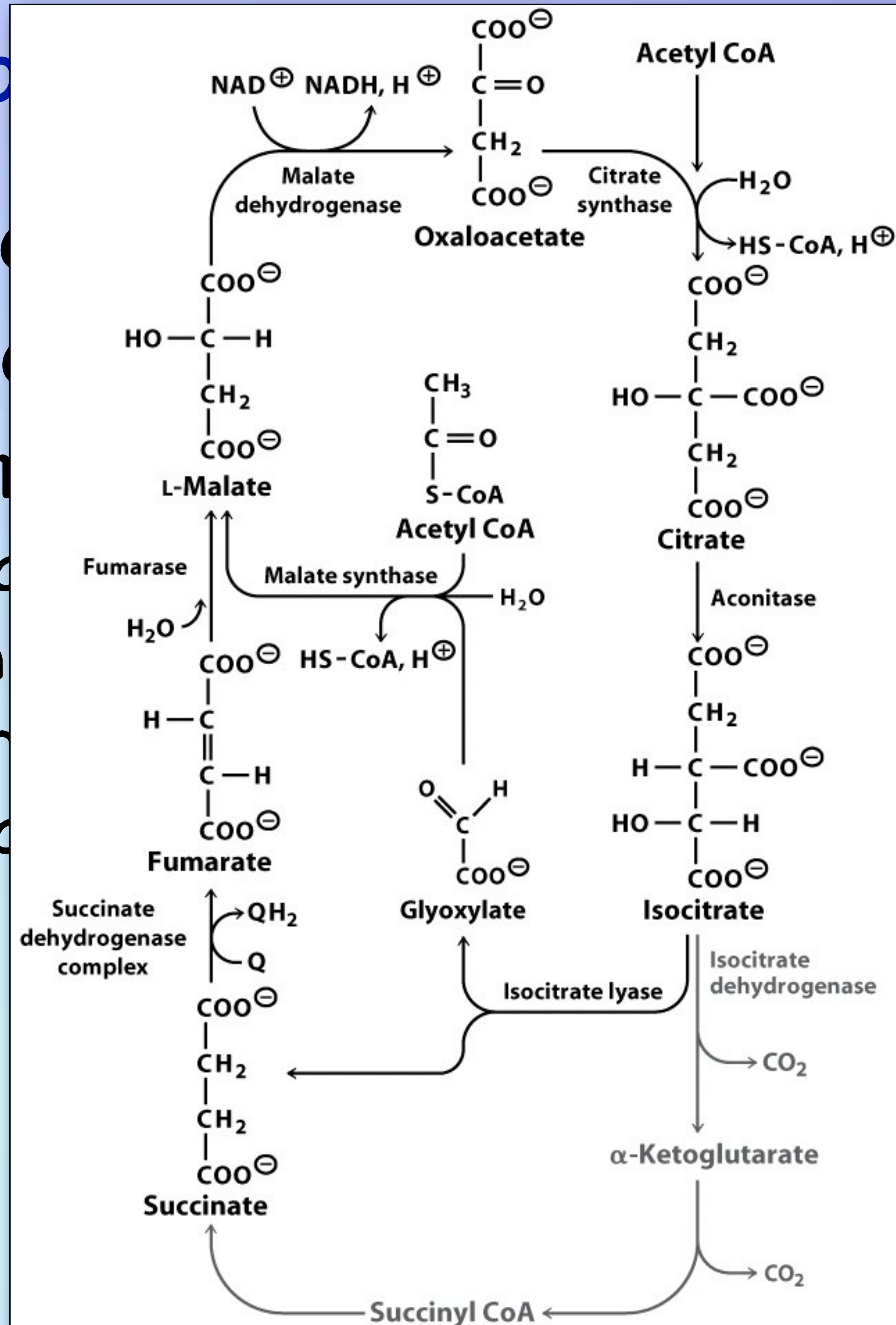
The Glyoxylate Pathway (Shunt)

- Many organisms are able to bypass the two decarboxylation reactions in the citric acid cycle.
  - This allows Acetyl-CoA to be used to build up the levels of the citric acid cycle intermediates.
  - This allows Acetyl-CoA that is derived from fatty acids to be used for glucose synthesis.

The Glyo ... t)

•Many ... bypass the tw... tions in the citr...

- This ... to build up th... cle intern...
- This ... rived from fatty ... synthesis.



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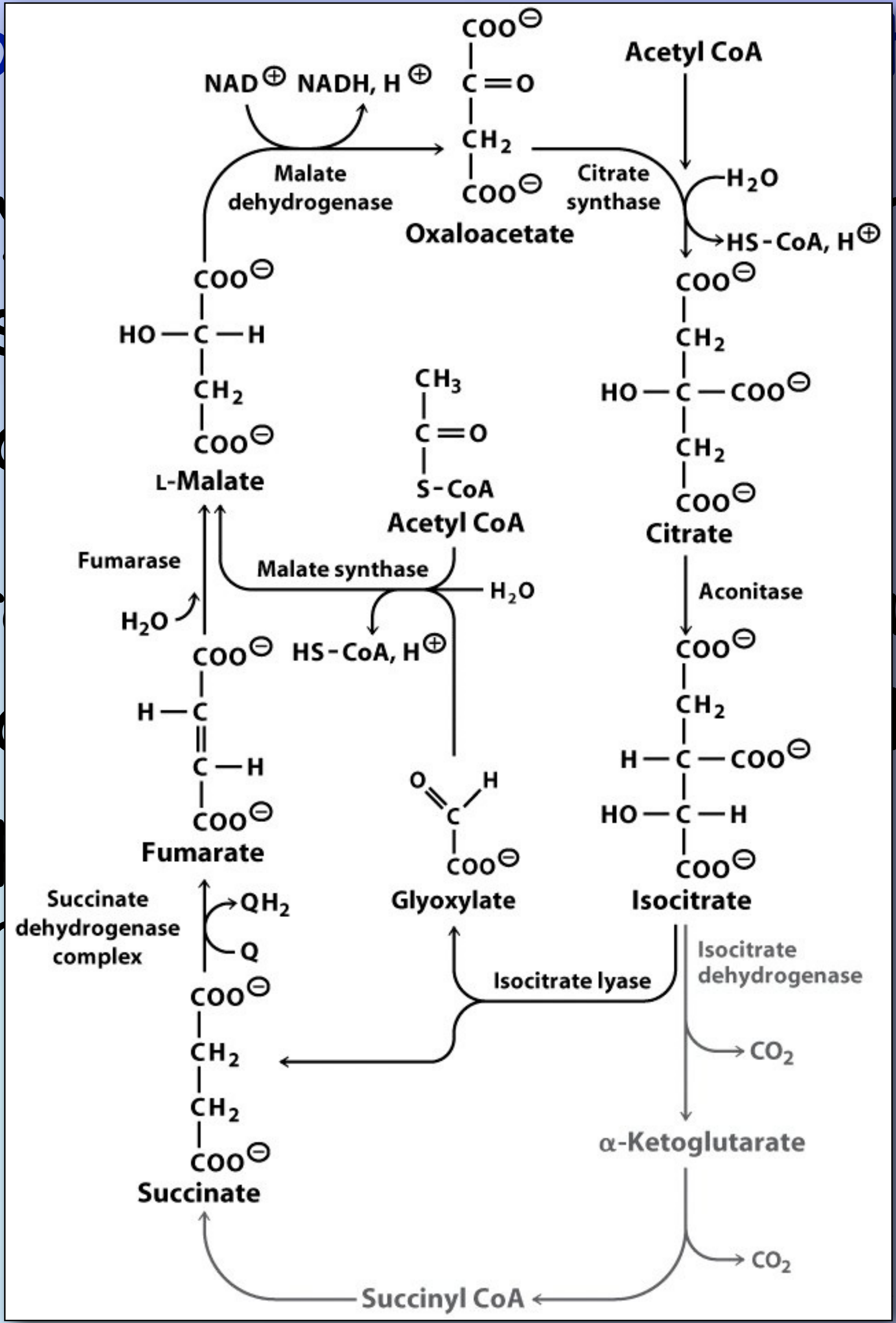
The Glyoxylate Pathway (Shunt)

- The glycoxylate shunt is turned on by phosphorylating isocitrate dehydrogenase
- Isocitrate, oxaloacetate, pyruvate, 3-phosphoglycerate, PEP promote dephosphorylation
  - Turning off the glyoxylate shunt.

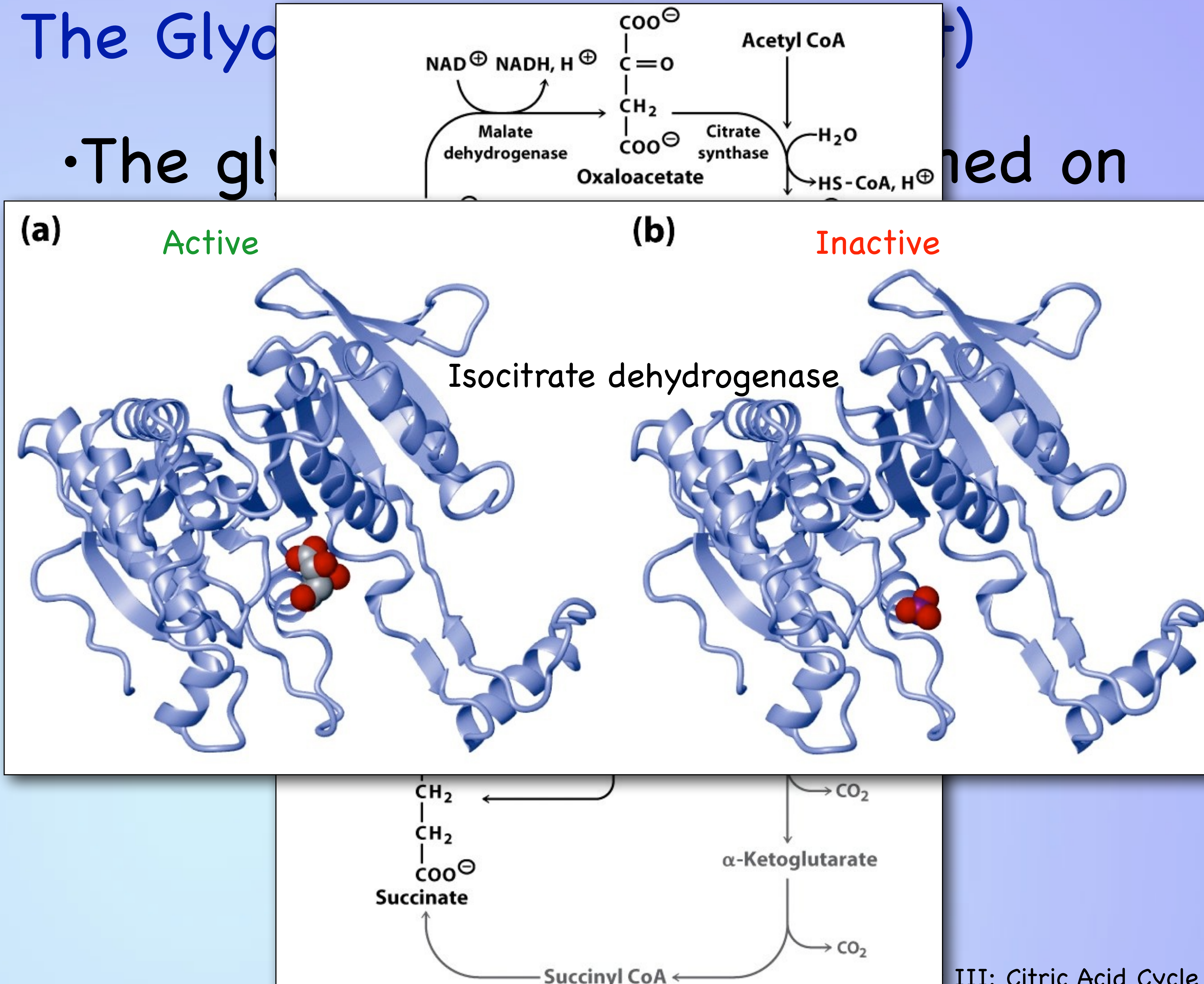
The Glyo t)

- The gl ned on by phos dehydr
- Isocitr vate, 3-phosph te dephos
  - Turnir



The Glyo t)

- The gl ned on



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by phos
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•Isocitr   vate, 3-
phosph   te
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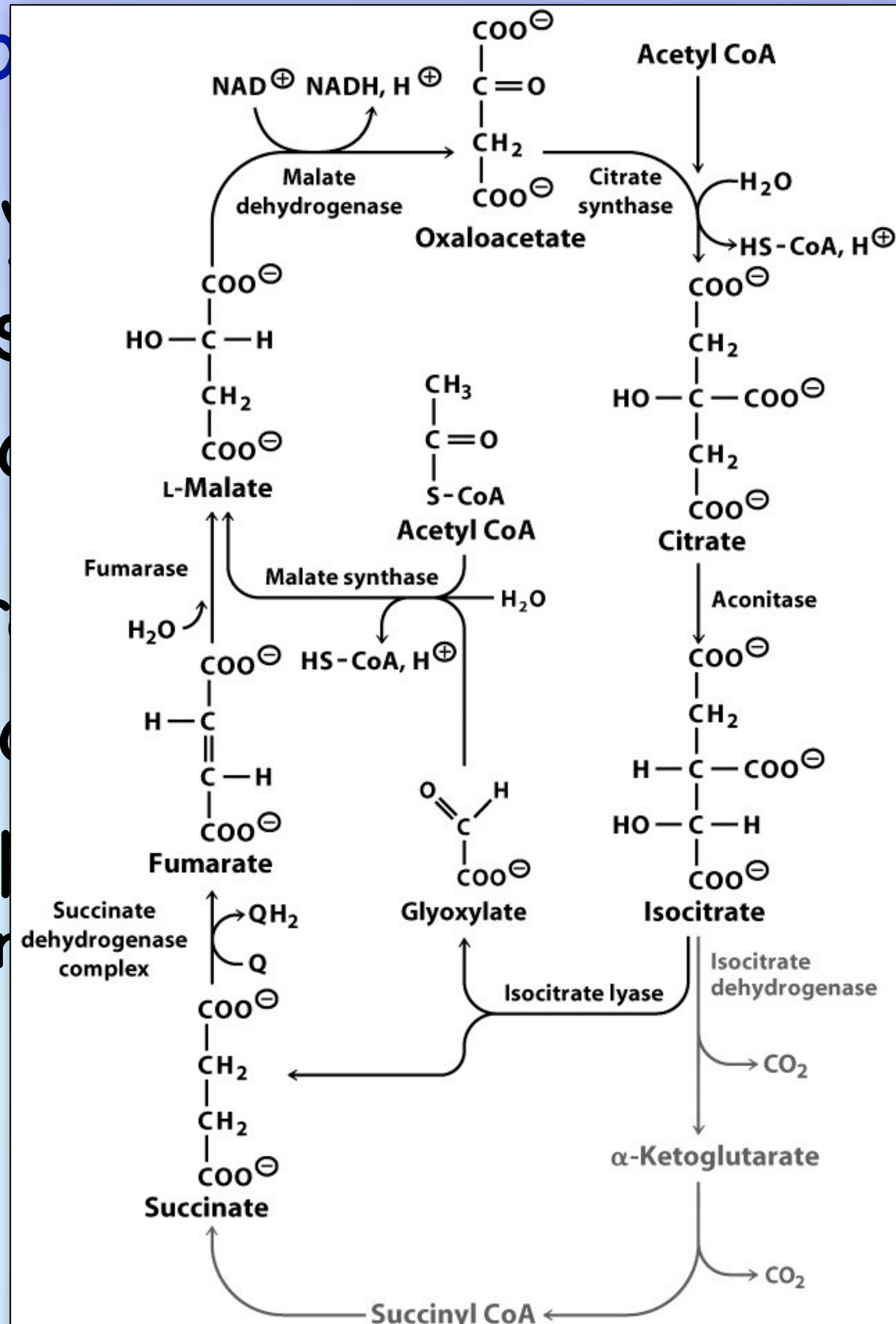

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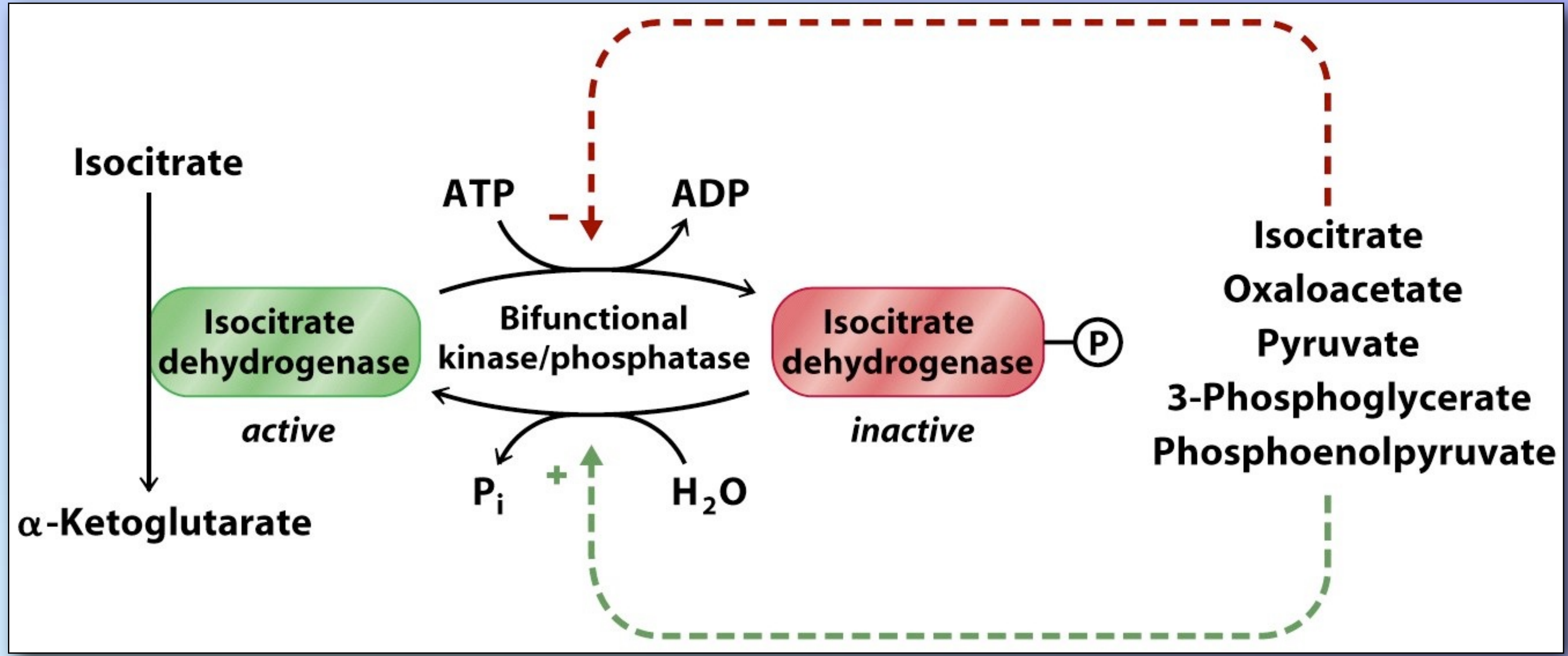

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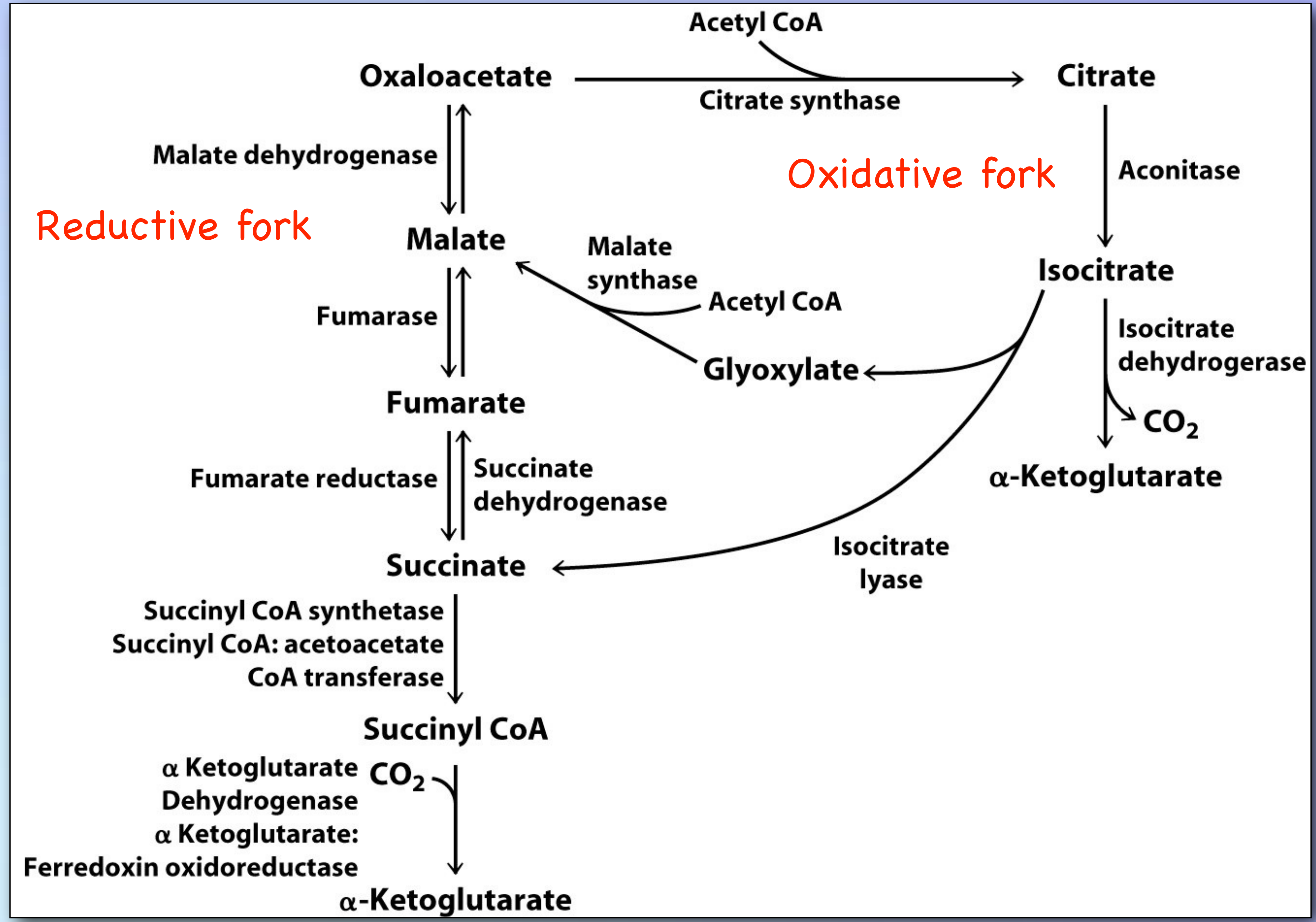
Evolution of the Citric Acid Cycle



Next Up

- Lecture 8 – Carbohydrate Metabolism
  - Part IV: Electron Transport and ATP Synthesis (Moran et al., Chapter 14)