# Biochemistry

# Metabolism

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The fate of pyruvate
Citrate cycle

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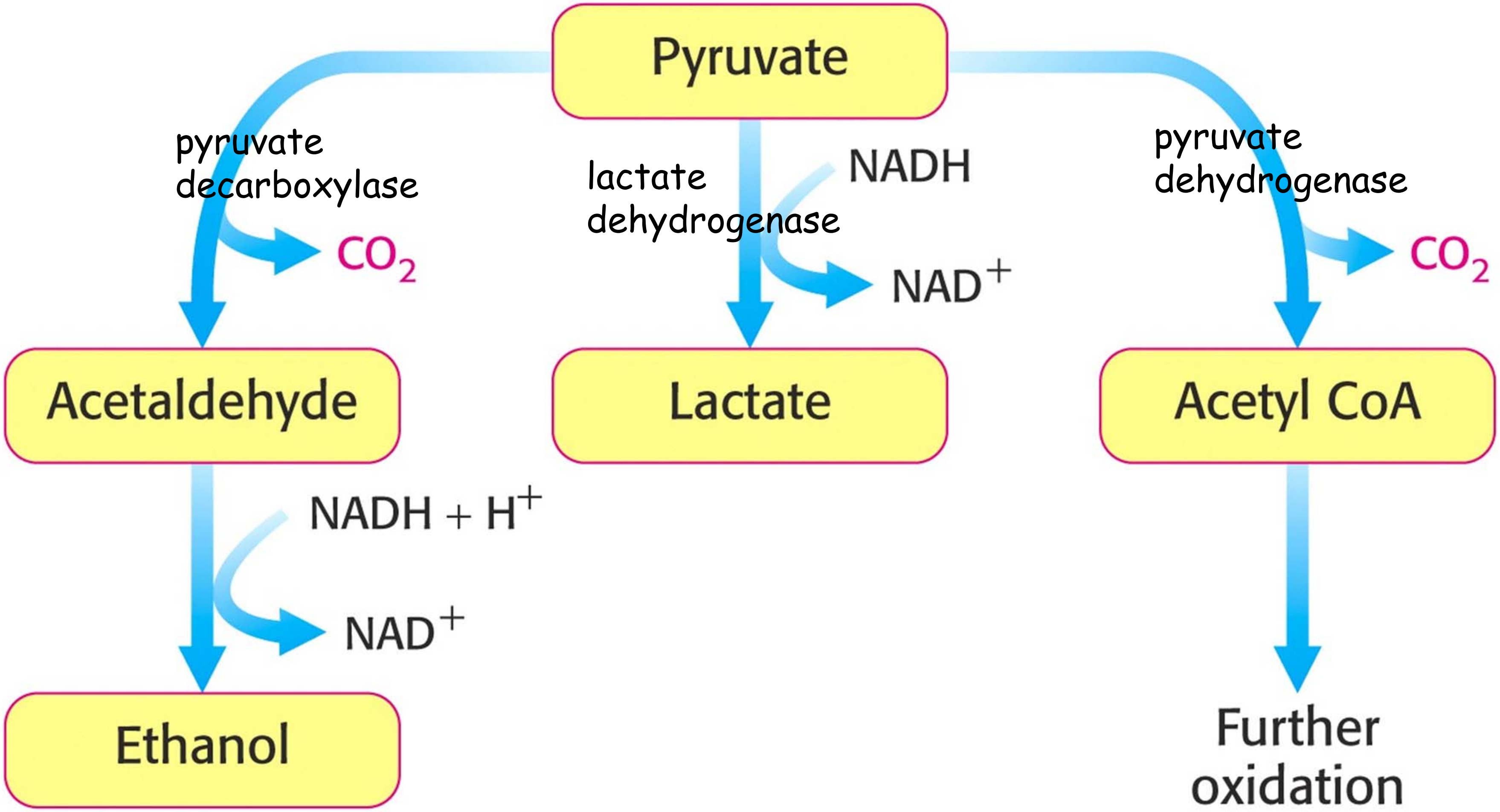
# Utilization of pyruvate

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Thiamine pyrophosphate (TPP), the cofactor of pyruvate decarboxylase

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

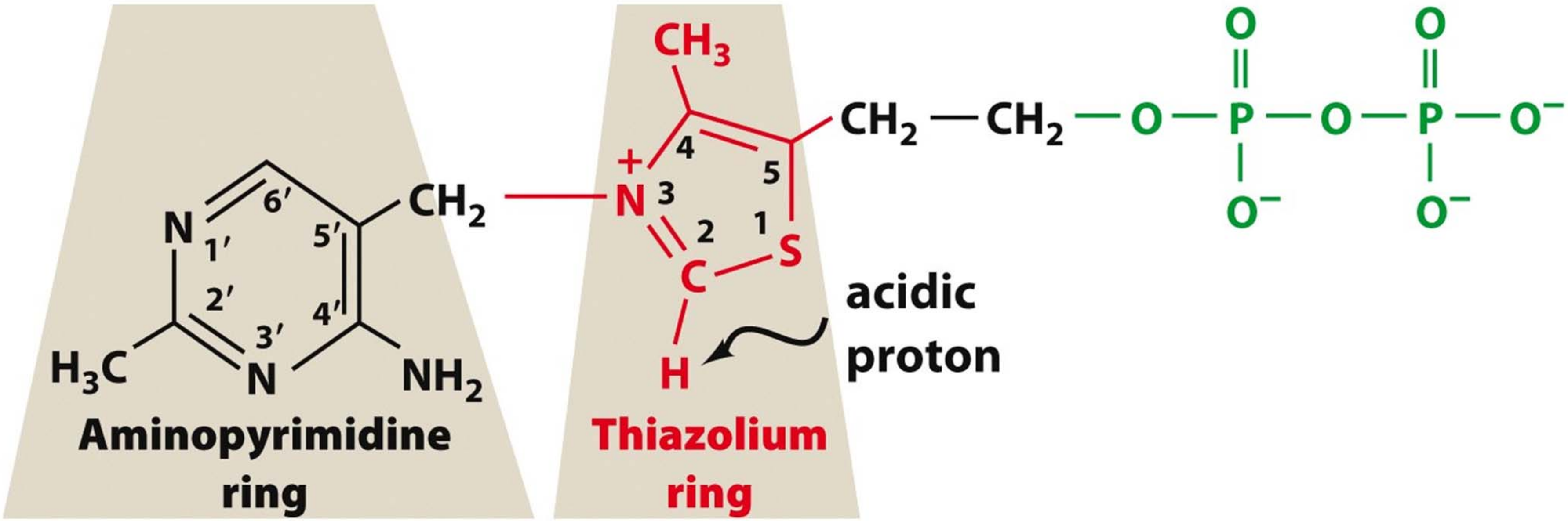
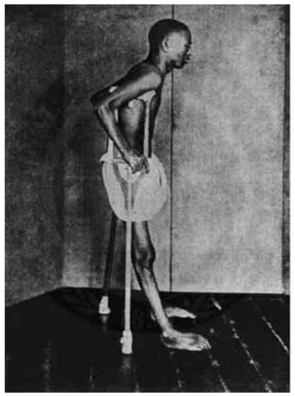



Figure 17-26

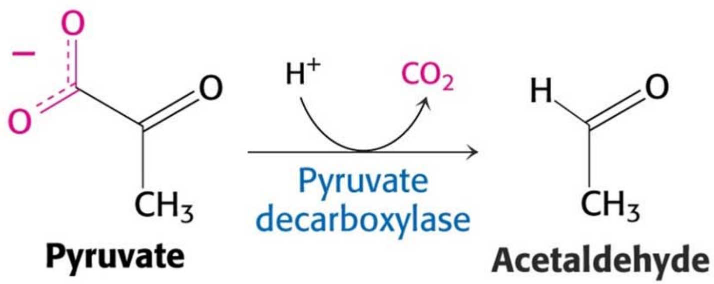


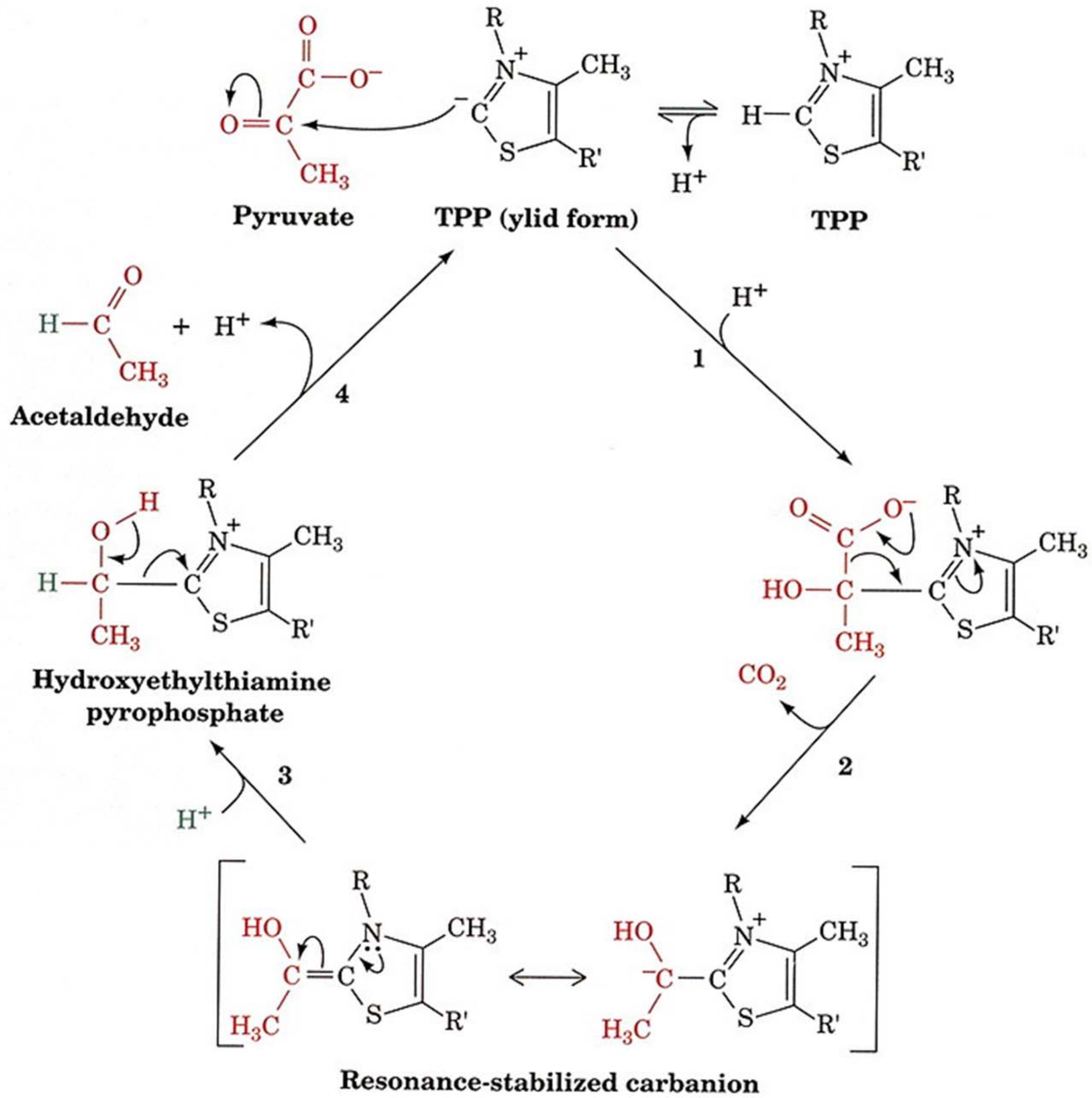


Thiamine, vitamin $B_1$

Deficiency: Beriberi disease

# Catalytic Mechanism of Pyruvate Decarboxylase



## Beriberi – deficiency of thiamine (vit. B1)

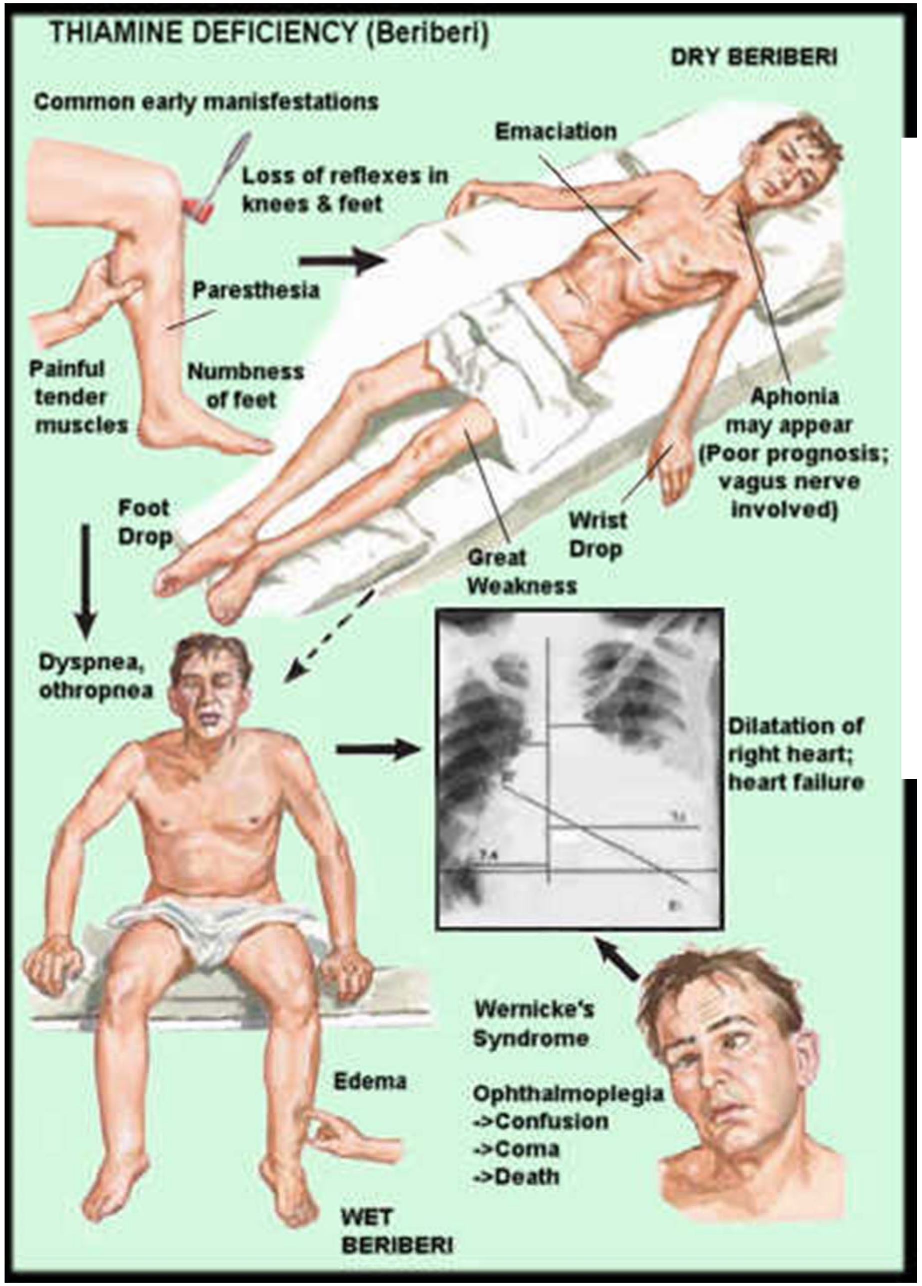
- There are **two major types of beriberi**:
  - Wet beriberi affects the **cardiovascular system**.
  - rare in the United States because most foods are now vitamin enriched.
  - Dry beriberi/Wernicke Korsakoff syndrome affects **the nervous system**.
- Today, beriberi occurs mostly in patients who abuse alcohol. Ethanol interferes with thiamine uptake in the gastrointestinal tract, its storage in the liver and its transformation in the active form (pyrophosphate). Moreover, 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

- **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

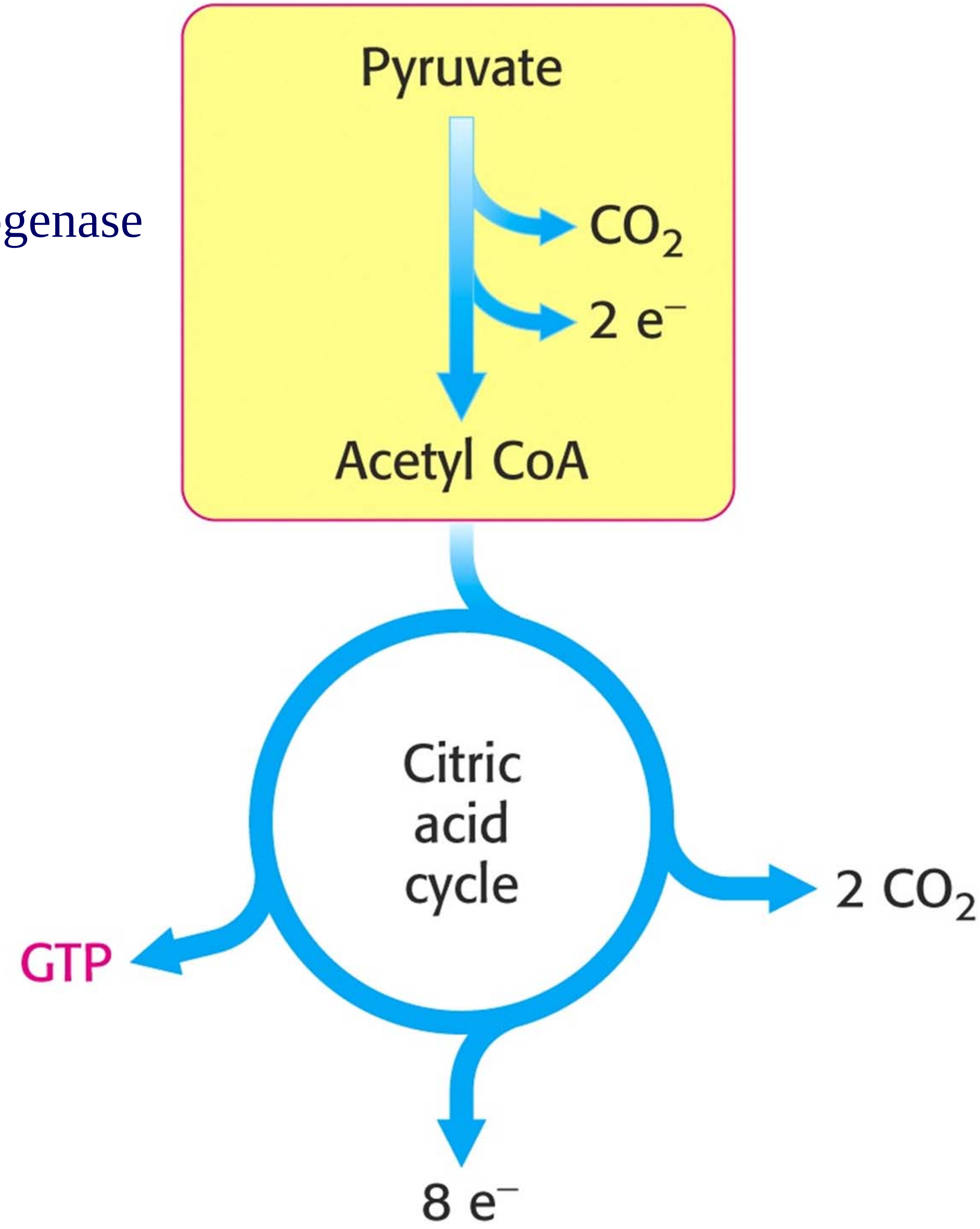
- **Symptoms of wet beriberi**: affects the cardiovascular system; awakening at night short of breath; increased heart rate; shortness of breath with activity; swelling of the lower legs.

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

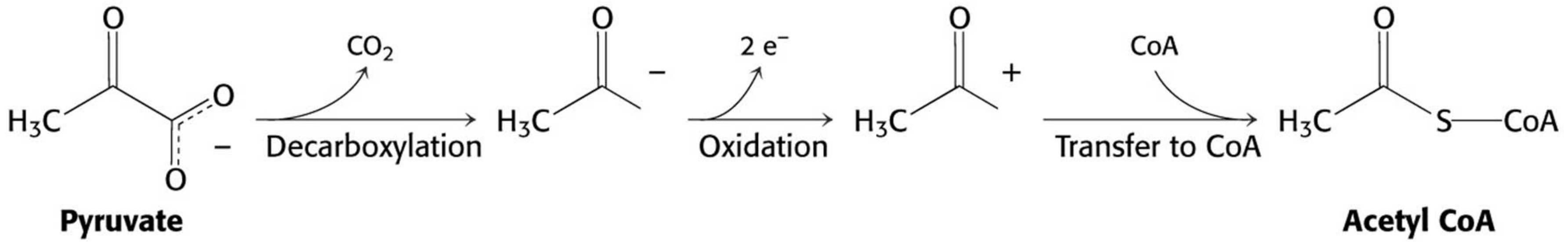



# The „aerobic fate“ of pyruvate

Pyruvat Dehydrogenase
(PDH)



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



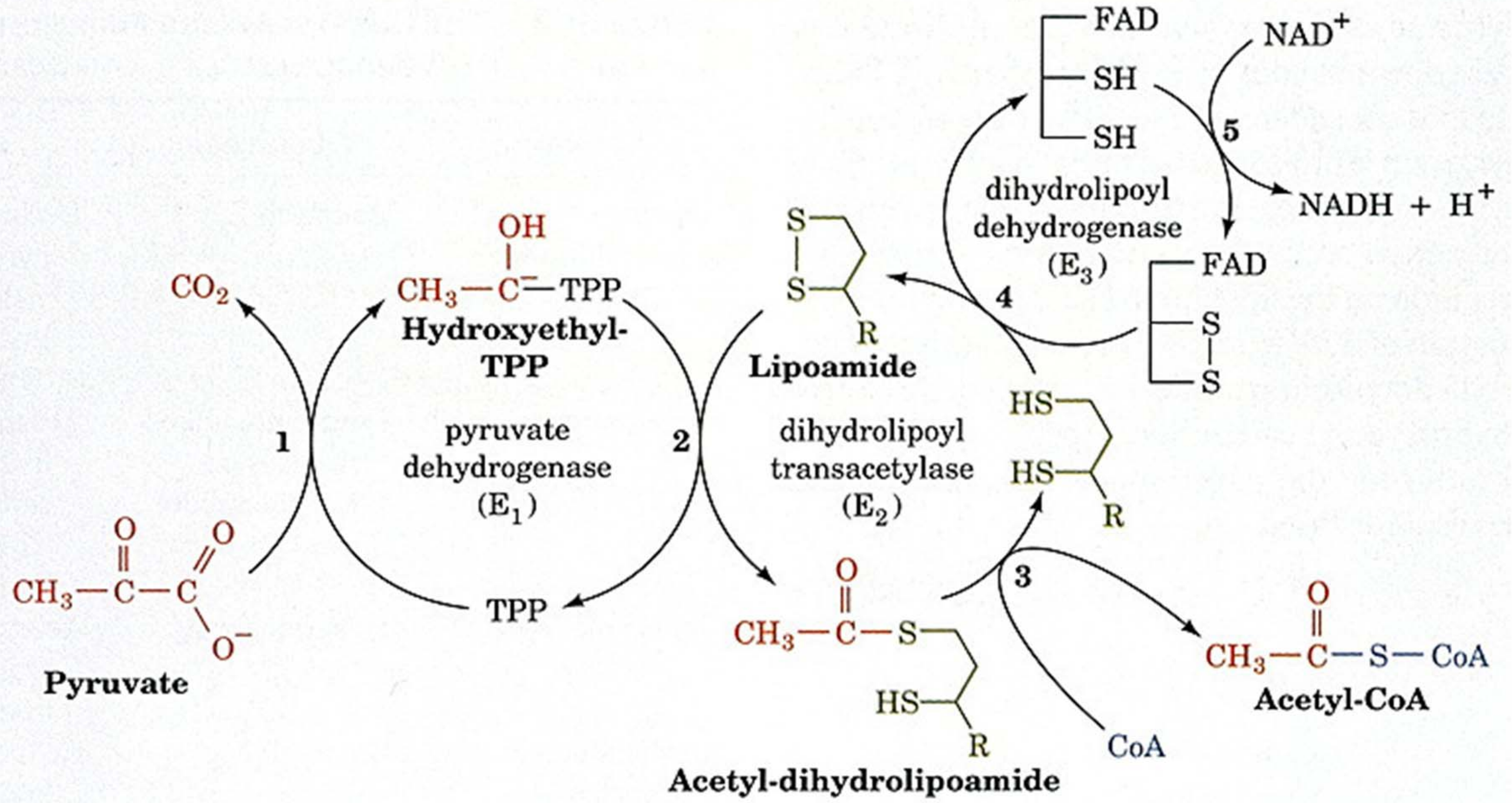




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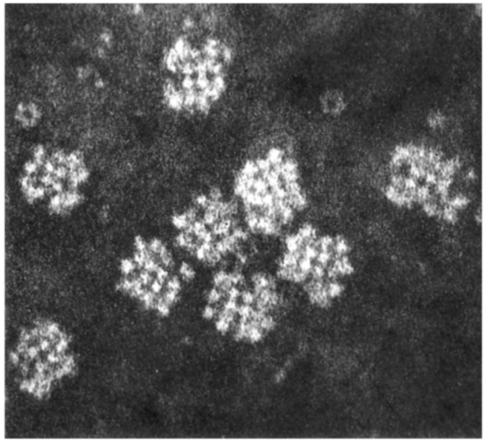
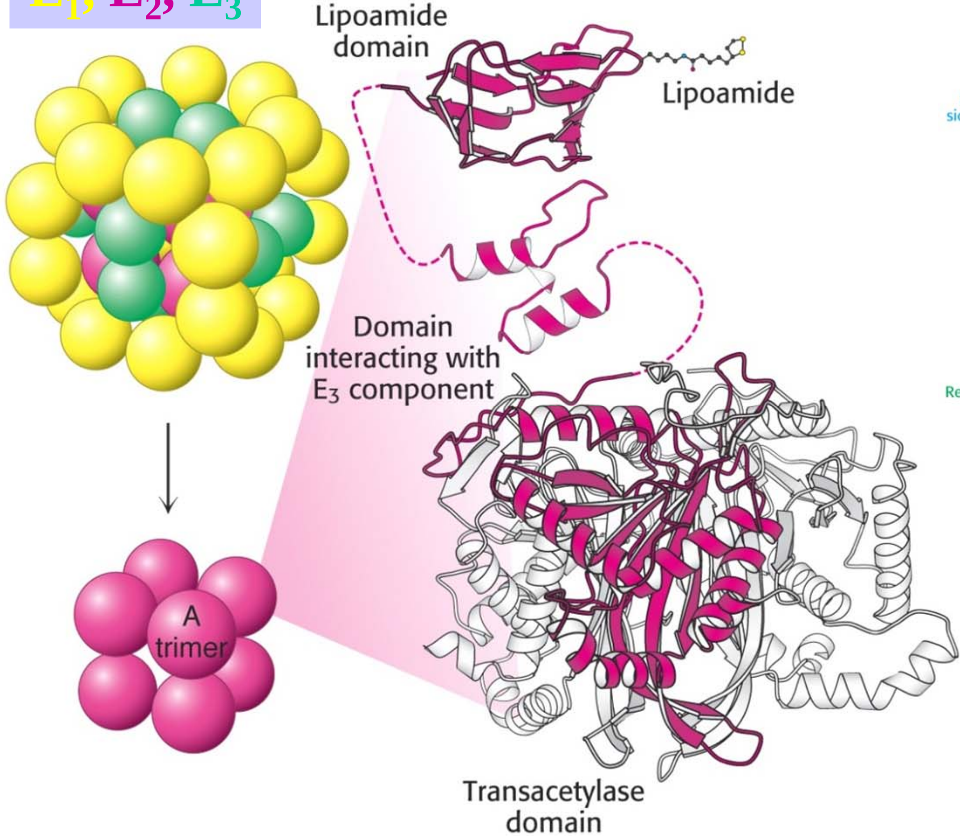
**TABLE 17.1 Pyruvate dehydrogenase complex of *E. coli***

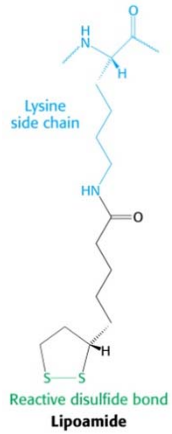
| Enzyme | Abbreviation | Number of chains | Prosthetic group | Reaction catalyzed |
|---|---|---|---|---|
| Pyruvate dehydrogenase component | $E_1$ | 24 | TPP | Oxidative decarboxylation of pyruvate |
| Dihydrolipoyl transacetylase | $E_2$ | 24 | Lipoamide | Transfer of the acetyl group to CoA |
| 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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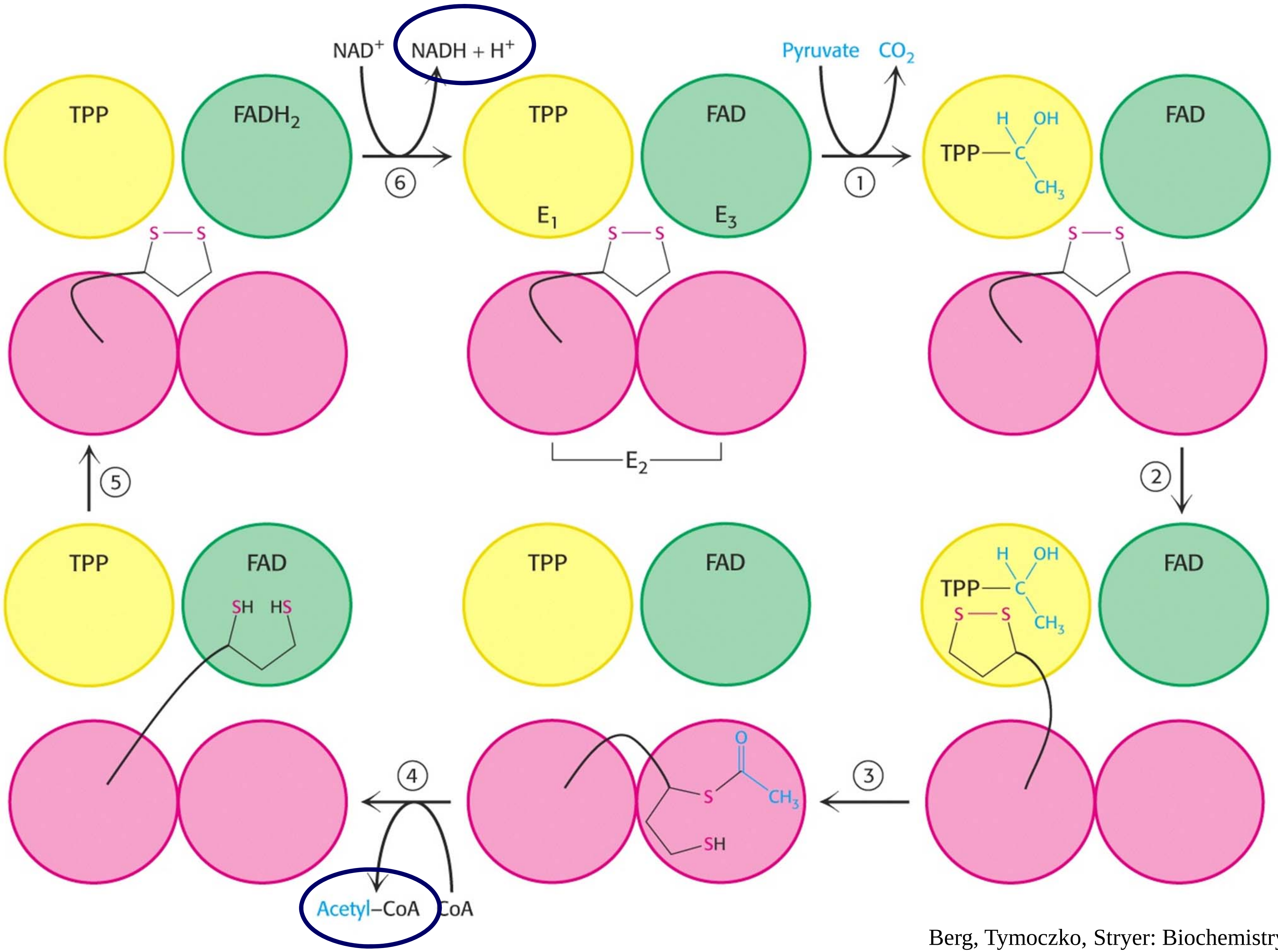


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# Regulation of the PDH multienzyme complex

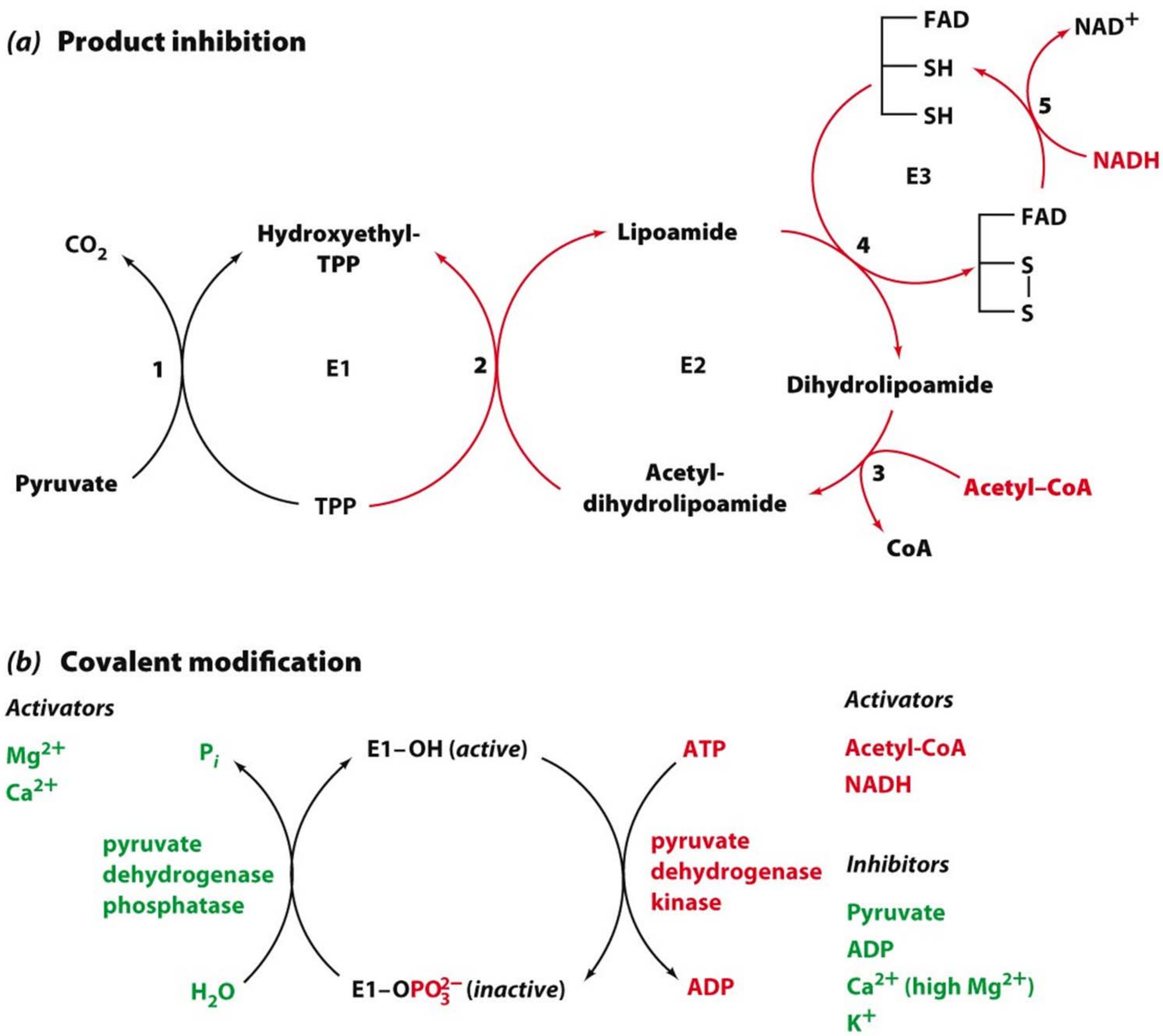
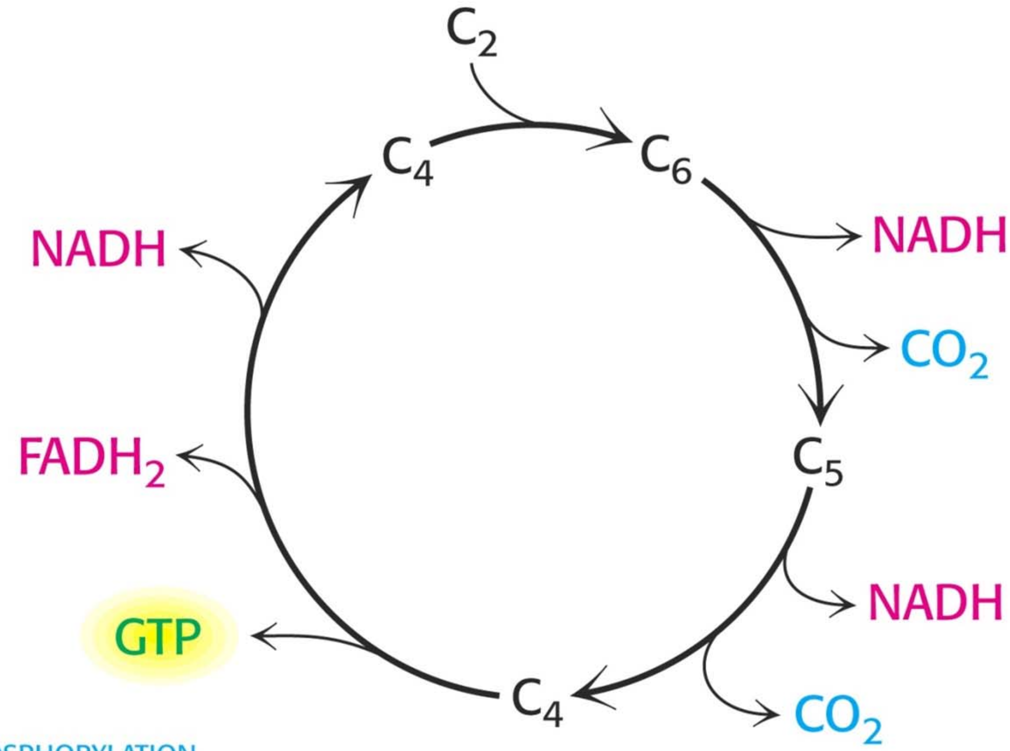
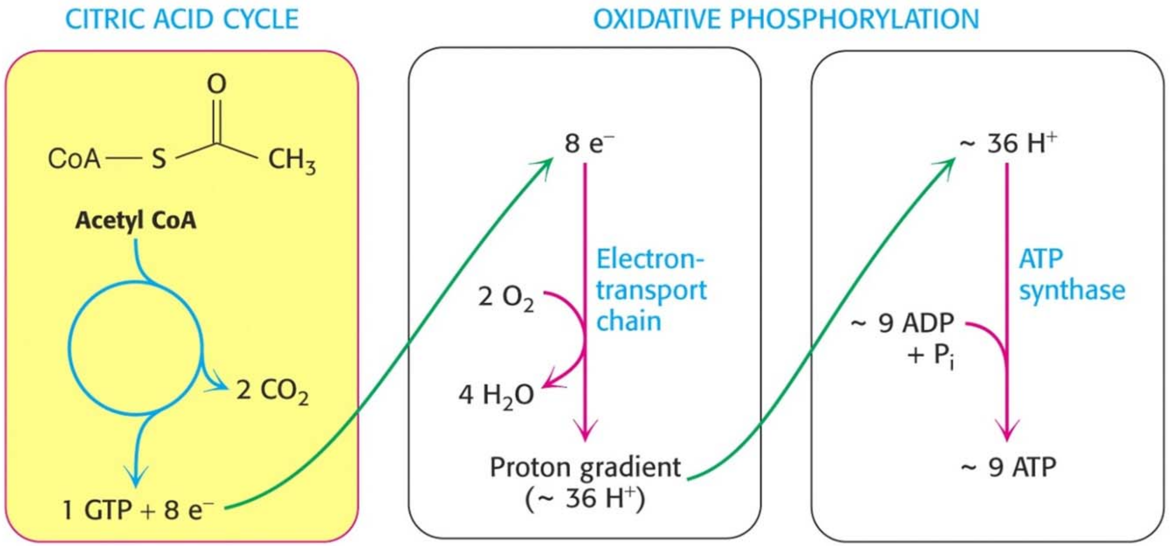



Figure 21-17

# Energy metabolism in mitochondria

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# Reactions of the citric acid cycle

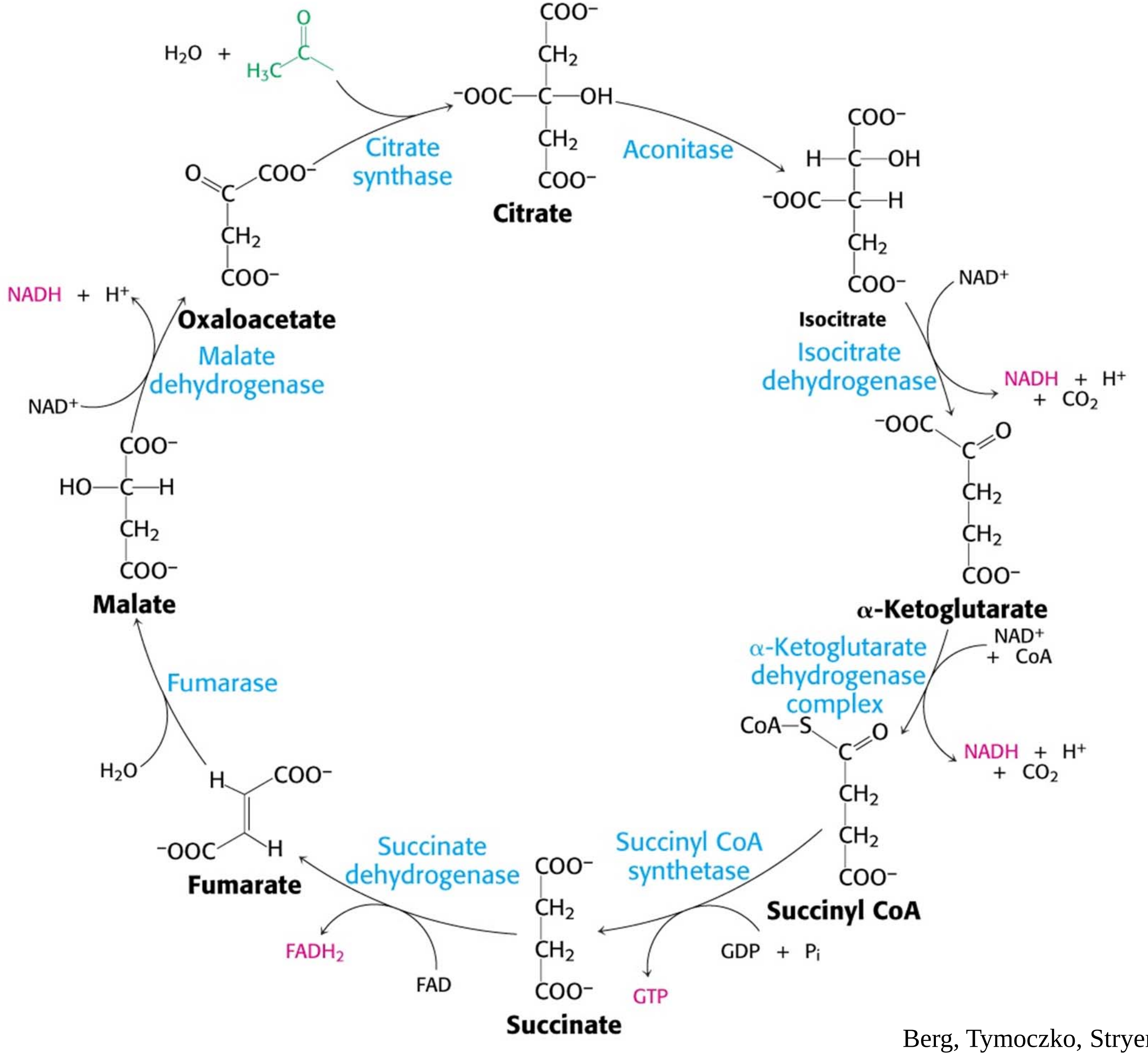


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**TABLE 17.2** **Citric acid cycle**

| 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.

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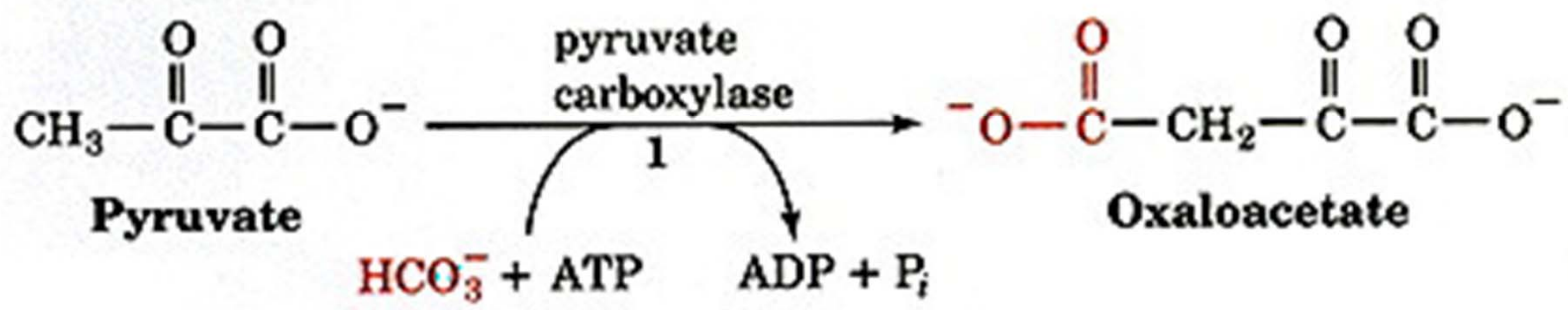
The most important anaplerotic reaction of the citric acid cycle:
(Biotin, co-factor)




AcetylCoA = allosteric activator of pyruvate carboxylase !!!

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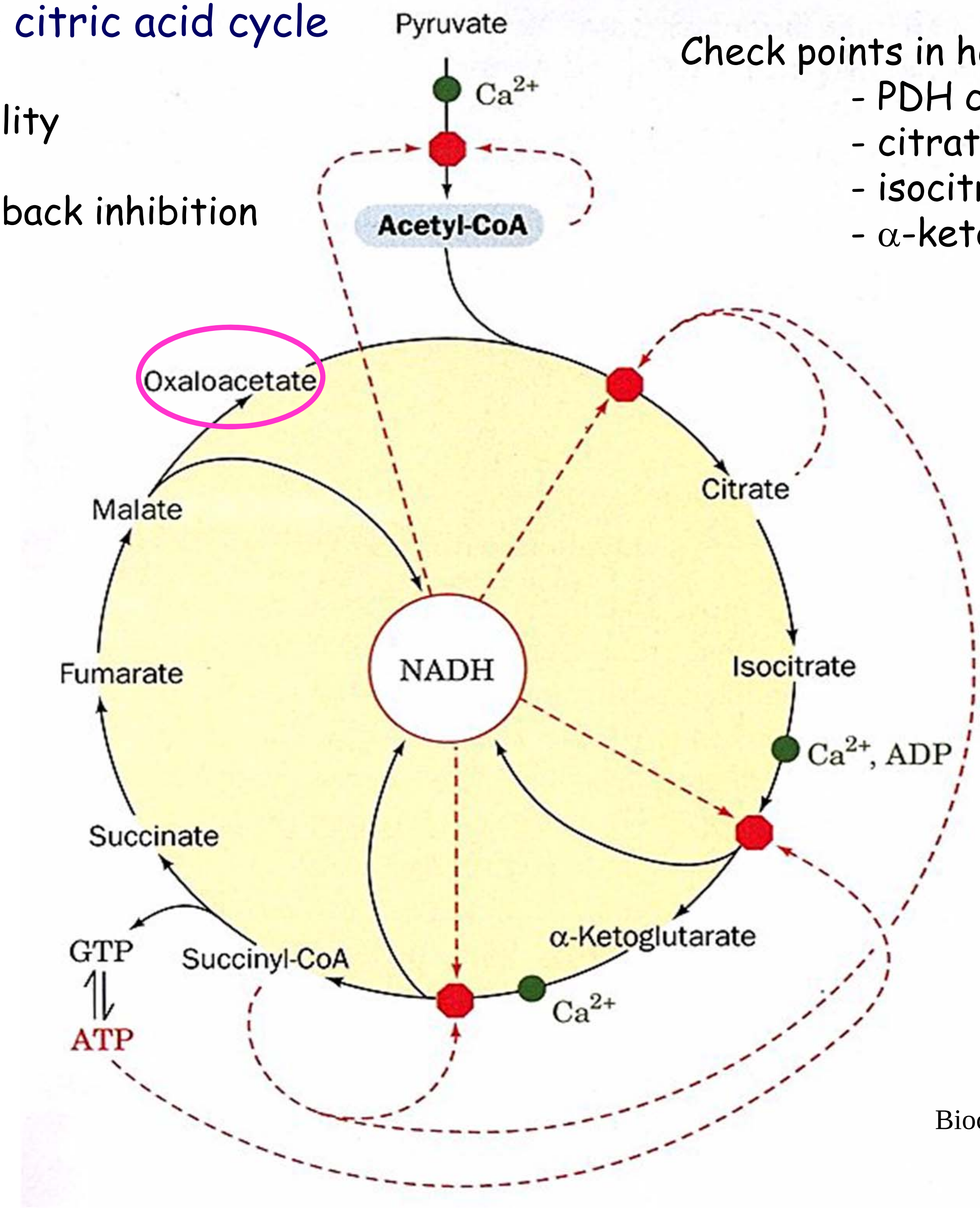
## Regulation of the citric acid cycle

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

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

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# Amphibolic functions of the citric acid cycle

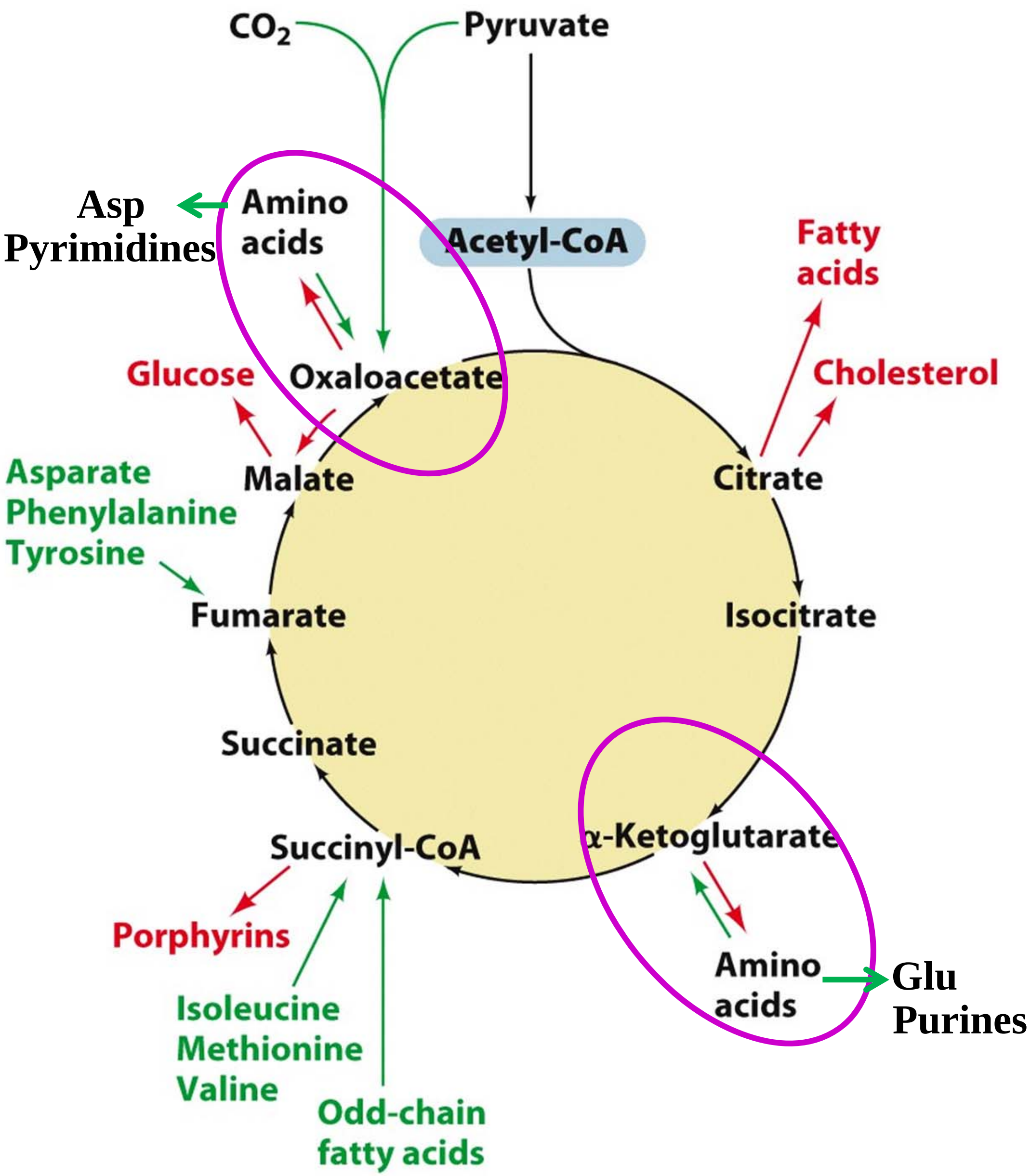
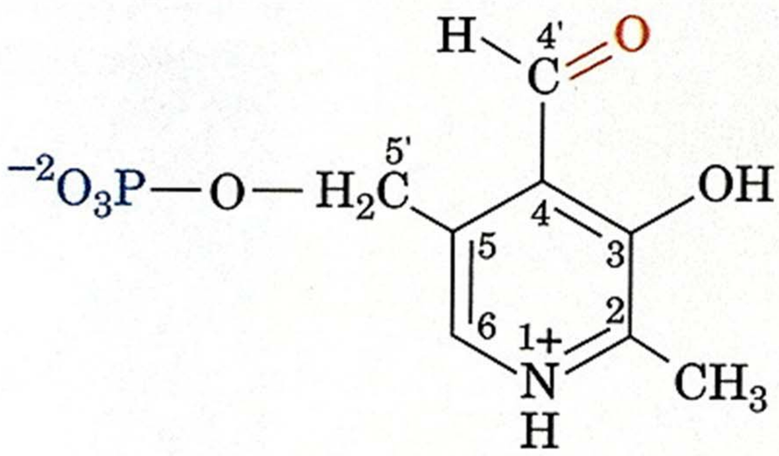
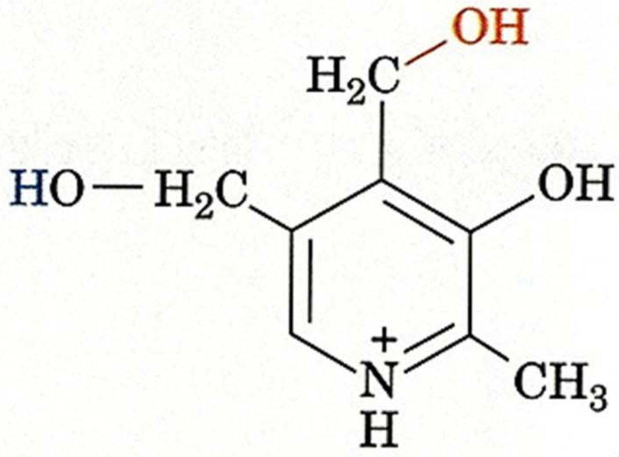



Figure 21-26

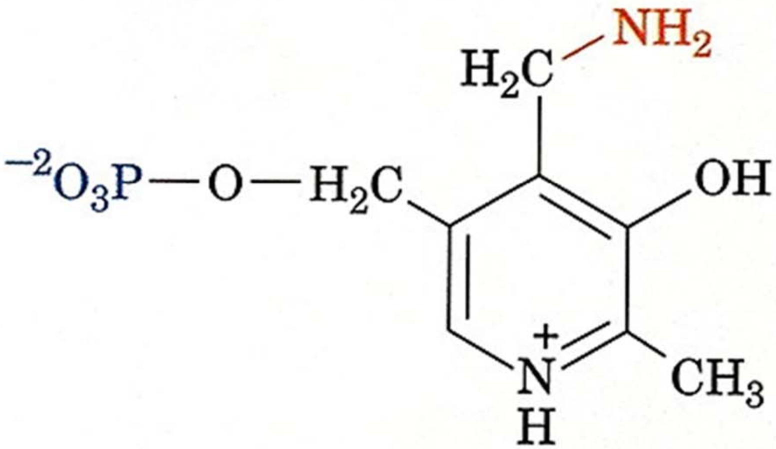
# Vitamin $B_6$ derived co-enzymes




**Pyridoxal-5'-phosphate (PLP)**




**Pyridoxine (vitamin $B_6$)**




**Pyridoxamine-5'-phosphate (PMP)**

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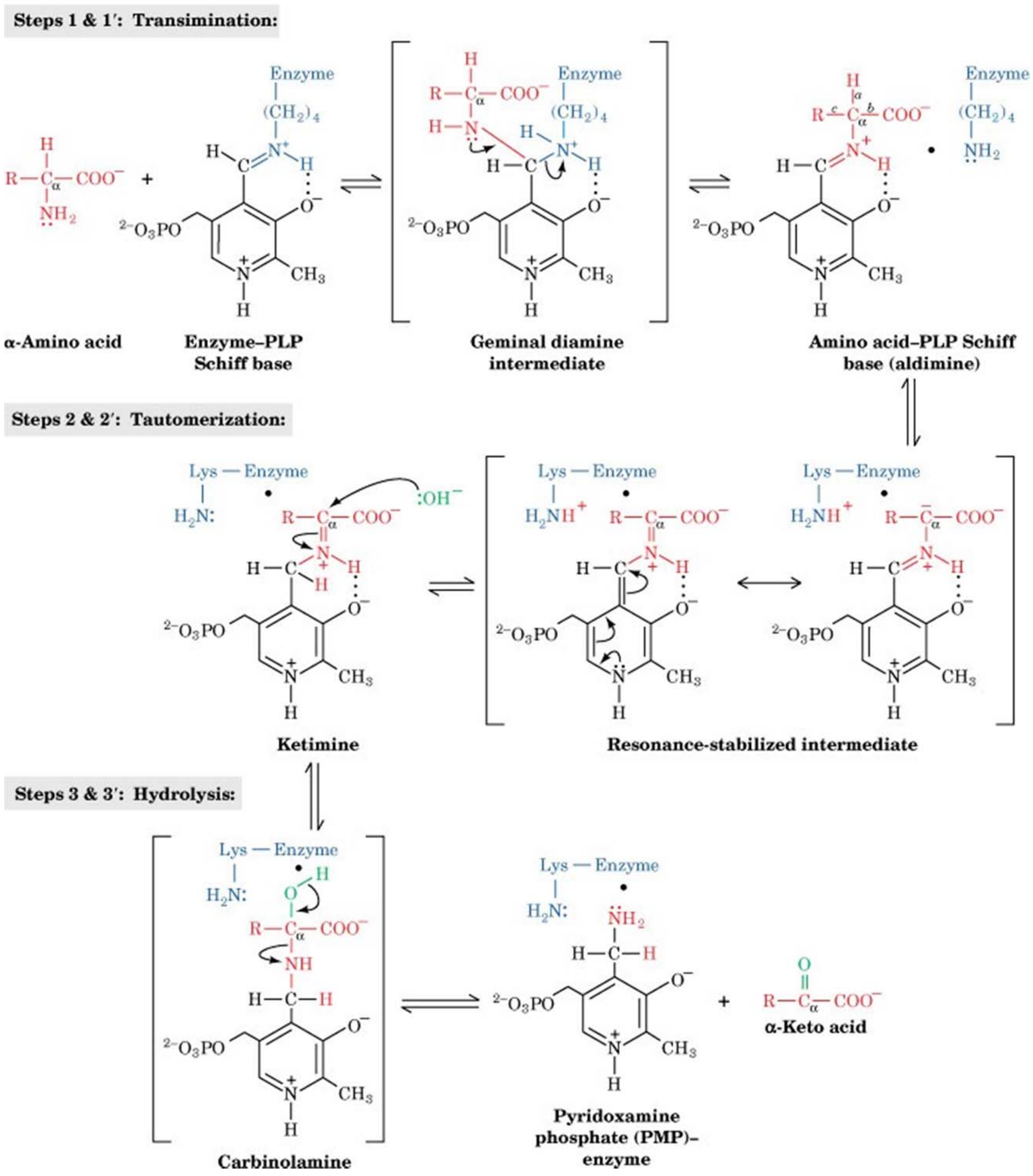
# The mechanism of PLP-dependent enzyme-catalyzed transamination

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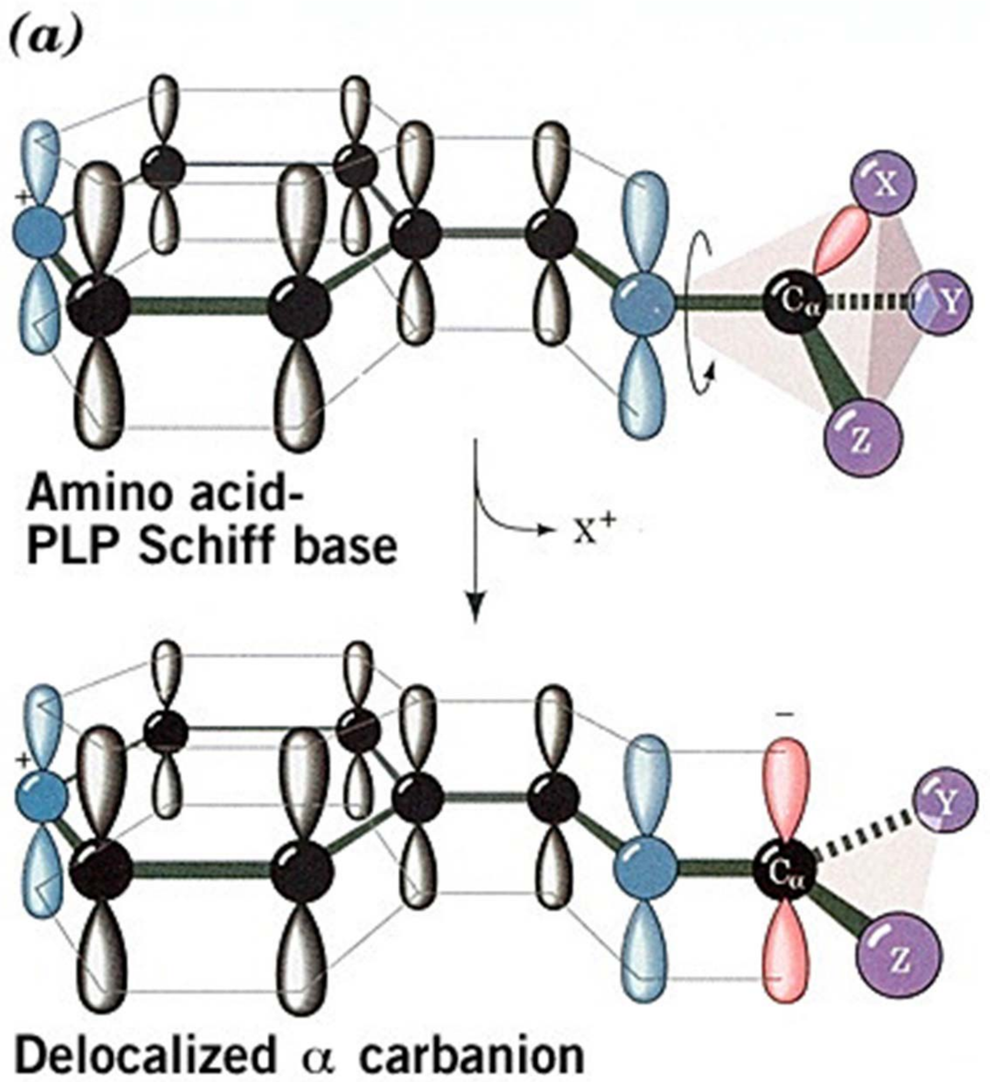
The π-orbital framework of a PLP-amino acid Schiff base

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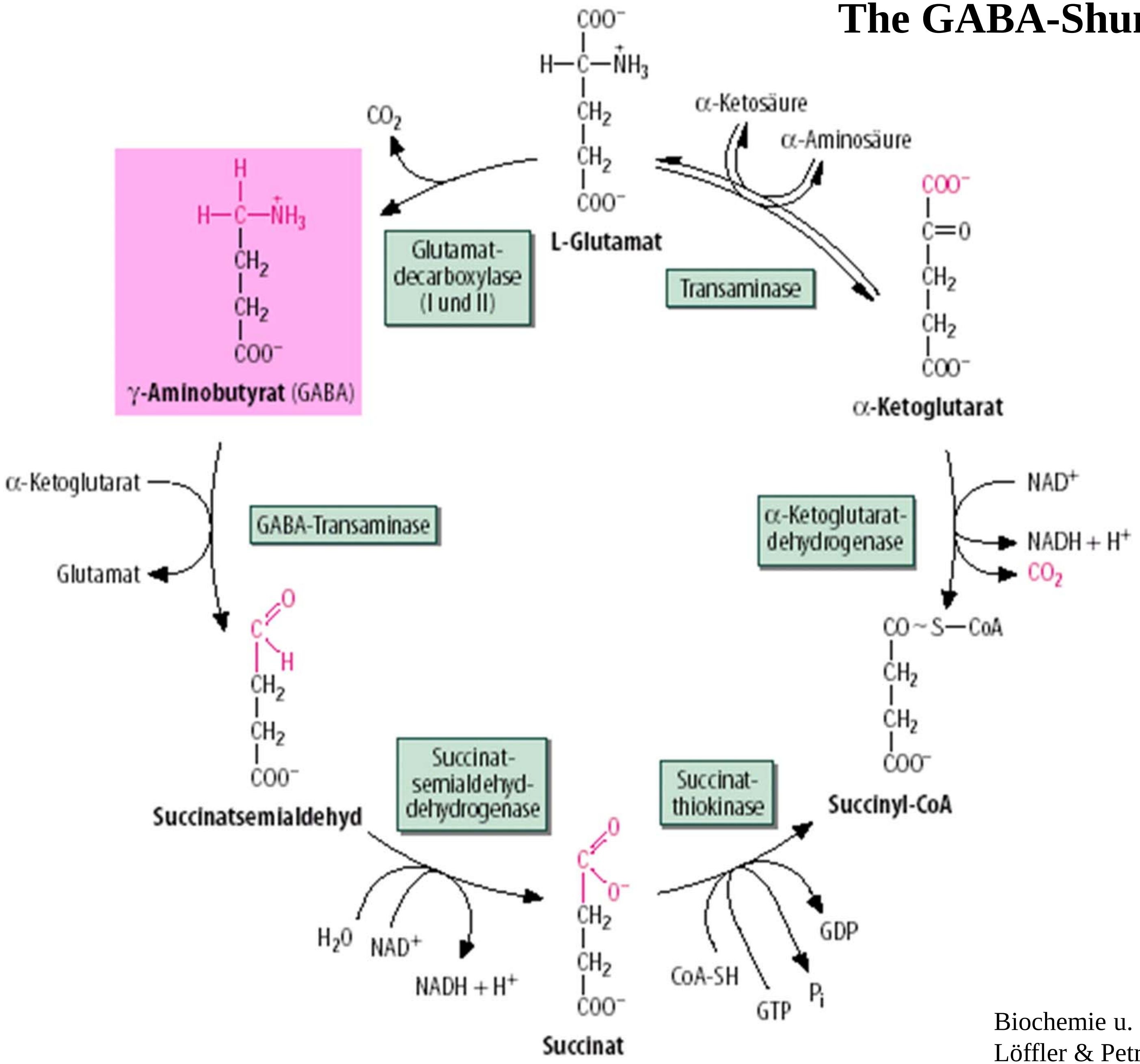
# The GABA-Shunt

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Löffler & Petrides