Biochemistry

Metabolism

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The fate of pyruvate
Citrate cycle

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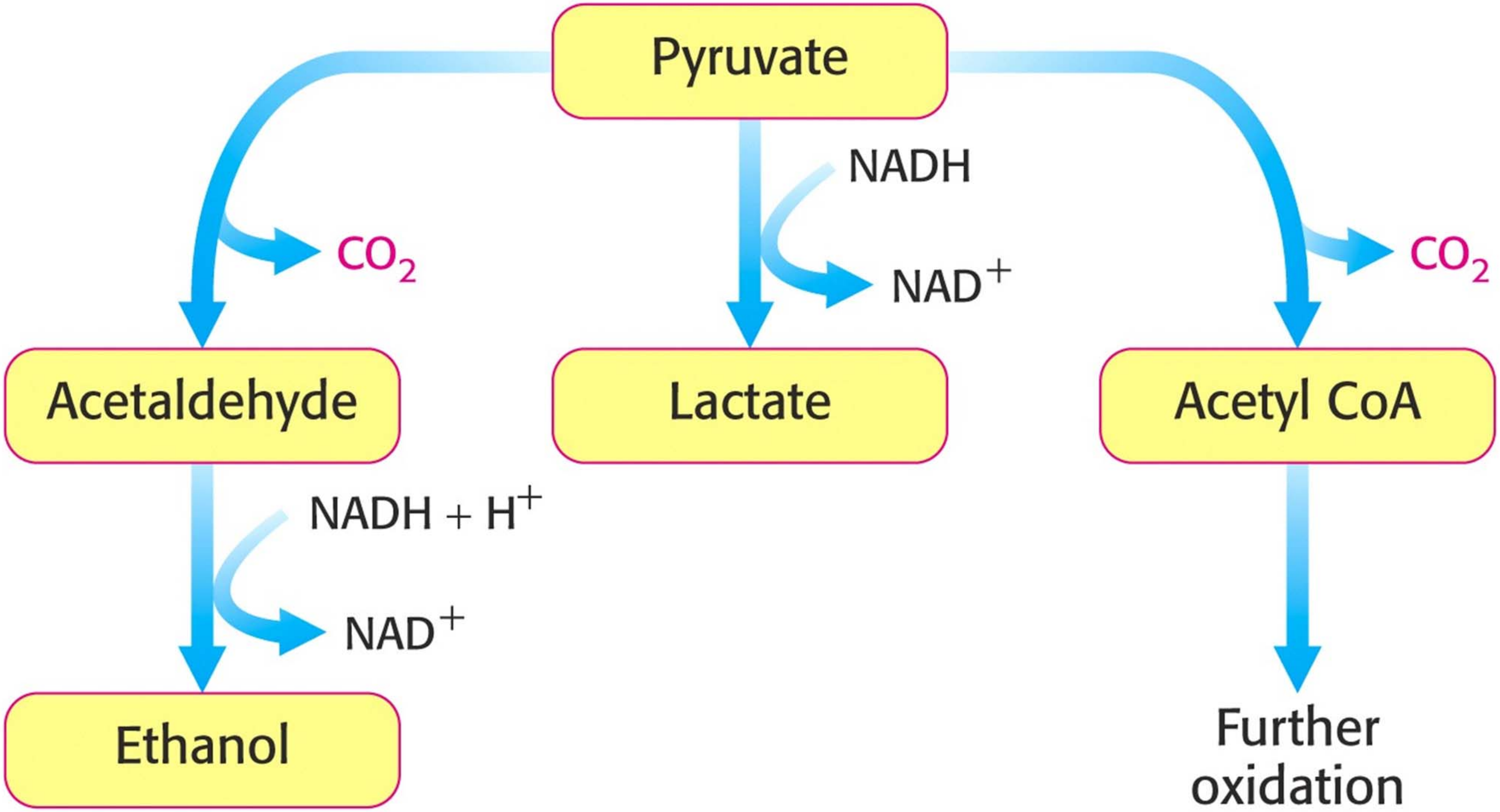
Utilization of pyruvate



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Thiamine pyrophosphate (TPP), the cofactor of pyruvate decarboxylase

Also co-factor of: pyruvate-DH, ∝-ketoglutarate-DH, transketolase

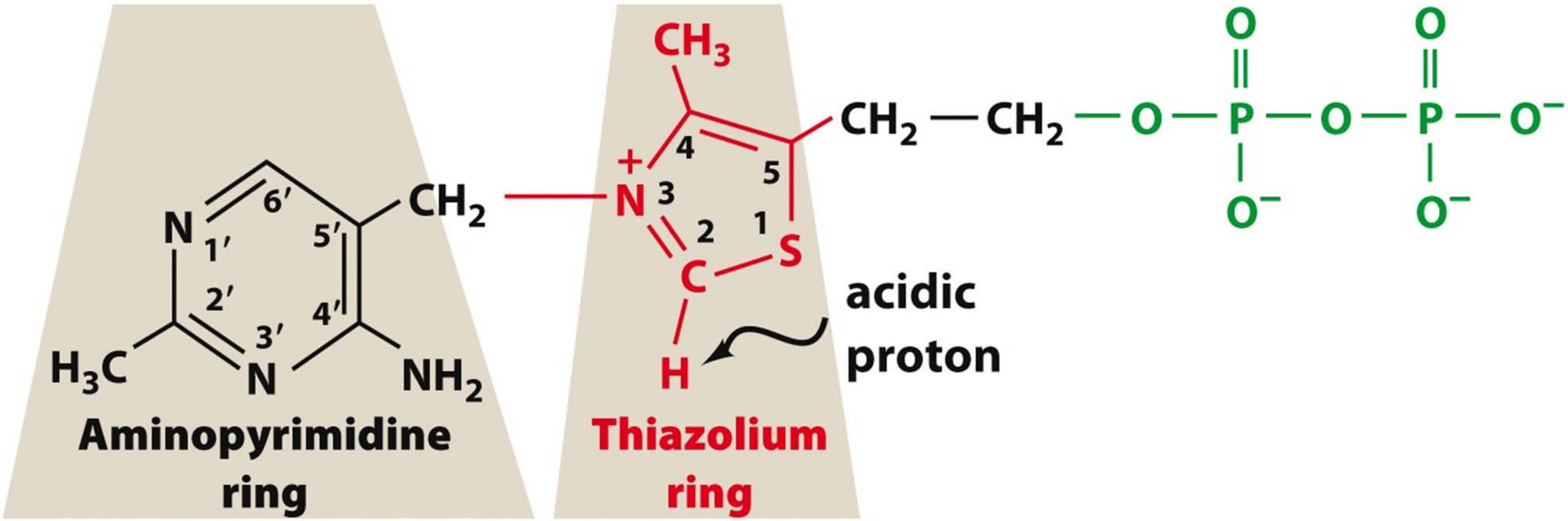
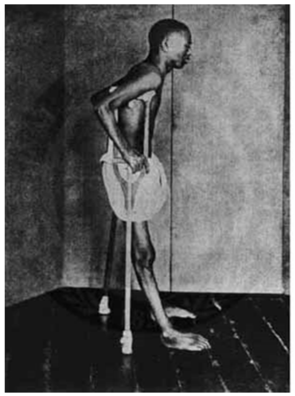


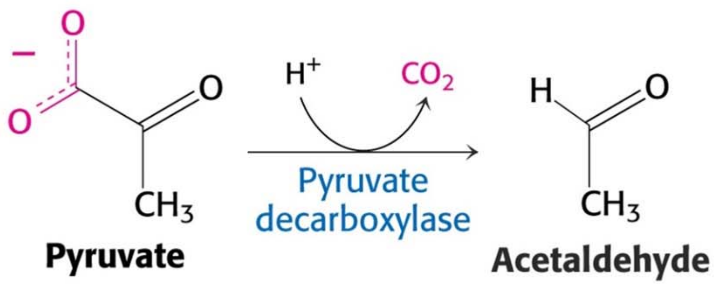
Figure 17-26

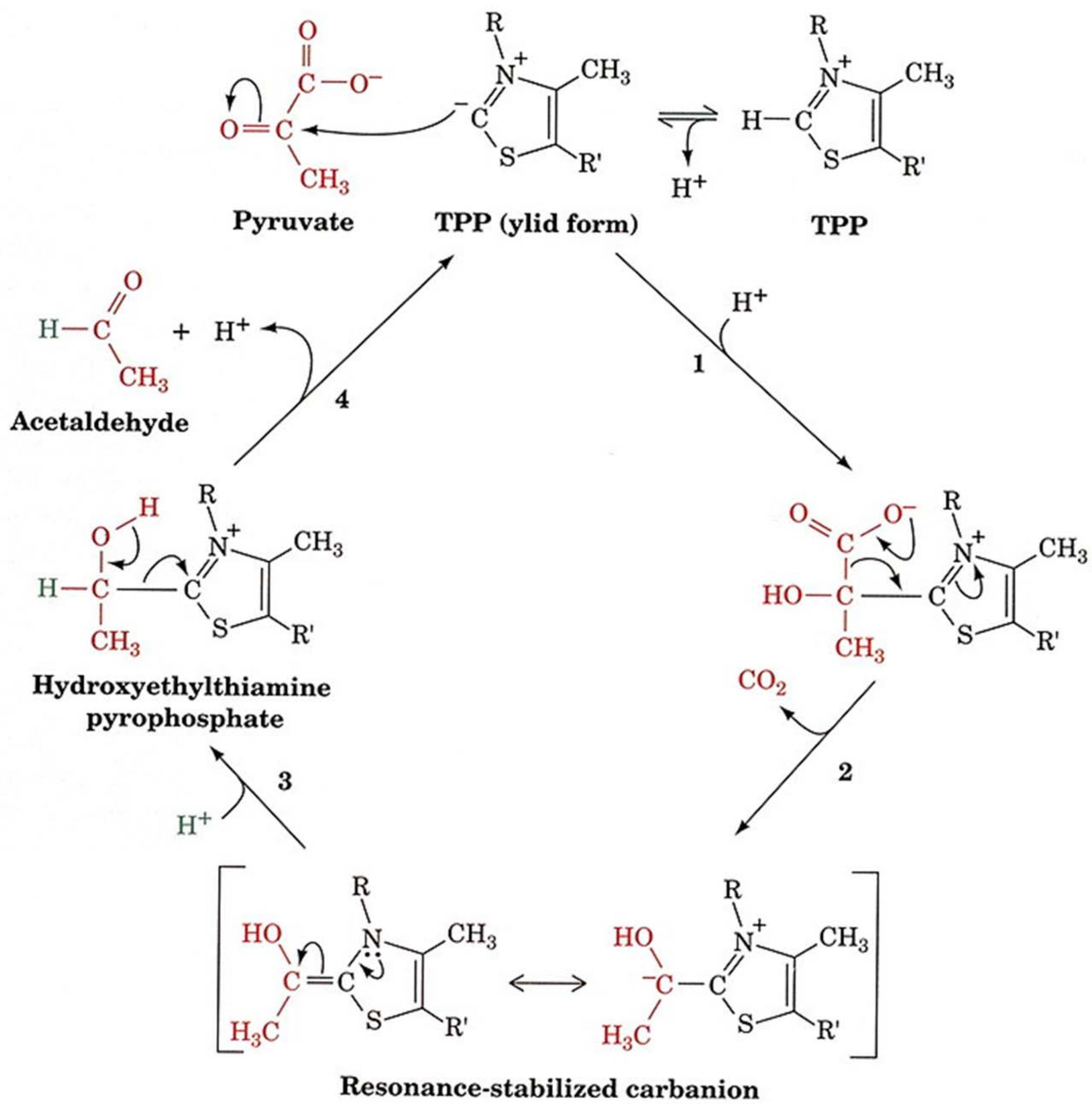


Thiamine, vitamin B_1

Deficiency: Beriberi disease

Catalytic Mechanism of Pyruvate Decarboxylase





Other metabolic diseases: Beriberi – deficiency of thiamine (vit. B1)

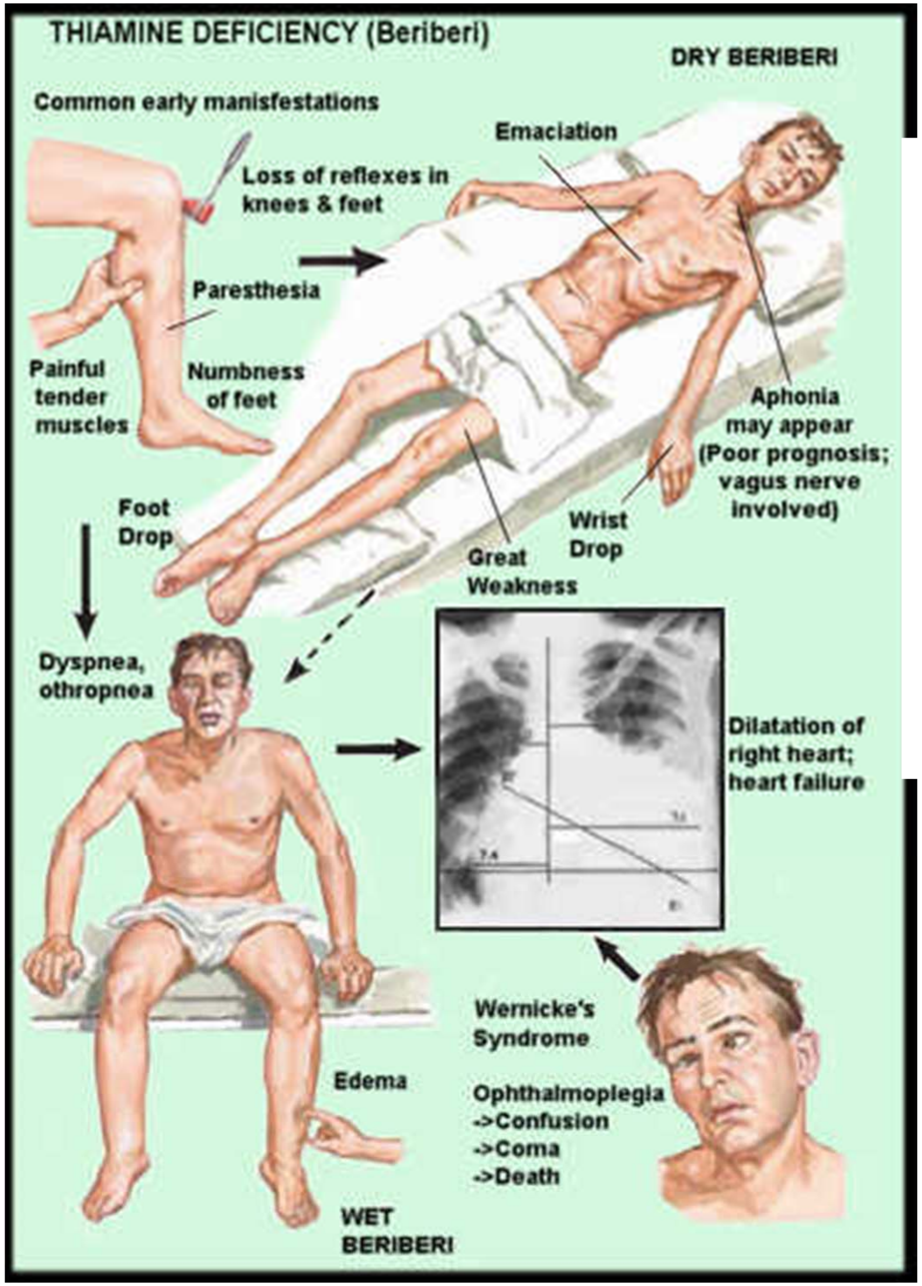
- There are **two major types of beriberi**:
  - Wet beriberi affects the **cardiovascular system**.
  - rare in the United States because most foods are now vitamin enriched.
  - Dry beriberi/Wernicke Korsakoff syndrome affects **the nervous system**.
- Today, beriberi occurs mostly in patients who abuse alcohol. Drinking heavily can lead to poor nutrition and makes it harder to eat.
- Beriberi can occur in breast-fed infants when the mother's body is lacking in thiamine. The condition can also affect infants who are fed unusual formulas that don't have enough thiamine.
- Getting dialysis and taking high doses of diuretics raise the risk of Beriberi.

Dry and wet Beriberi

- **Symptoms of dry beriberi**: affects the nervous system. **Wernicke-Korsakoff syndrome** is a brain disorder caused by thiamine deficiency that results in a number of neurologic symptoms and can lead to psychosis, confusion and hallucinations. Difficulty walking; loss of feeling in hands and feet; loss of muscle function or paralysis of the lower legs; mental confusion/speech difficulties; pain; strange eye movements (nystagmus); tingling; vomiting

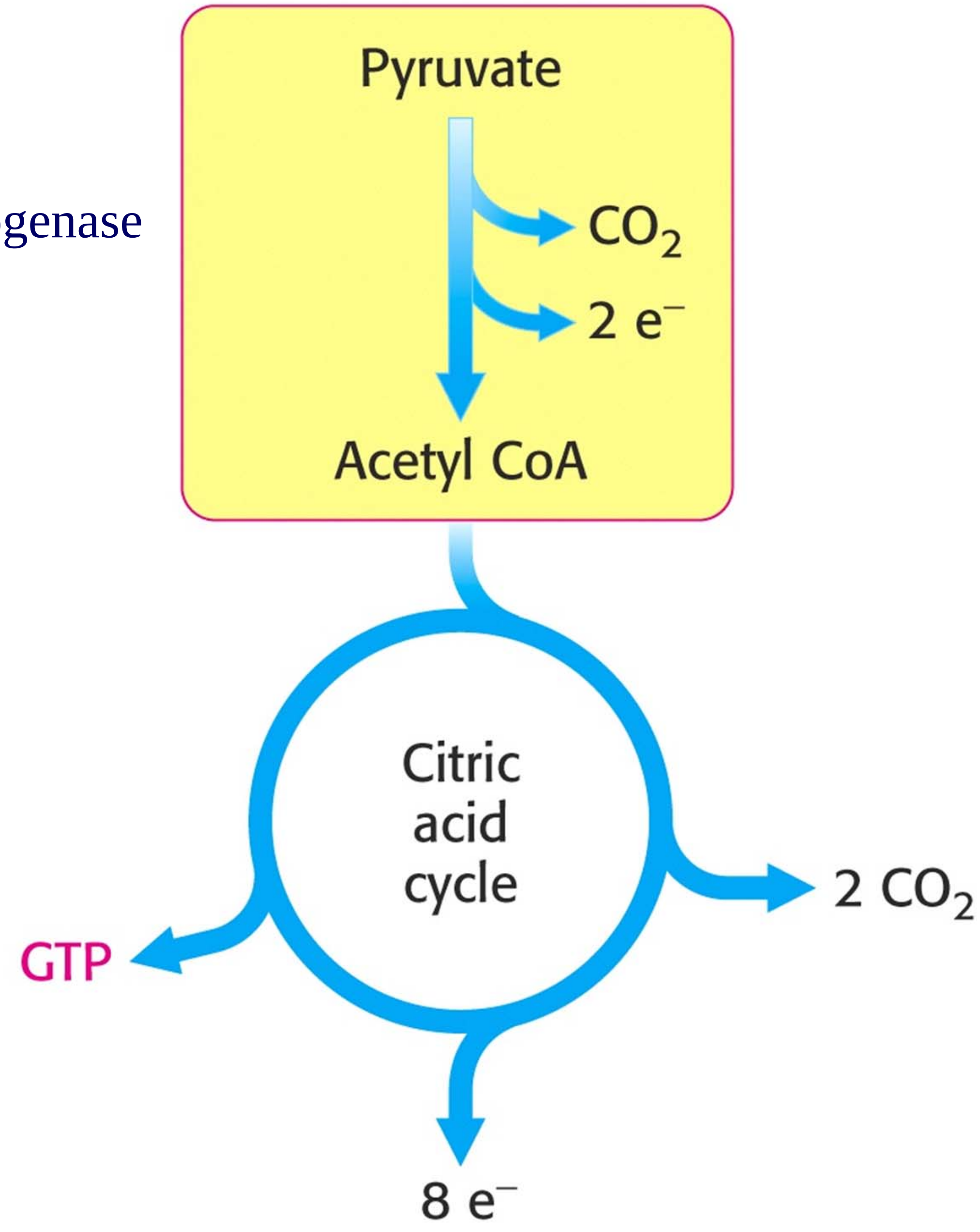
- **Symptoms of wet beriberi**: affects the cardiovascular system; awakening at night short of breath; increased heart rate; shortness of breath with activity; swelling of the lower legs.

Thiamine Deficiency: treatment is to replace the thiamine your body is lacking

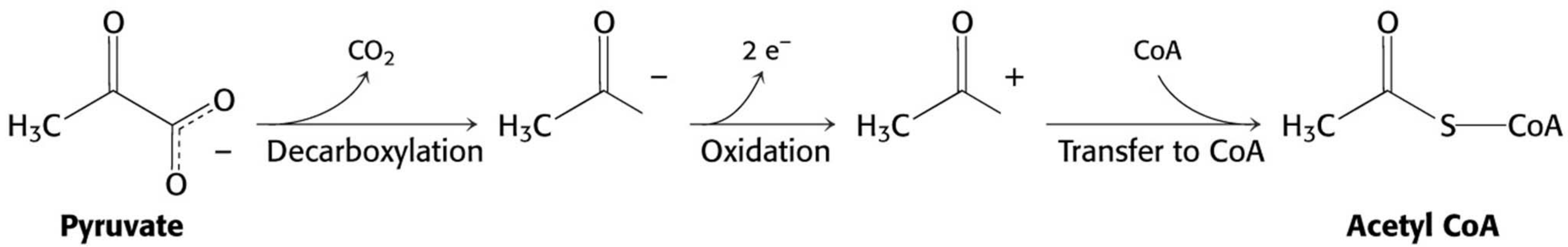


The „aerobic fate“ of pyruvate

Pyruvat Dehydrogenase (PDH)



The reactions of the PDH multienzyme complex (**PDC**)



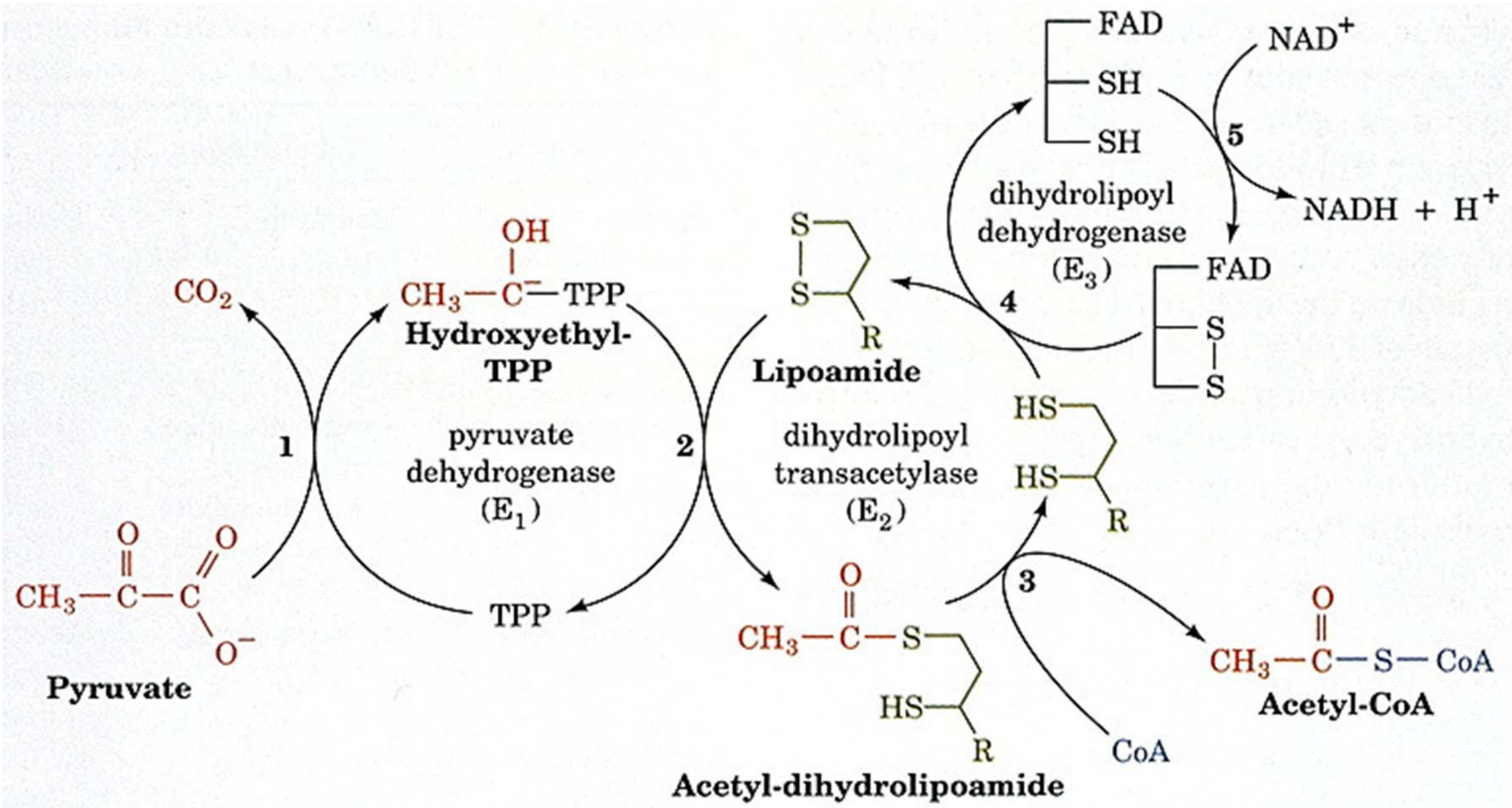


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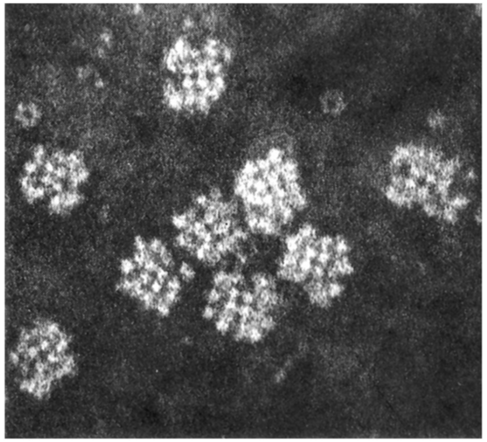
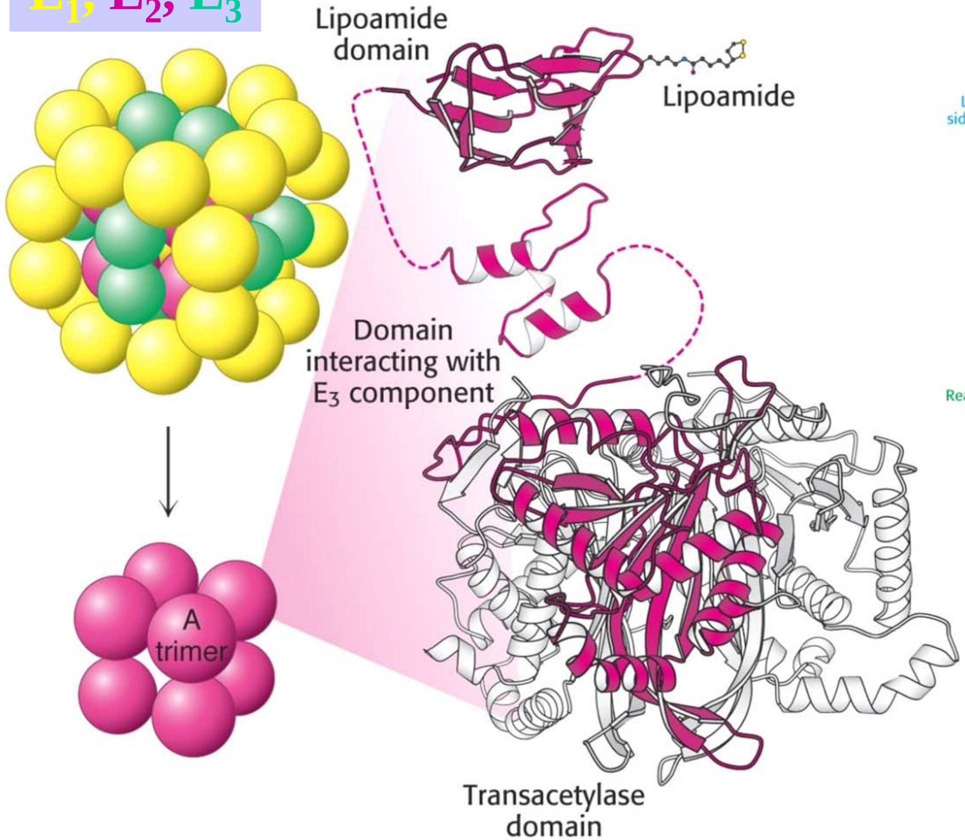
TABLE 17.1 **Pyruvate dehydrogenase complex of *E. coli***

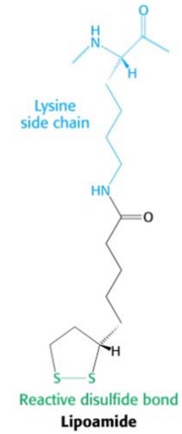
Enzyme	Abbreviation	Number of chains	Prosthetic group	Reaction catalyzed
Pyruvate dehydrogenase component	E_1	24	TPP	Oxidative decarboxylation of pyruvate
Dihydrolipoyl transacetylase	E_2	24	Lipoamide	Transfer of the acetyl group to CoA
Dihydrolipoyl dehydrogenase	E_3	12	FAD	Regeneration of the oxidized form of lipoamide



Electron micrograph

E_1, E_2, E_3





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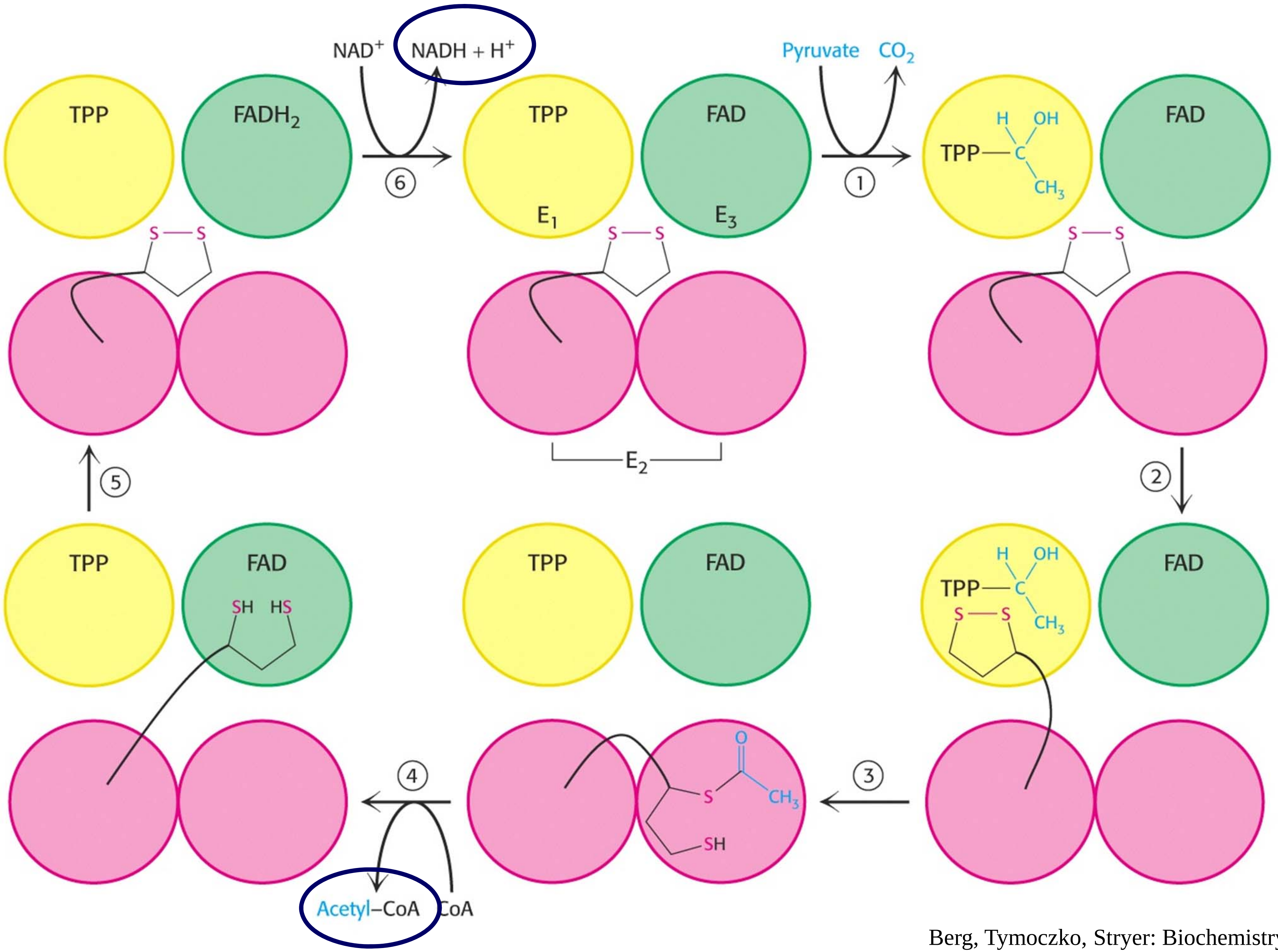

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Regulation of the PDH multienzyme complex

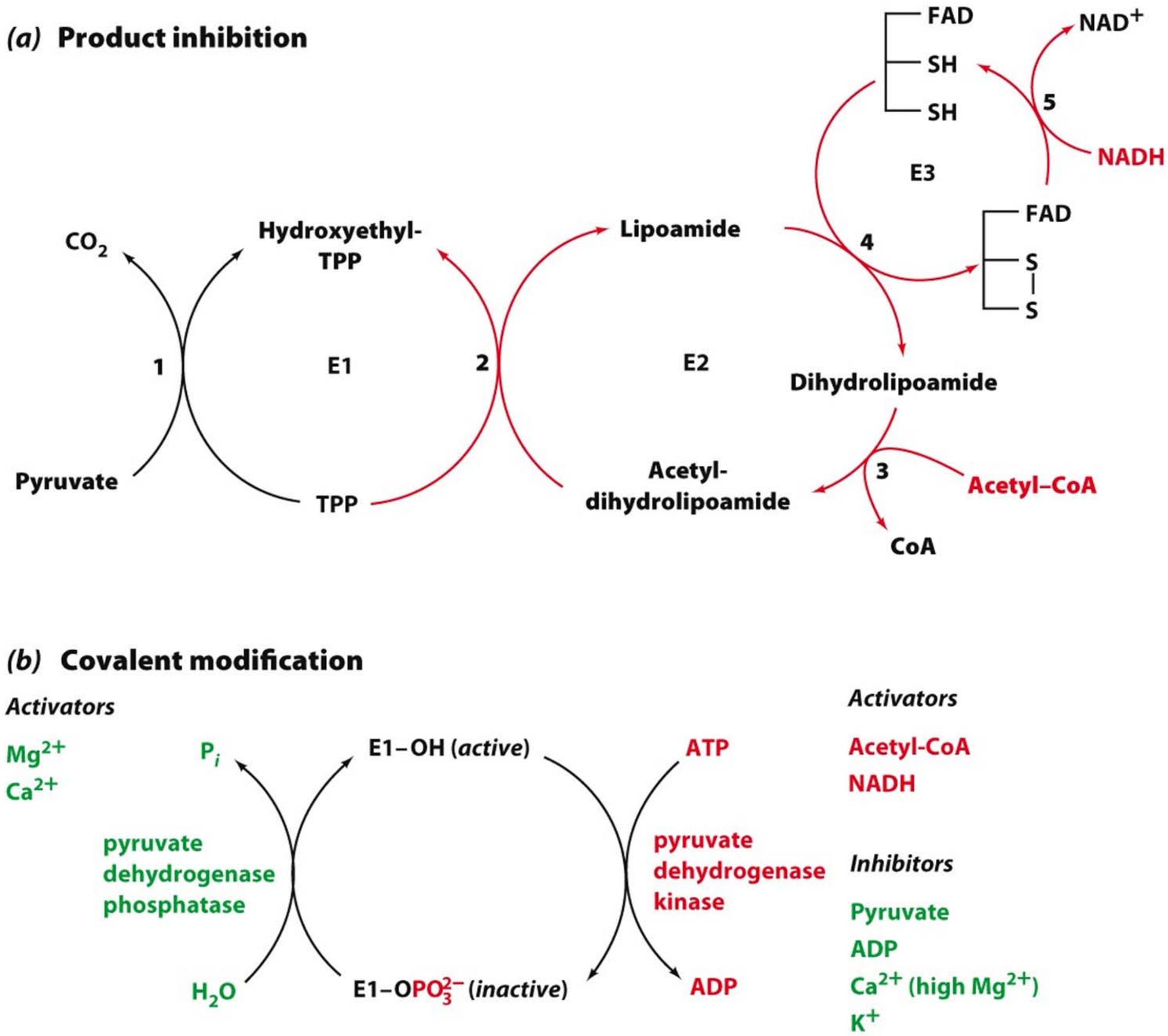
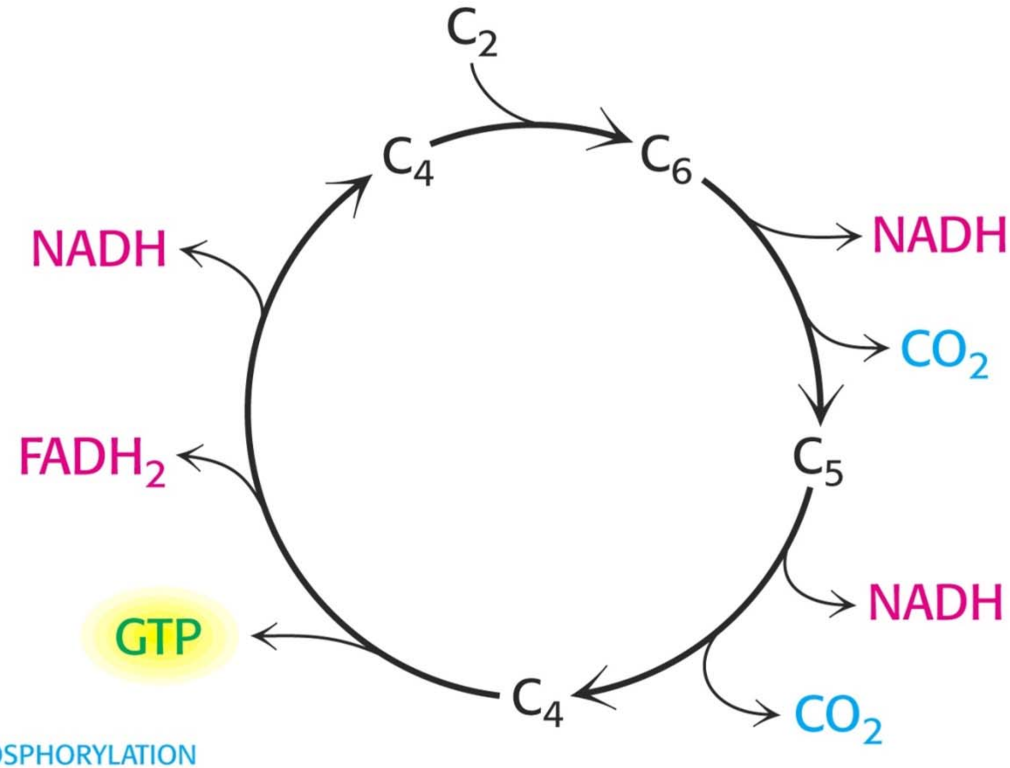
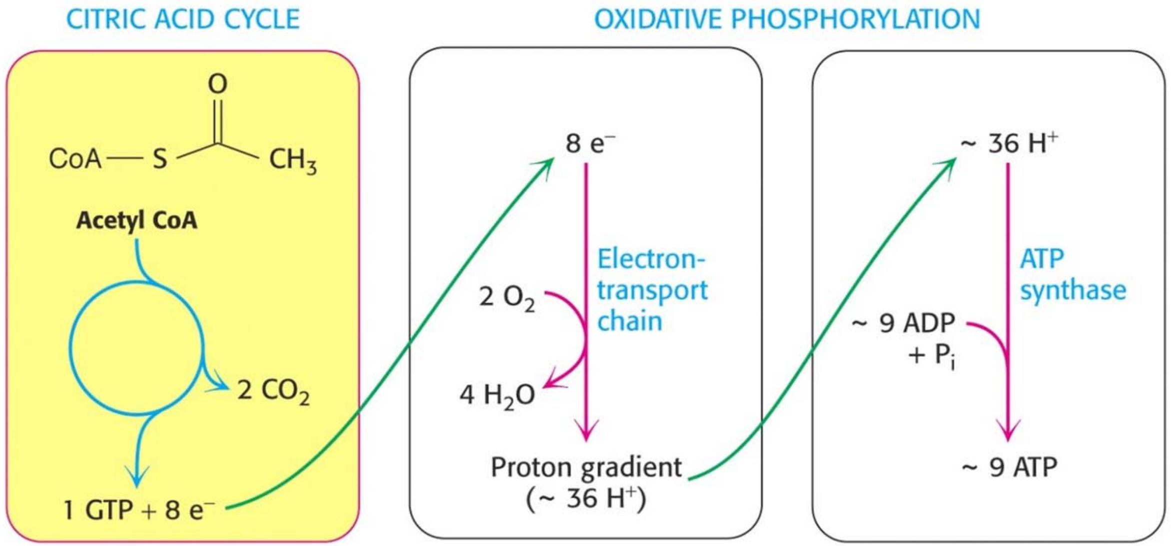


Figure 21-17

Energy metabolism in mitochondria





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Reactions of the citric acid cycle

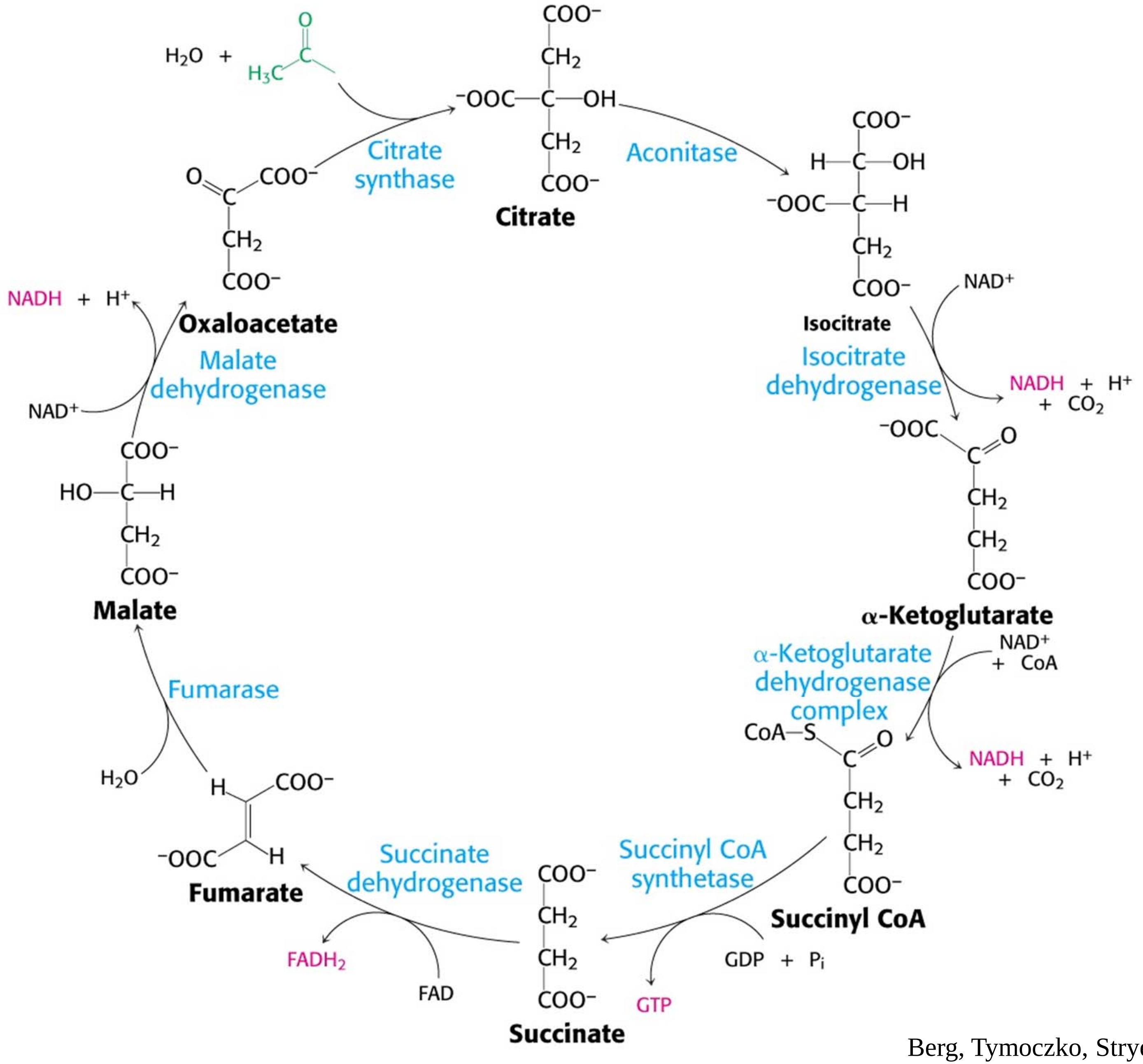

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TABLE 17.2 **Citric acid cycle**

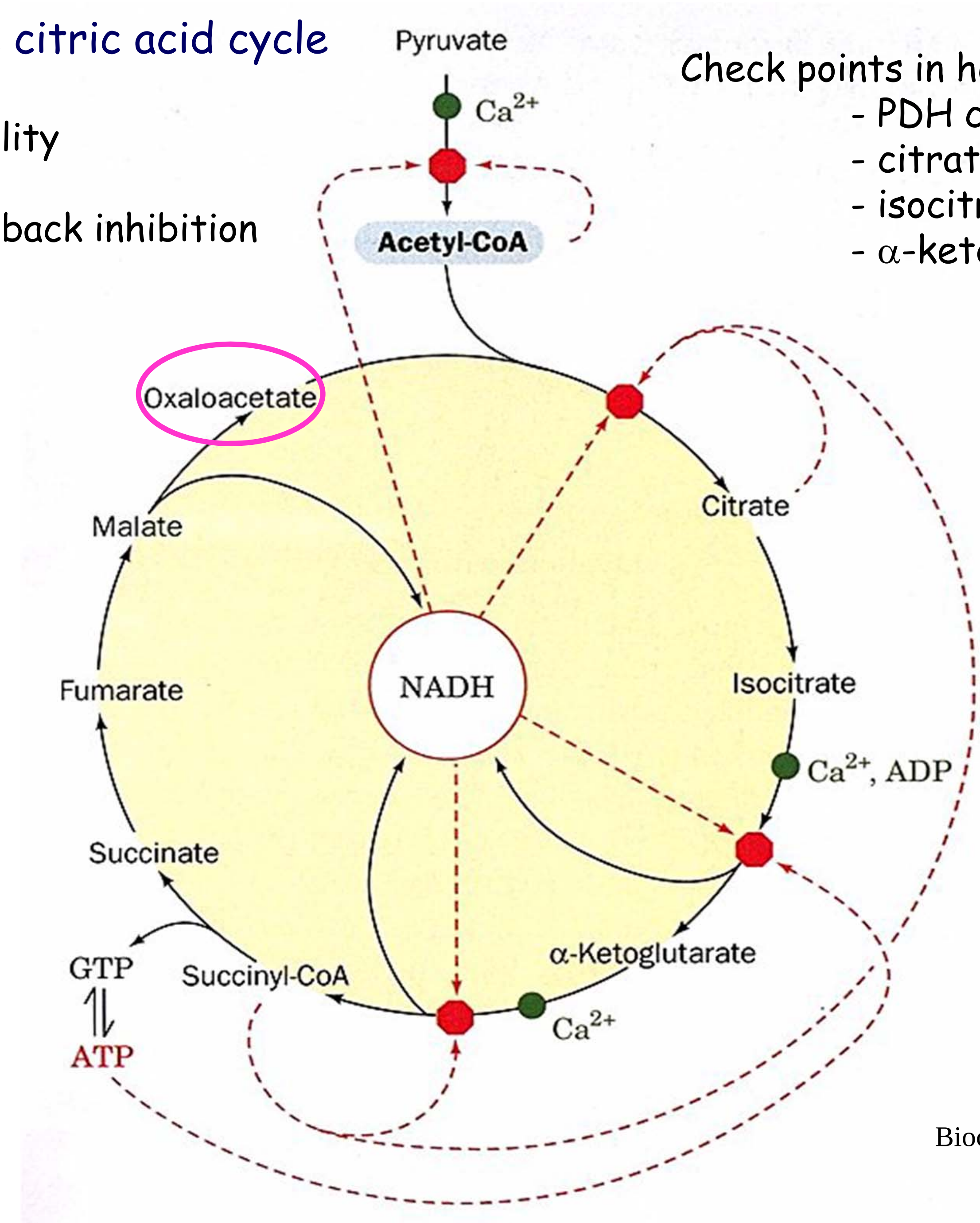
Step	Reaction	Enzyme	Prosthetic group	Type*	$\Delta G^{\circ\prime}$ kcal mol^{-1}	$\Delta G^{\circ\prime}$ kJ mol^{-1}
1	Acetyl CoA + oxaloacetate + $H_2O \longrightarrow$ citrate + CoA + H^+	Citrate synthase		a	−7.5	−31.4
2a	Citrate $\rightleftharpoons$ *cis*-aconitate + H_2O	Aconitase	Fe–S	b	+2.0	+8.4
2b	*cis*-Aconitate + $H_2O \rightleftharpoons$ isocitrate	Aconitase	Fe–S	c	−0.5	−2.1
3	Isocitrate + $NAD^+ \rightleftharpoons$ α-ketoglutarate + CO_2 + NADH	Isocitrate dehydrogenase		d + e	−2.0	−8.4
4	α-Ketoglutarate + NAD^+ + CoA $\rightleftharpoons$ succinyl CoA + CO_2 + NADH	α-Ketoglutarate dehydrogenase complex	Lipoic acid, FAD, TPP	d + e	−7.2	−30.1
5	Succinyl CoA + P_i + GDP $\rightleftharpoons$ succinate + GTP + CoA	Succinyl CoA synthetase		f	−0.8	−3.3
6	Succinate + FAD (enzyme-bound) $\rightleftharpoons$ fumarate + $FADH_2$ (enzyme-bound)	Succinate dehydrogenase	FAD, Fe–S	e	~0	0
7	Fumarate + $H_2O \rightleftharpoons$ L-malate	Fumarase		c	−0.9	−3.8
8	L-Malate + $NAD^+ \rightleftharpoons$ oxaloacetate + NADH + H^+	Malate dehydrogenase		e	+7.1	+29.7

*Reaction type: (a) condensation; (b) dehydration; (c) hydration; (d) decarboxylation; (e) oxidation; (f) substrate-level phosphorylation.

Regulation of the citric acid cycle

- substrate availability
- product inhibition
- competitive feed-back inhibition

Check points in heart muscle
- PDH complex
- citrate syntase
- isocitrate-DH
- α-ketoglutarate-DH



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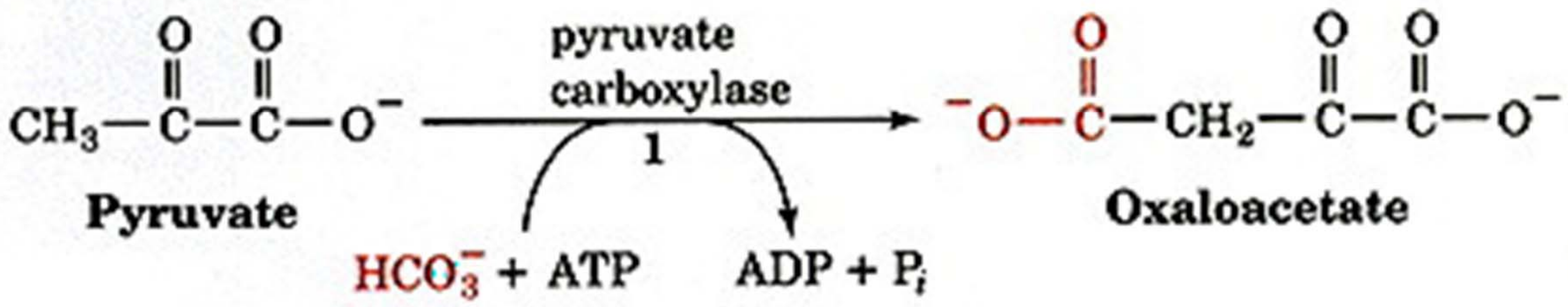
The most important anaplerotic reaction of the citric acid cycle:
(Biotin, co-factor)



AcetylCoA = allosteric activator of pyruvate carboxylase !!!

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Amphibolic functions of the citric acid cycle

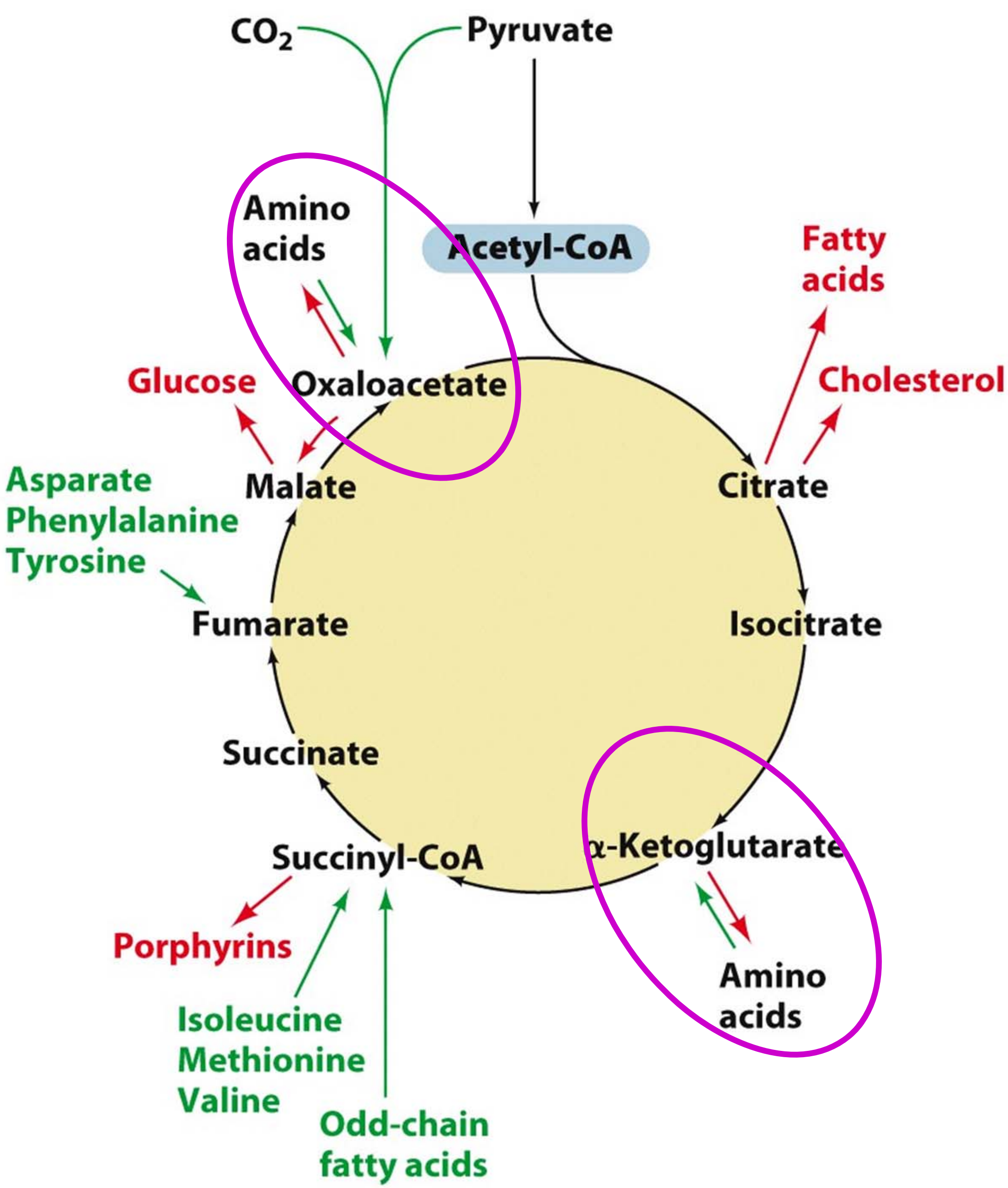
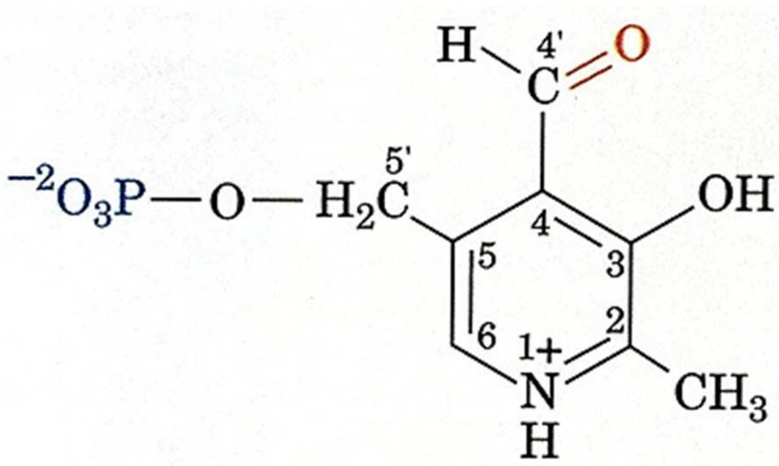
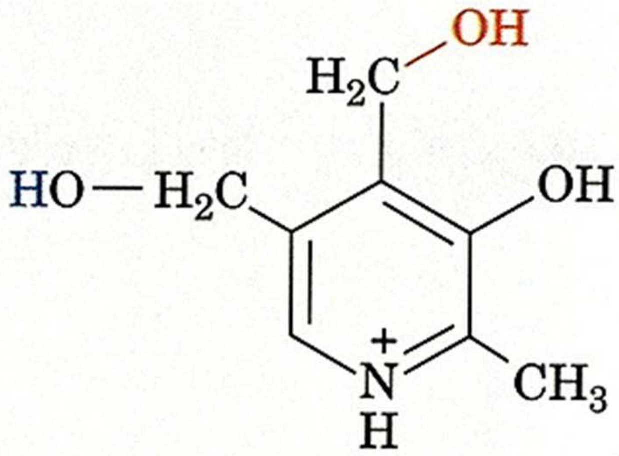


Figure 21-26

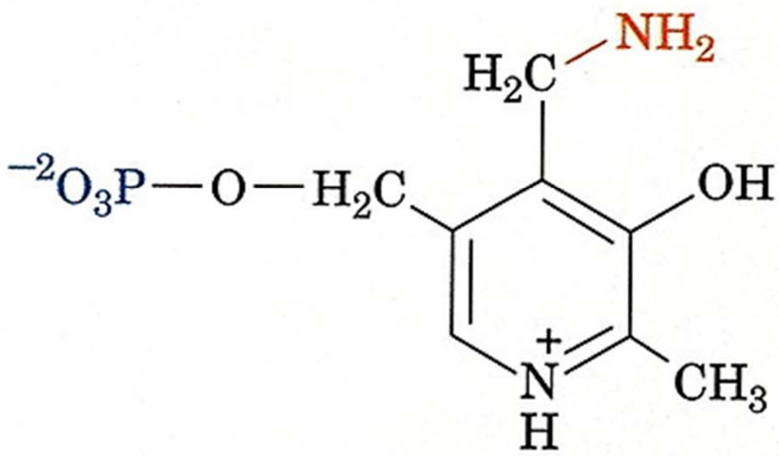
Vitamin B_6 derived co-enzymes



Pyridoxal-5'-phosphate (PLP)



Pyridoxine (vitamin B_6)



Pyridoxamine-5'-phosphate (PMP)

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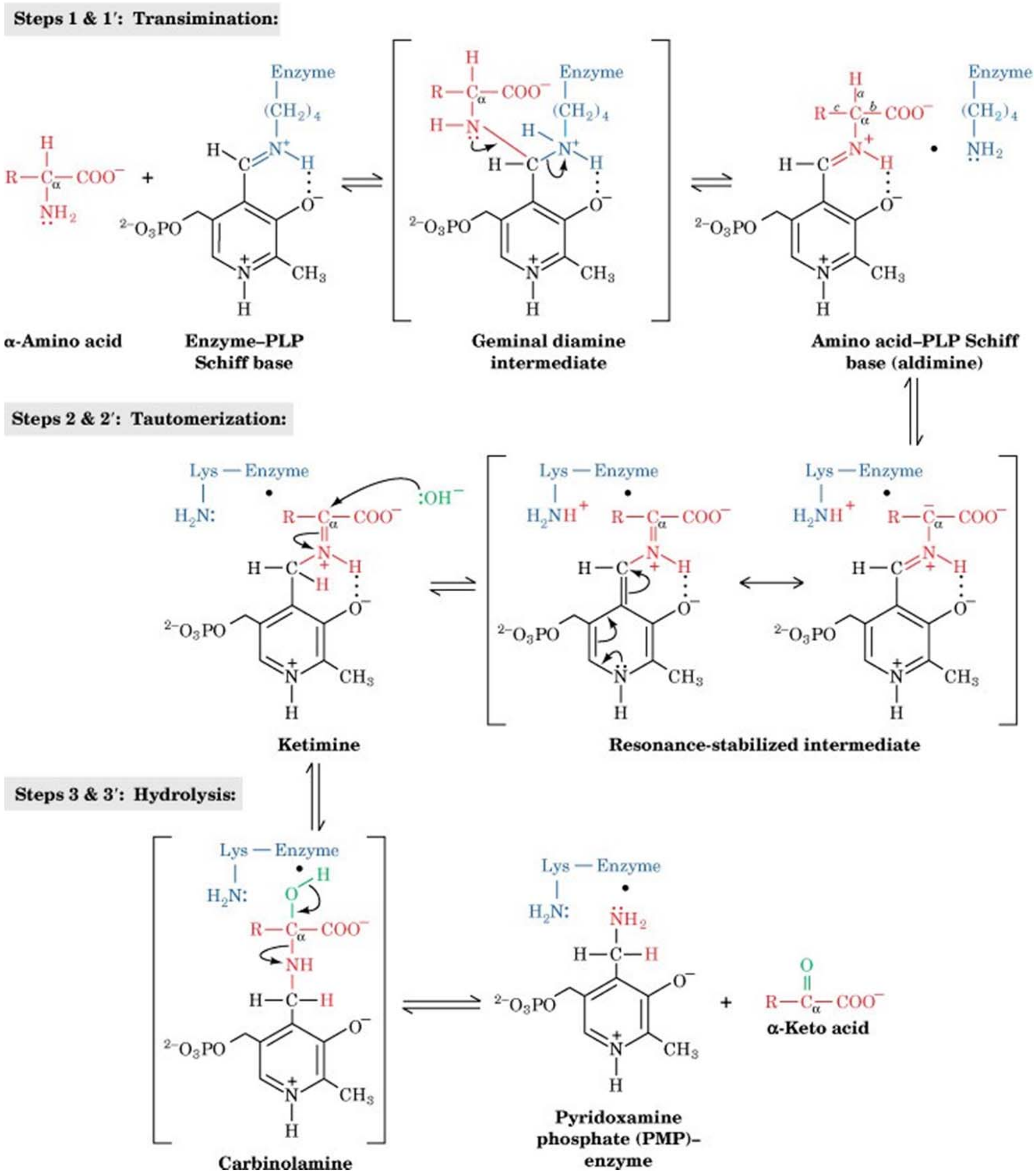
The mechanism of PLP-dependent enzyme-catalyzed transamination



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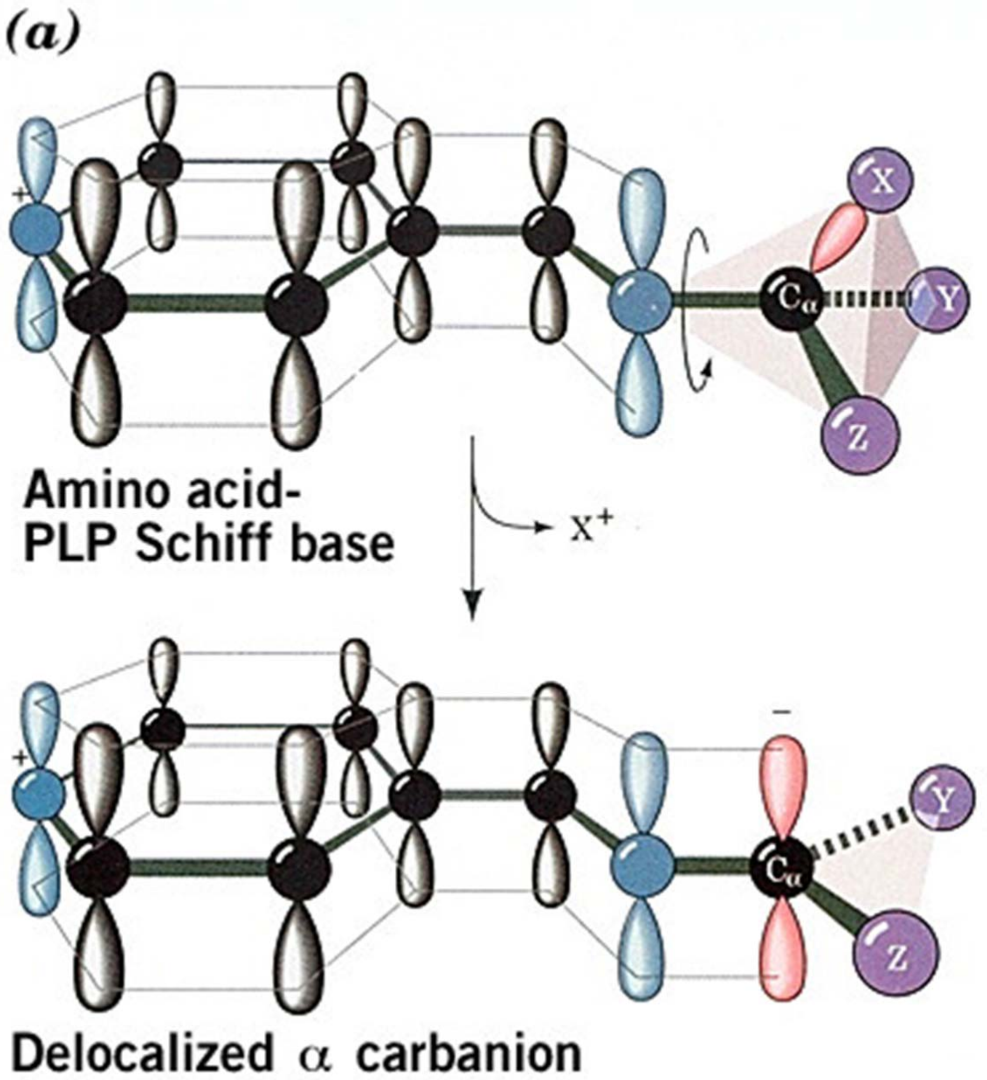
The π-orbital framework of a PLP-amino acid Schiff base



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