Medicinal Chemistry/ CHEM 458/658

Special Topics – Micronutrients: Vitamins and Minerals

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Introduction

- Nutrients and diseases

  - Scurvy – Great Explorations (1400s)
  - 19th centrury chemistry becomes powerful
    Organic Chemistry - Justus Liebig's theory of nutrition
    J. B. H. Dumas (1871) – it did not work with infants
    N. I. Lunin – mice exp. milk but not artifical formula
  - first concept of deficiency diseases
  - deficiency diseases in 18th century (Casal, 1755) – pellagra
  - Takaki, 1882, Japanese navy beri-beri problems, German diet "cured" conclusion: protein deficiency
  - J. Goldberger, US PHS, still pellagra – milk/eggs "cured" conclusion: the disease is due to the lack of dietary factors

Introduction

- Nutrients and dieseases

  - 1912 C. Funk: rice husk "cures" beri beri
    isolated the material from the husk named it "vitamines" (*vital amines*)

  - 1920 e was dropped – not all vitamins are amines

  - 1920s vitamins A, B, D

  - 1930s vitamin C

  - 1930s-40s, W. Castle pernicious anaemia – B_{12}

  - 1950s – present : processed food, junk food

Introduction

Nobel Laureates and Their Work with Vitamins

Nobel Prize in Physiology or Medicine

Discovery of Vitamins

Christiaan Eijkman (1929)	Vitamin B_1
Sir Frederick Gowland Hopkins (1929)	Growth Stimulating Vitamins
George Hoyt Whipple (1934)*	Vitamin B_{12}
George Richards Minot (1934)*	Vitamin B_{12}
William Parry Murphy (1934)*	Vitamin B_{12}
Henrik Carl Peter Dam (1943)	Vitamin K

Isolation of Vitamins

Adolf Otto Reinhold Windaus (1928)*	Vitamin D
Albert von Szent-Györgyi Nagyrapolt (1937)	Vitamin C
Richard Kuhn (1938)	Vitamin B_2 and B_6
Edward Adelbert Doisy (1943)	Vitamin K

Nobel Prize in Chemistry

Synthesis of Vitamins

Walter Norman Haworth (1937)	Vitamin C
Paul Karrer (1937)	Vitamin E
Robert Burns Woodward (1965)*	Vitamin B_{12}

Structure of Vitamins

Paul Karrer (1937)	Vitamin A and B
Richard Kuhn (1938)	Vitamin B_2
Lord (Alexander R.) Todd (1957)*	Vitamin B_{12}
Dorothy Crowfoot Hodgkin (1964)*	Vitamin B_{12}

* The Nobel Laureate has worked and contributed in this area, but was awarded for another achievement. See Prize Motivation.

Biomedical Importance

- Vitamins – organic nutrients required in small quantities to maintain metabolic integrity

  - lipid soluble vitamins (ADEK)

  - water soluble vitamins (BHC + niacin)

  - structurally heterogeneous

  - multiple deficiency states

Determination of Micronutrients

- Criteria of adequacy
  - usually broad ranges – clinical deficiency to toxicity

Table 14-1 Characteristics of Common Vitamins

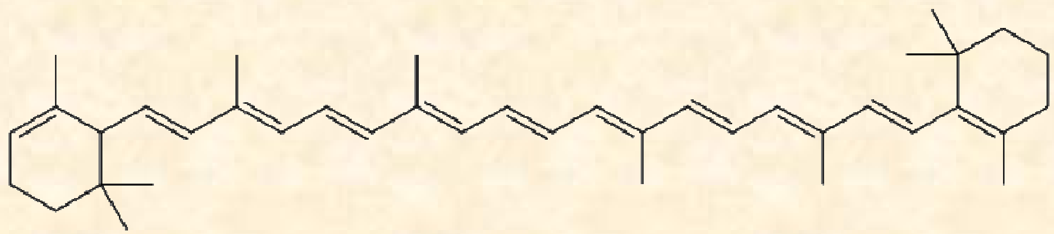
Vitamin	Coenzyme Product	Reaction Mediated	Human Deficiency Disease
Water-Soluble			
Biotin	Biocytin	Carboxylation	*a*
Pantothenic acid	Coenzyme A	Acyl transfer	*a*
Cobalamin (B_{12})	Cobalamin coenzymes	Alkylation	Pernicious anemia
Riboflavin (B_2)	Flavin coenzymes	Oxidation–reduction	*a*
—	Lipoic acid	Acyl transfer	*a*
Nicotinamide (niacin)	Nicotinamide coenzymes	Oxidation–reduction	Pellagra
Pyridoxine (B_6)	Pyridoxal phosphate	Amino group transfer	*a*
Folic acid	Tetrahydrofolate	One-carbon group transfer	Megaloblastic anemia
Thiamine (B_1)	Thiamine pyrophosphate	Aldehyde transfer	Beriberi
Ascorbic acid (C)	Ascorbate	Hydroxylation	Scurvy
Fat-Soluble			
Vitamin A		Vision	Night blindness
Vitamin D		Ca^{2+} absorption	Rickets
Vitamin E		Antioxidant	*a*
Vitamin K		Blood clotting	Hemorrhage

[a] No specific name; deficiency in humans is rare or unobserved.

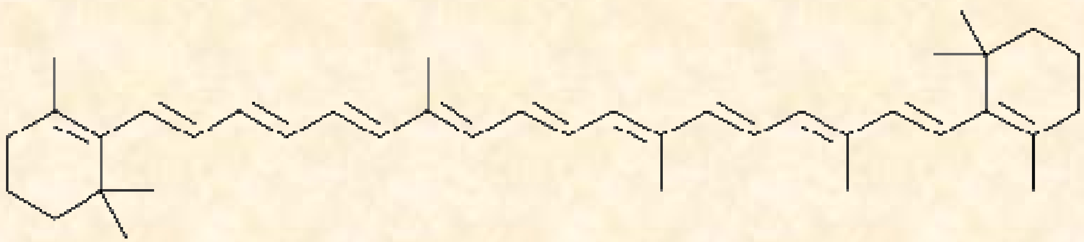
Lipid-Soluble Vitamins

- VITAMIN A

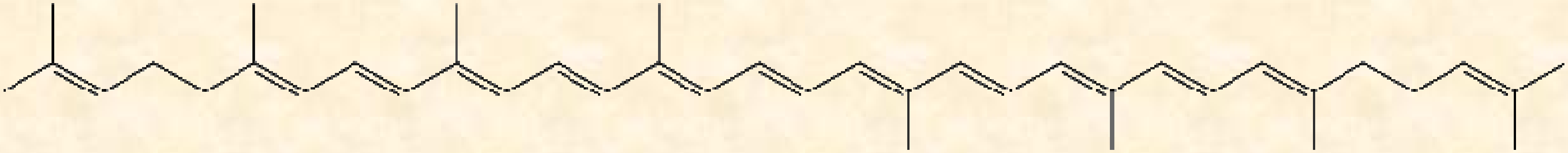
  - Two groups : a) retinol, retinal; b) retinoic acid (Vitamin A)



α-carotene



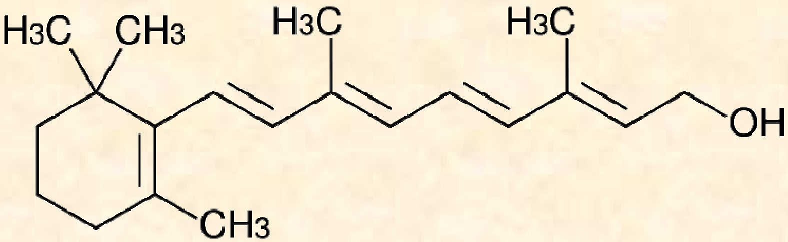
β-carotene



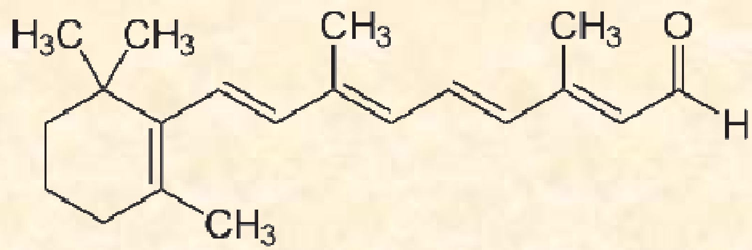
lycopene

Lipid-Soluble Vitamins

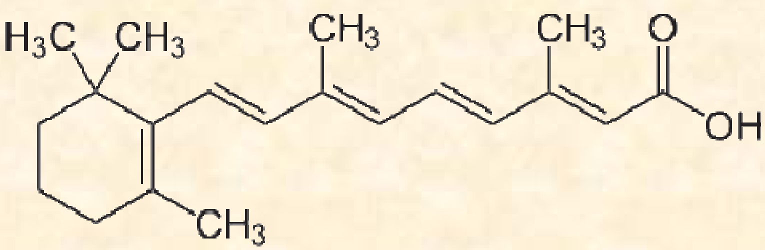
- VITAMIN A



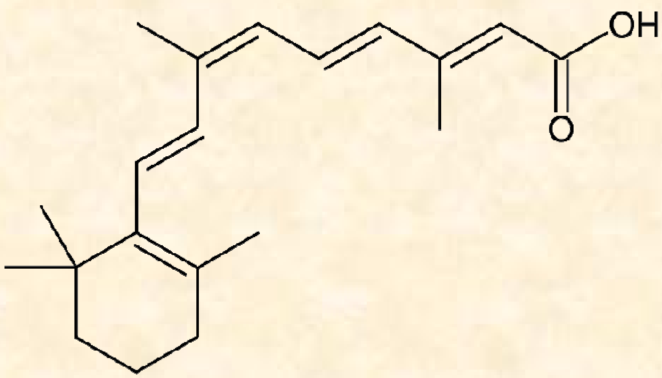
retinol



retinal



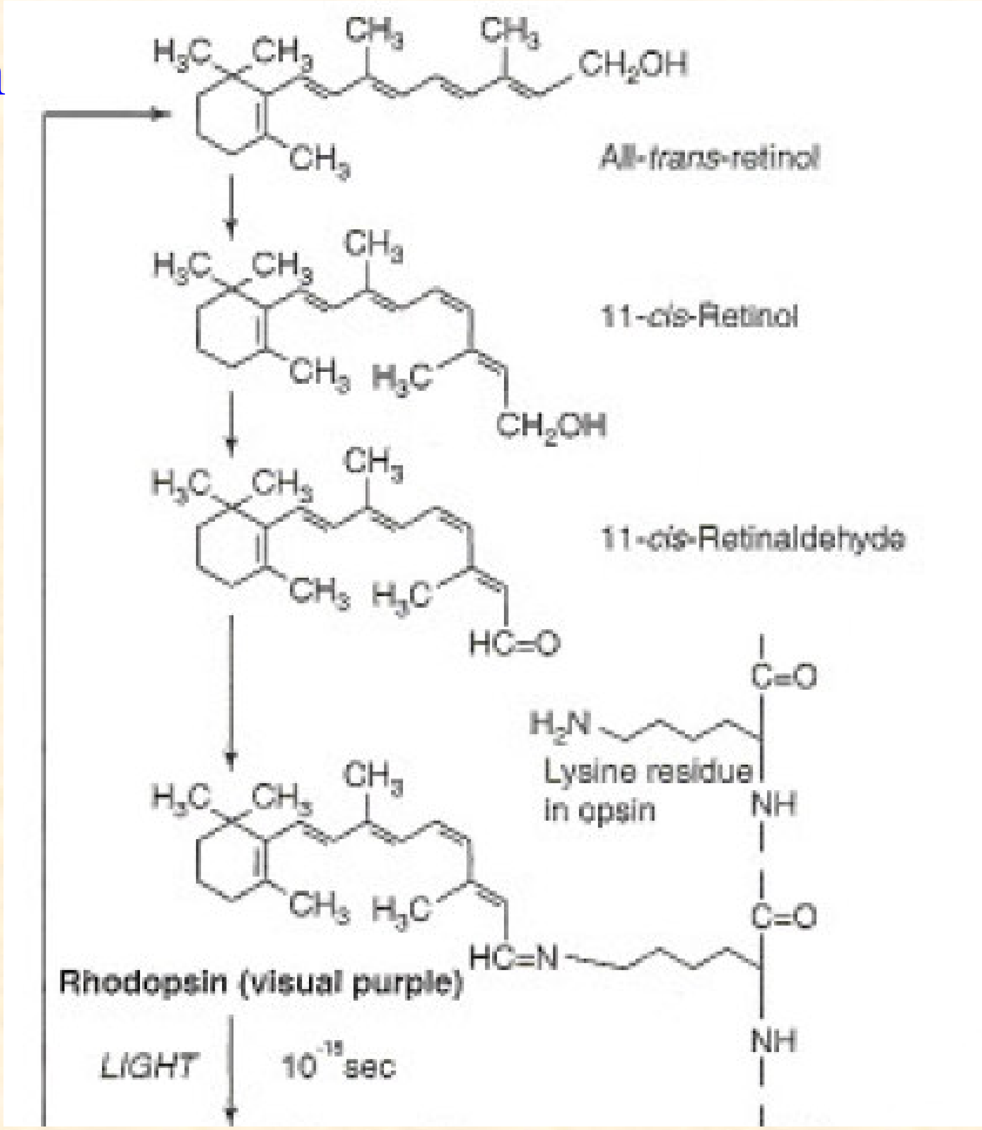
All-*trans*-retinoic acid
(Tretinoin)



9-*cis*-retinoic acid
(Alitretinoin)

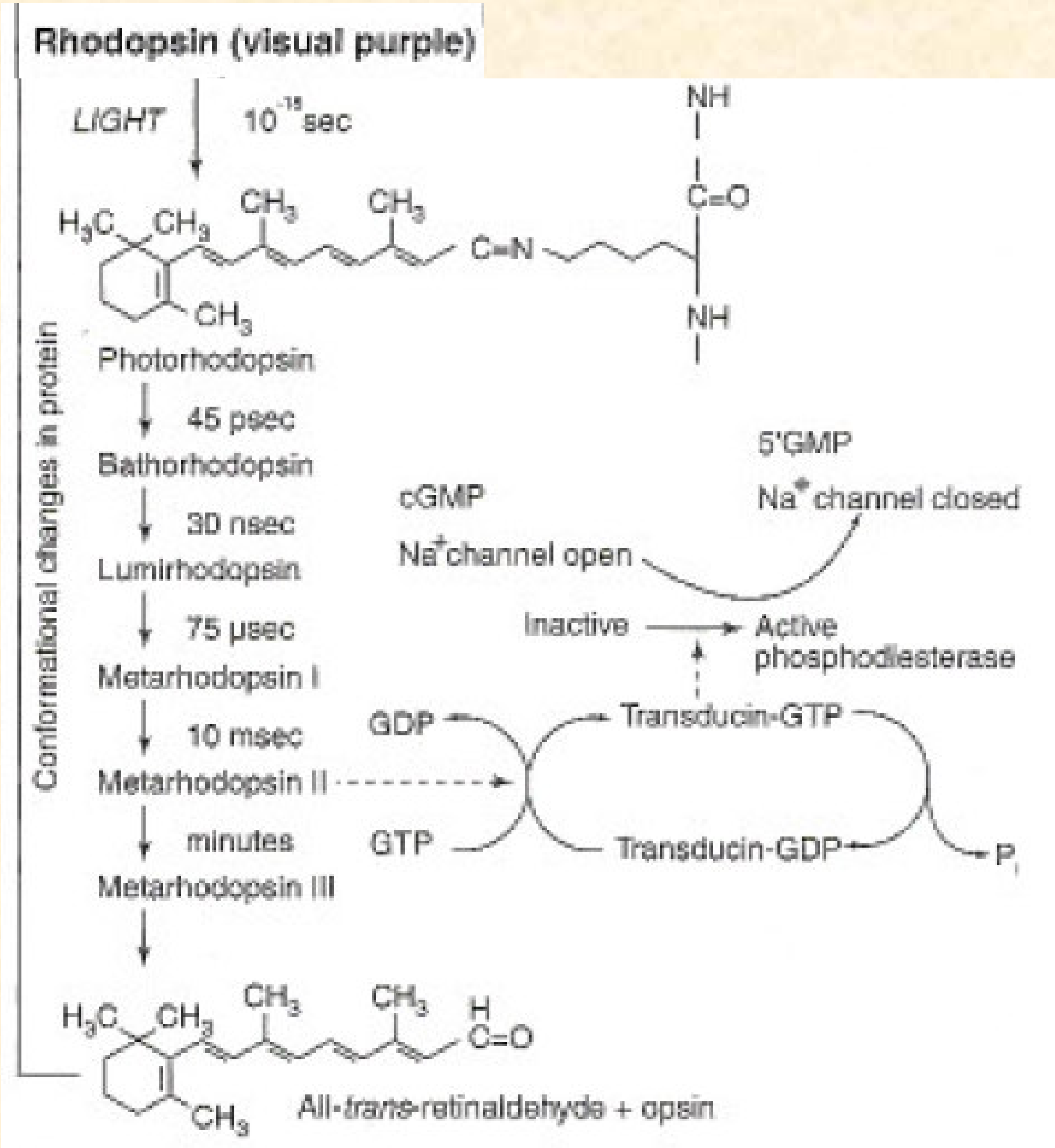
Lipid-Soluble Vitamins

- VITAMIN A
  - role in vision



Lipid-Soluble Vitamins

- VITAMIN A
  - role in vision



Lipid-Soluble Vitamins

- VITAMIN A
  - deficiency: blindness
    - loss of sensitivity to green light
    - night blidness
    - xerophthalmia
  - excess: TOXIC
    - liver problems
    - calcium homeostasis, hypercalcemia

Lipid-Soluble Vitamins

- VITAMIN D

  - not really a vitamin, rather a hormone
  - can be synthesized in the skin (major source!)
  - role in rickets development E. Mellanby, 1919

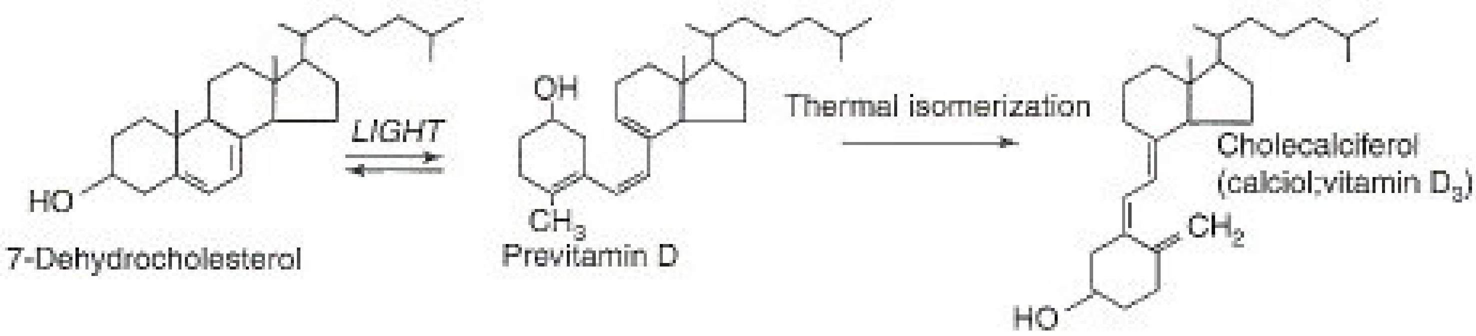


Figure 44–3. The synthesis of vitamin D in the skin.

Lipid-Soluble Vitamins

- VITAMIN D

  - its metabolism is regulated by/regulates Calcium homeostasi

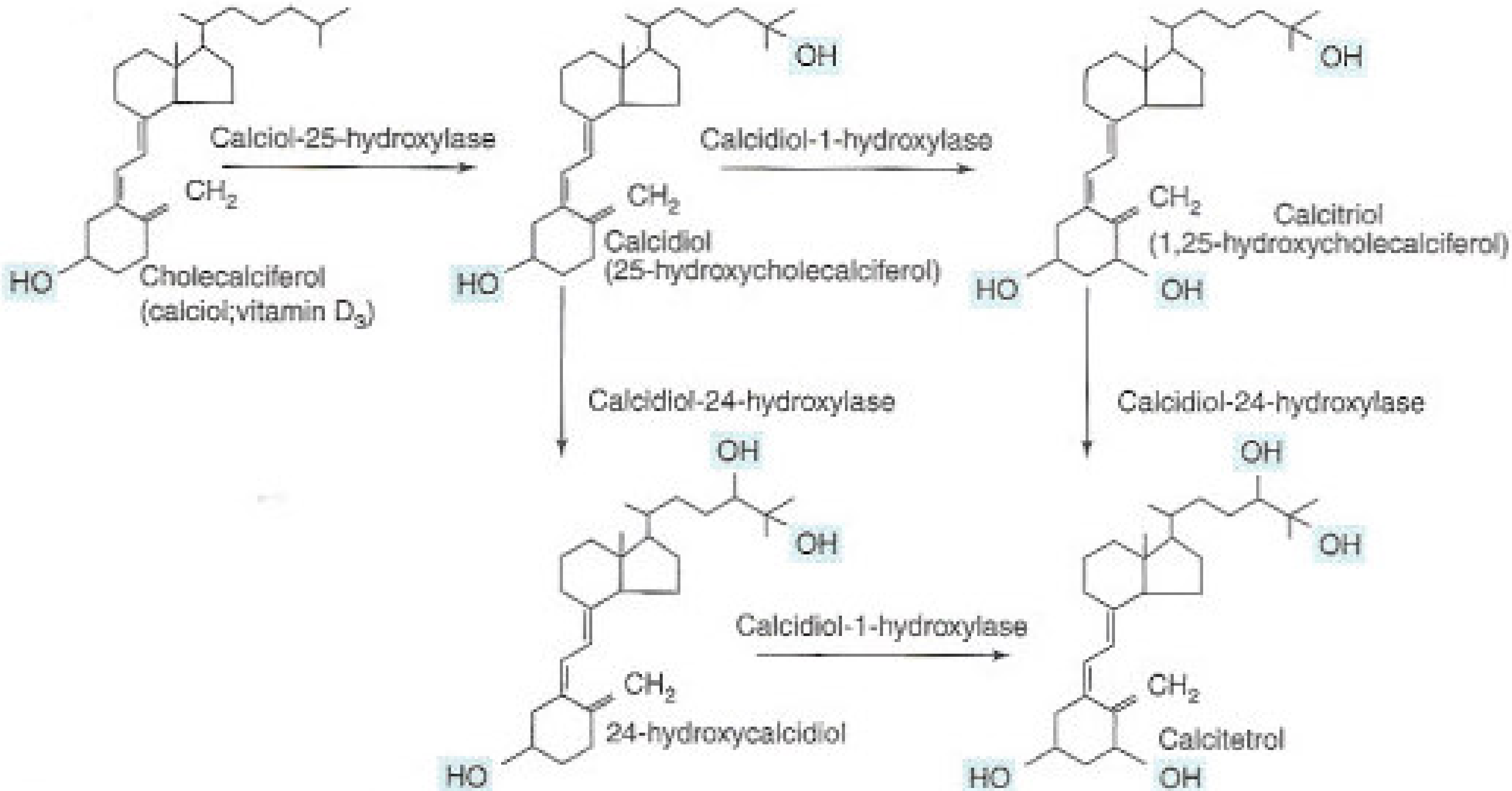


Figure 44–4. Metabolism of vitamin D.

Lipid-Soluble Vitamins

- VITAMIN D
  - deficiency:
    - risk factors:
      - exclusively breast fed infants
      - dark skin
      - aging
      - religious/cultural reasons
      - cyctic fibrosis/cholestatic liver disease
      - obesity
  - diseases
    - rickets
    - osteomalacia
    - muscle wekaness/pain

Lipid-Soluble Vitamins

- VITAMIN D

  - excess: TOXIC

  hypervitaminosis D

  daily intake: 400 IU   toxic above ~ 40,000 IU

  hypercalcemia

  anorexia, nausea

  polyuria etc.

Lipid-Soluble Vitamins

- VITAMIN E

  - H. M. Evans, 1922 – its lack caused infertility problems in rats
  - no precisely defined metabolic function
  - lipid soluble antioxidant
  - two groups of compounds

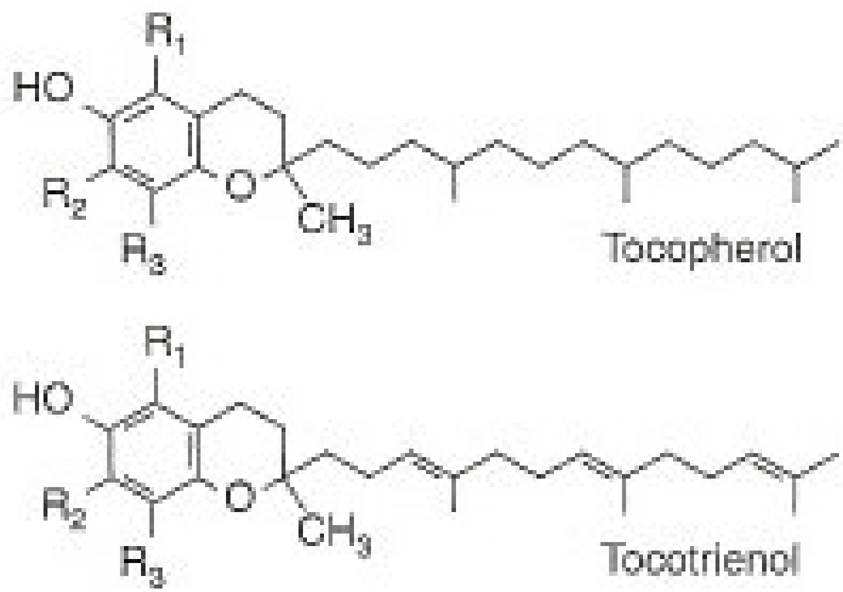
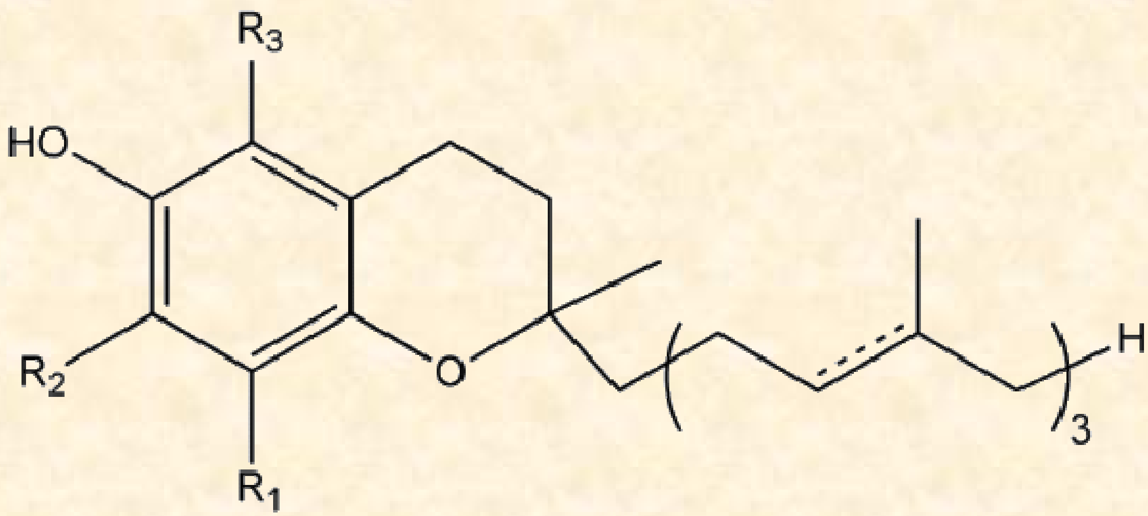


Figure 44–5. Vitamin E vitamers. In α-tocopherol and tocotrienol R_1, R_2, and R_3 are all —CH_3 groups. In the β-vitamers R_2 is H, in the γ-vitamers R_1 is H, and in the δ-vitamers R_1 and R_2 are both H.

"pregnancy carrier"

Lipid-Soluble Vitamins

- VITAMIN E
  - α, β, γ, δ forms



α-tocopherol, $R_1 = R_2 = R_3 = CH_3$
α-tocotrienol, $R_1 = R_2 = R_3 = CH_3$

β-tocopherol, $R_1 = R_3 = CH_3$; $R_2 = H$
β-tocotrienol, $R_1 = R_3 = CH_3$; $R_2 = H$

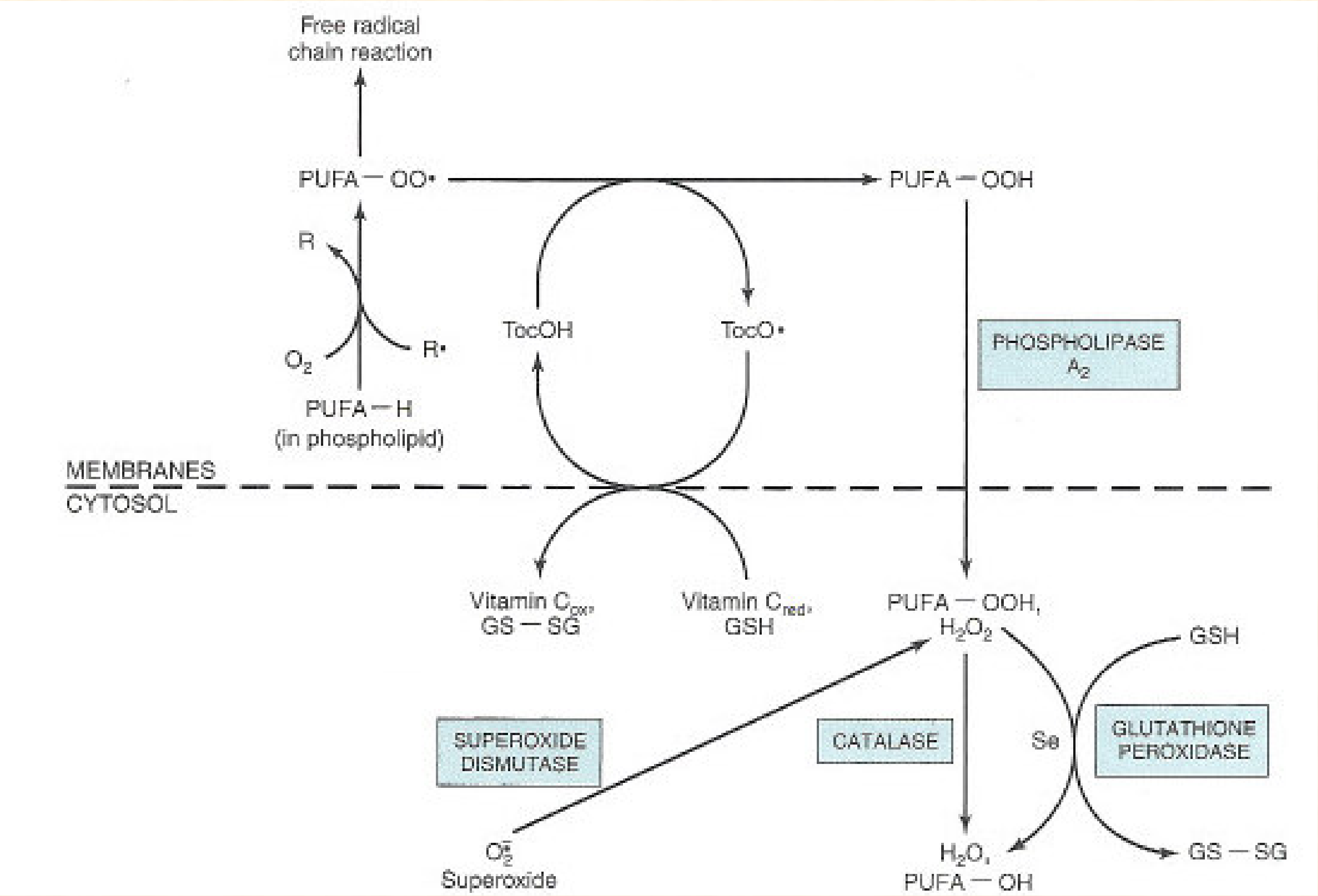
γ-tocopherol, $R_1 = R_2 = CH_3$ $R_3 = H$
γ-tocotrienol, $R_1 = R_2 = CH_3$ $R_3 = H$

δ-tocopherol, $R_1 = R_2 = R_3 = H$
δ-tocotrienol, $R_1 = R_2 = R_3 = H$

Lipid-Soluble Vitamins

- VITAMIN E

  - the major lipid-soluble antioxidant in cell membranes and plasma lipoproteins



Lipid-Soluble Vitamins

- VITAMIN E
  - deficiency:
    - resorption of fetuses
    - testicular atrophy
    - premature birth
  - excess: slightly TOXIC
    - heart failure

Lipid-Soluble Vitamins

- VITAMIN K
  - “koagulations” vitamin
  - required for the synthesis of blood clotting proteins
  - H. Dam, 1929, E. A. Doisy 1930s

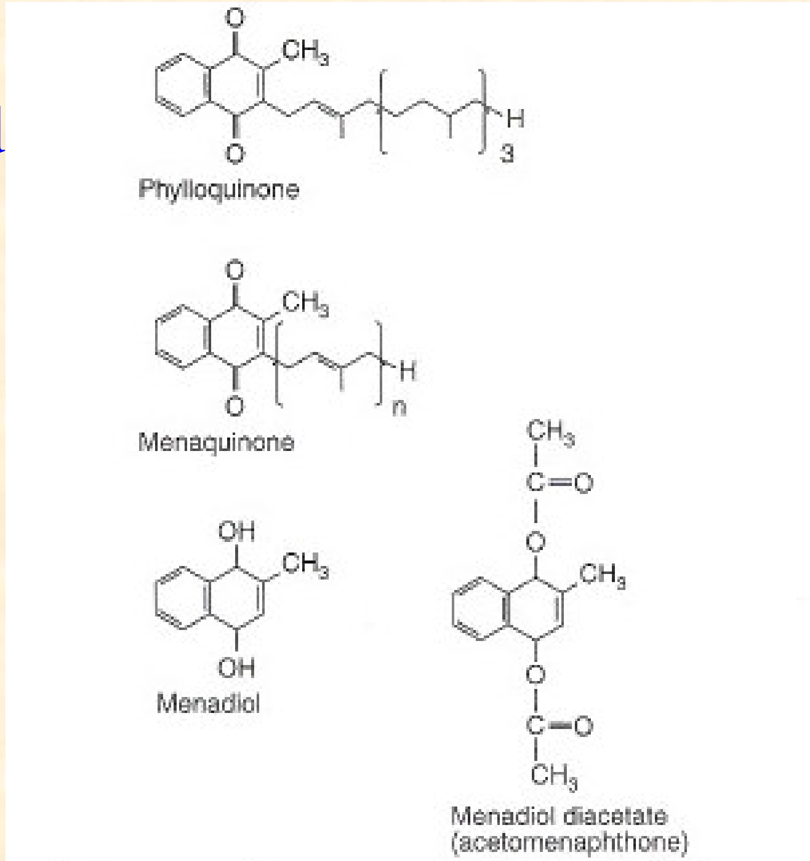


Figure 44–7. The vitamin K vitamers. Menadiol (or menadione) and menadiol diacetate are synthetic compounds that are converted to menaquinone in the liver.

Lipid-Soluble Vitamins

- VITAMIN K
  - "koagulations" vitamin

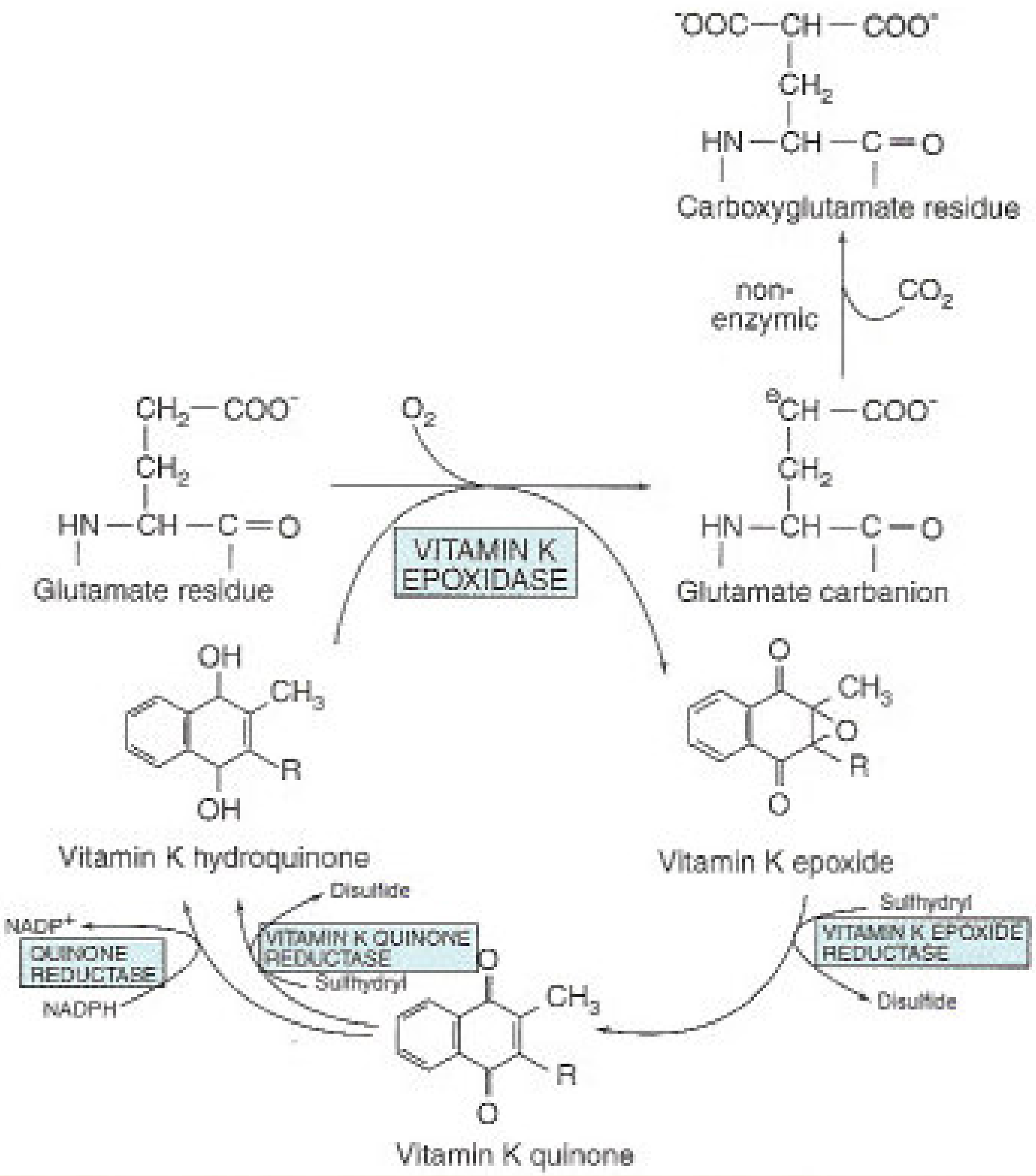
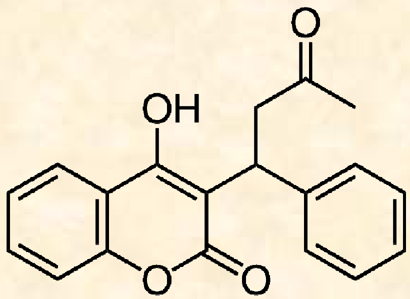


Figure 44–8. The role of vitamin K in the synthesis of γ-carboxyglutamate.

Lipid-Soluble Vitamins

- VITAMIN K
  - antidote to warfarin
  - important in the synthesis of calcium binding proteins

  - deficiency:
    hemorrhage (bleeding disorder)



warfarin

  - toxicity:
    thrombosis
    kidney tubule degeneration
    hemolytic anemia

Water-Soluble Vitamins

- VITAMIN B_1 (thiamine)
  - key role in carbohydrate metabolism
  - Takaki (1884), Eijkman (1897) - beriberi
  - multiple role

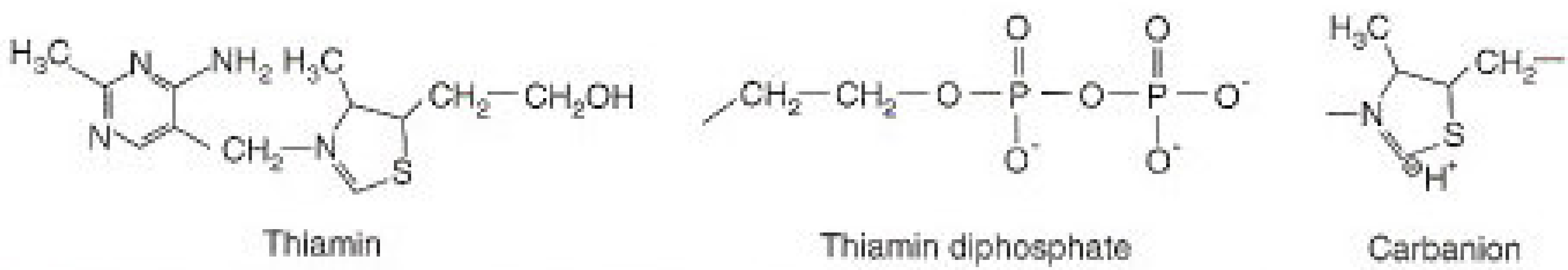


Figure 44–9. Thiamin, thiamin diphosphate, and the carbanion form.

Water-Soluble Vitamins

- VITAMIN B_1 (thiamine)
  - multiple role
  (pyruvate dehydrogenase complex)

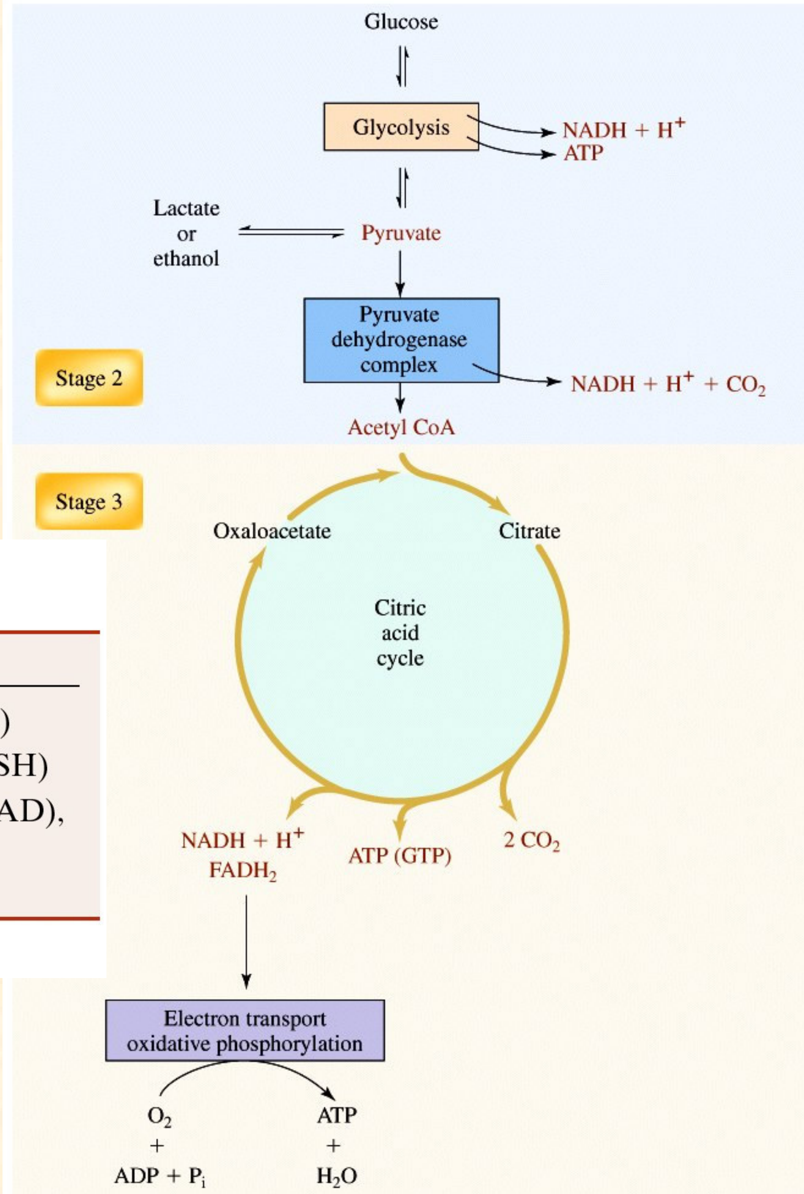


Figure 16-1 Concepts in Biochemistry, 3/e

Table 16.1
Enzymes and coenzymes of the pyruvate dehydrogenase complex

Enzyme	Abbreviation	Coenzyme
Pyruvate dehydrogenase	E_1	Thiamine pyrophosphate (TPP)
Dihydrolipoyl transacetylase	E_2	Lipoamide, coenzyme A (CoASH)
Dihydrolipoyl dehydrogenase	E_3	Flavin adenine dinucleotide (FAD), nicotinamide adenine dinucleotide (NAD^+)

Table 16-1 Concepts in Biochemistry, 3/e

Water-Soluble Vitamins

- VITAMIN B_1 (thiamine)
  - deficiency
    malnutrition, thiaminase rich food (raw fish, shelfish)

  myriad of neurodegeneration problems, then death
  Wernicke's encephalopathy (alcohol related syndrome)
  lactic acidosis

Water-Soluble Vitamins

- VITAMIN B_2 (riboflavine)
  - key role in carbohydrate metabolism
  - Paul Gyorgy (1920s)
  - multiple role (electron carriers, oxidoreduction)

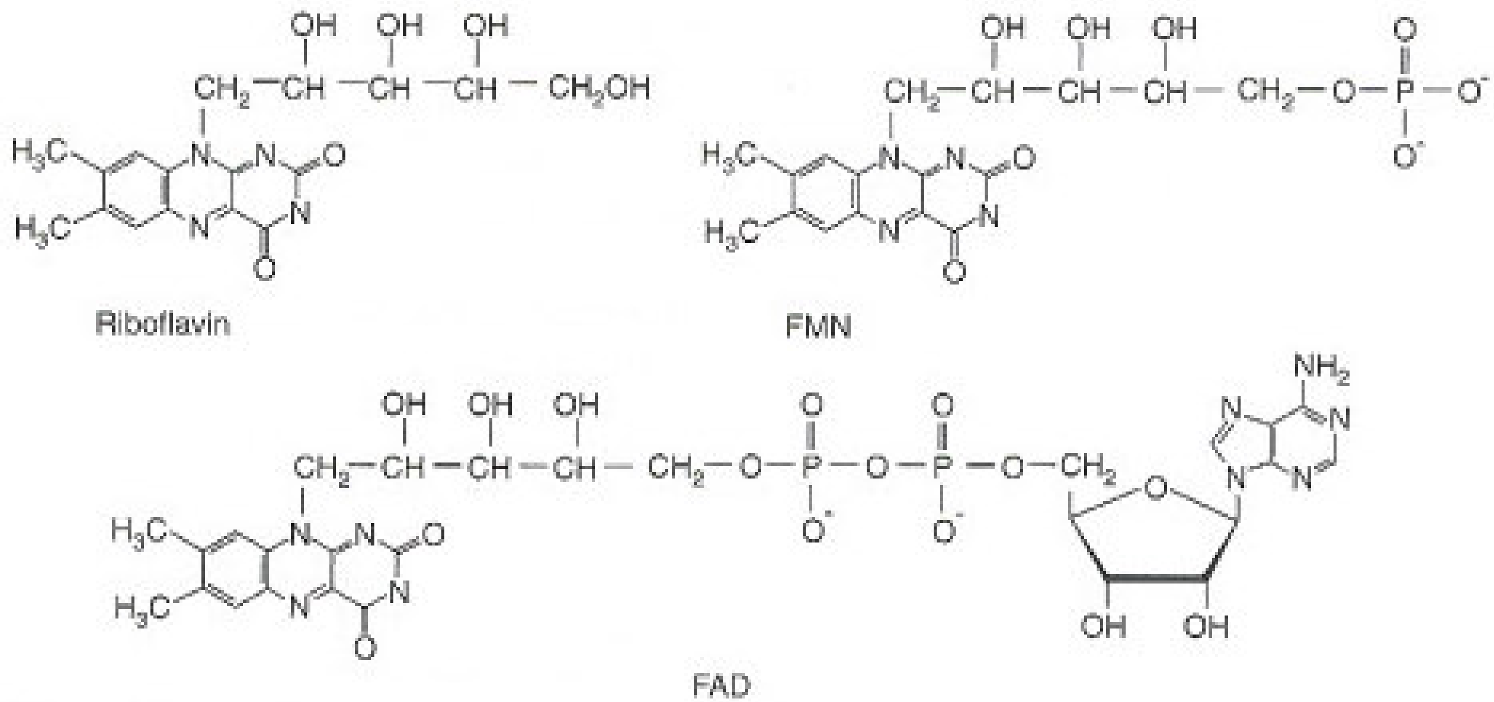


Figure 44–10. Riboflavin and the coenzymes flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD).

Water-Soluble Vitamins

Table 16.1
Enzymes and coenzymes of the pyruvate dehydrogenase complex

Enzyme	Abbreviation	Coenzyme
Pyruvate dehydrogenase	E_1	Thiamine pyrophosphate (TPP)
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Dihydrolipoyl dehydrogenase	E_3	Flavin adenine dinucleotide (FAD), nicotinamide adenine dinucleotide (NAD^+)

Table 16-1 Concepts in Biochemistry, 3/e

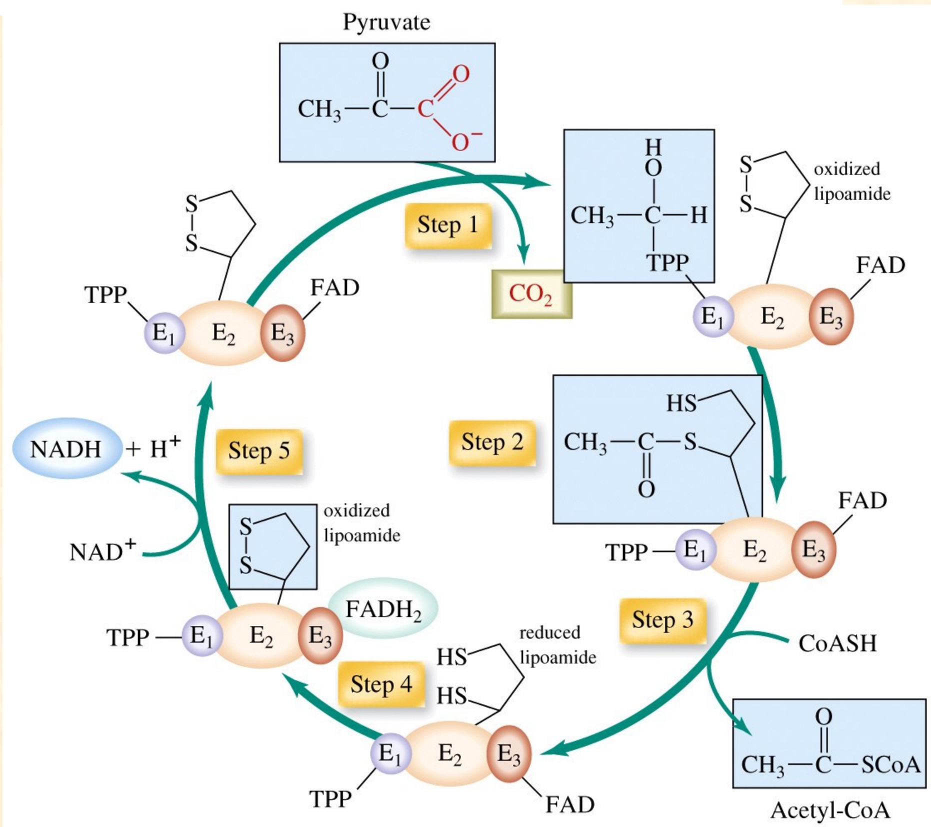


Figure 16-3 Concepts in Biochemistry, 3/e

Water-Soluble Vitamins

- VITAMIN B_2 (riboflavin) food coloring (orange)
  - deficiency
    malnutrition, widespread but usually not fatal

  cracked red lips, inflammation in mouth, sore throat
  iron deficiency anemia

Water-Soluble Vitamins

- Niacin not strictly a vitamin
  - can be synthesized from tryptophan
  - Hugo Weidel (1873)
  - multiple role (electron carriers, oxidoreduction)

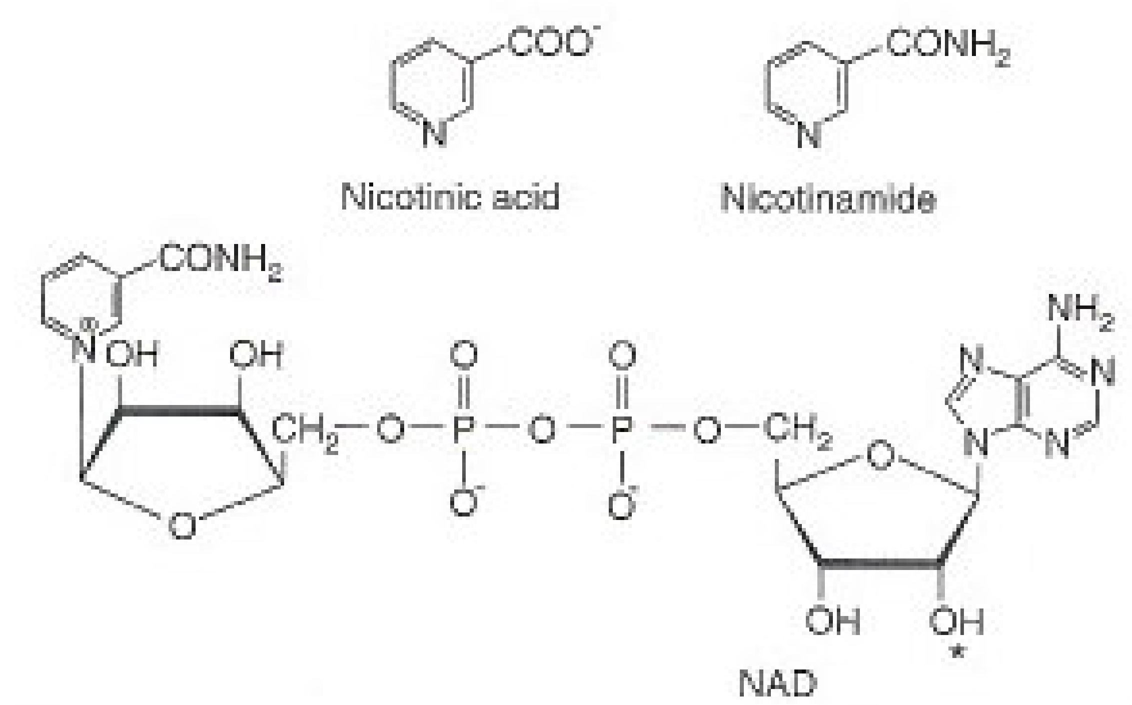


Figure 44–11. Niacin (nicotinic acid and nicotinamide) and nicotinamide adenine dinucleotide (NAD). Asterisk shows the site of phosphorylation in NADP.

Water-Soluble Vitamins

- Niacin
  - deficiency
    - malnutrition

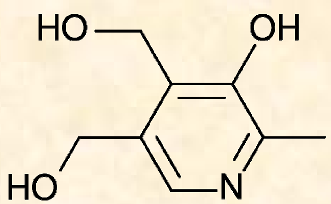
  pellagra (tryptophan and niacin deficiency)

  Hartnup disease (genetic pellagra, tryptophan loss due to enzyme malfunction)

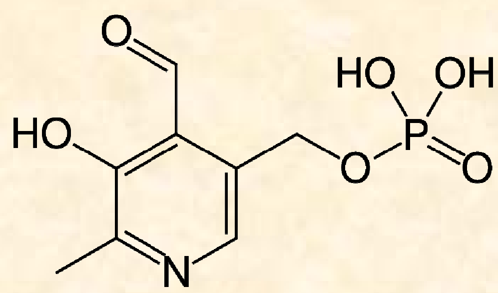
  toxic above 500 mg/day

Water-Soluble Vitamins

- Vitamin B_6
  - amino acid and glycogen metabolism, and steroid hormone action
  - Paul Gyorgy (1934)



pyridoxine



pyridoxal

Water-Soluble Vitamins

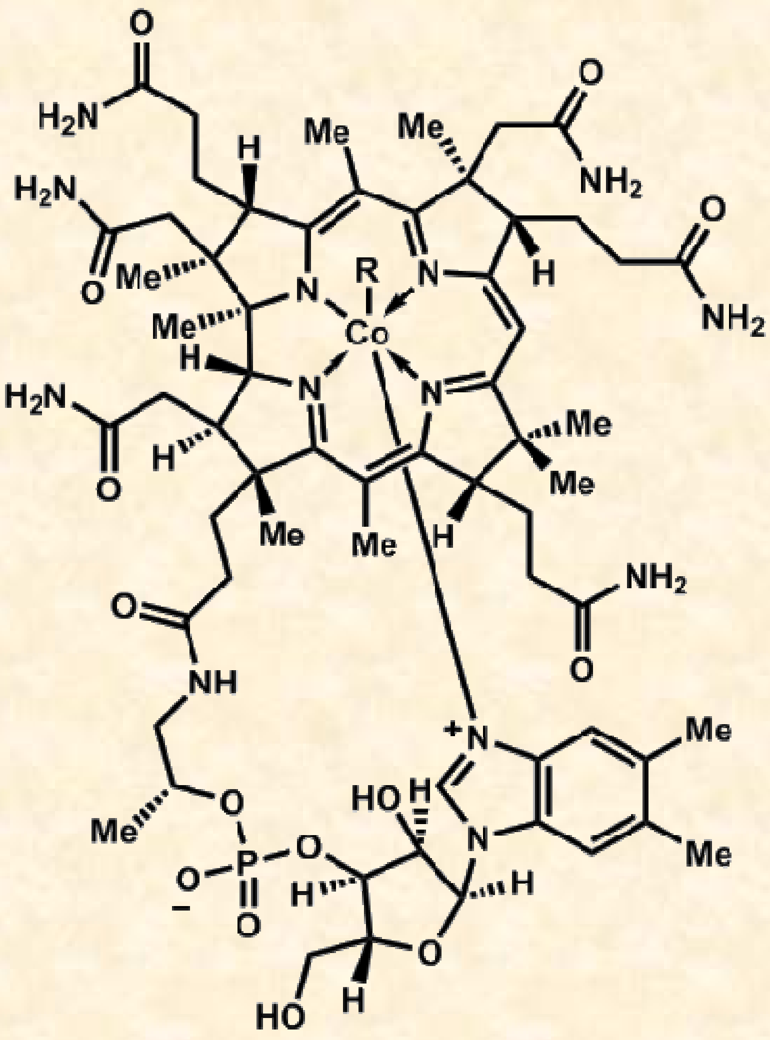
- Vitamin B_6
  - deficiency
    - malnutrition

  skin problems (seborrhoeic dermatitis)
  neurological problems

  could be toxic loss of proprioception

Water-Soluble Vitamins

- Vitamin B_{12}
  - amino acid and glycogen metabolism, and steroid hormone action
  - 1940s, structure, synthesis 1950-60s



R = CN, OH, Me, 5'-deoxyadenosyl

Water-Soluble Vitamins

- Vitamin B_{12}

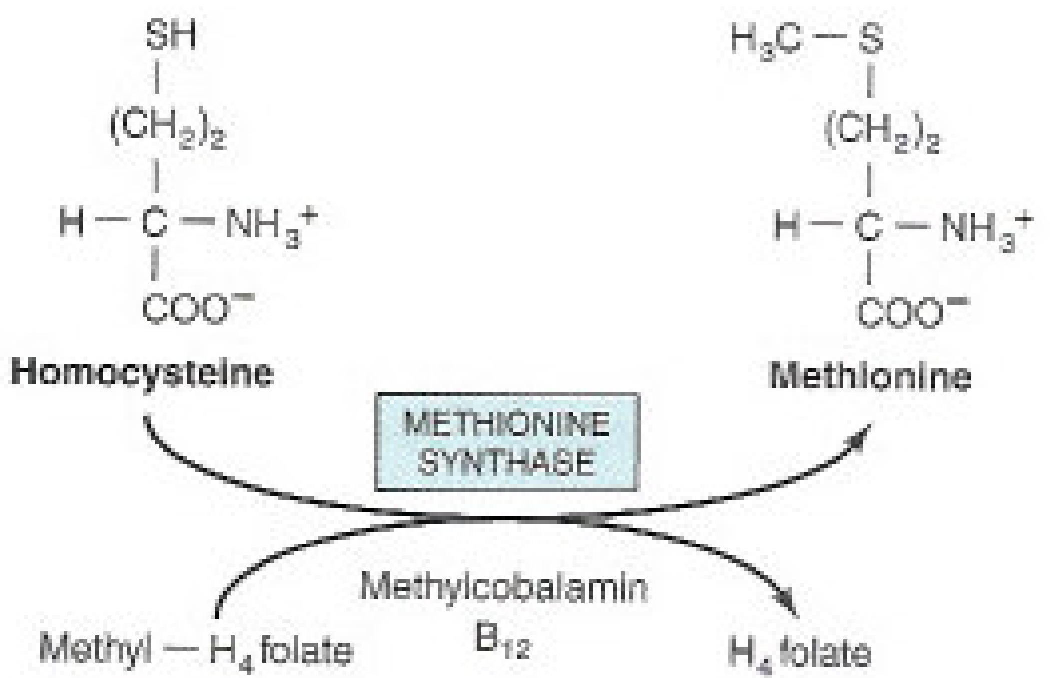


Figure 44–14. Homocysteine and the "folate trap." Vitamin B_{12} deficiency leads to impairment of methionine synthase, resulting in accumulation of homocysteine and trapping folate as methyltetrahydrofolate.

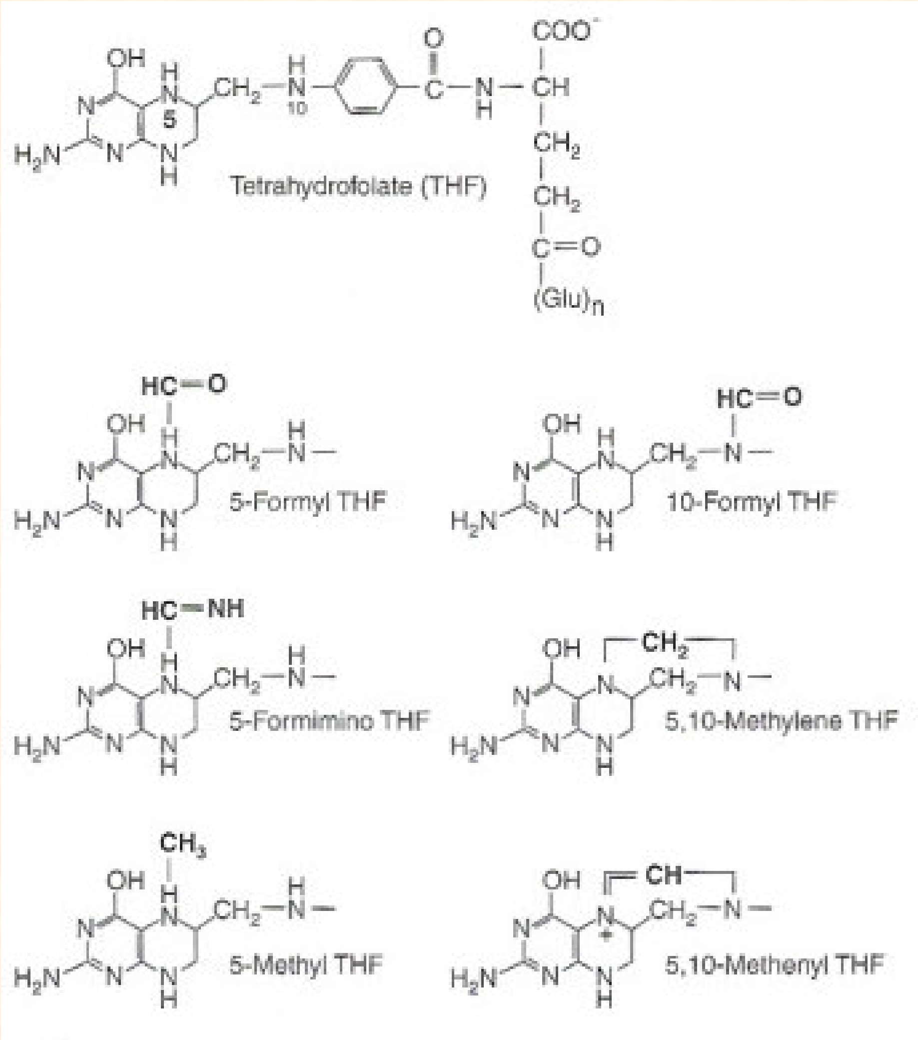
Water-Soluble Vitamins

- Vitamin B_{12}
  - deficiency
    - malnutrition

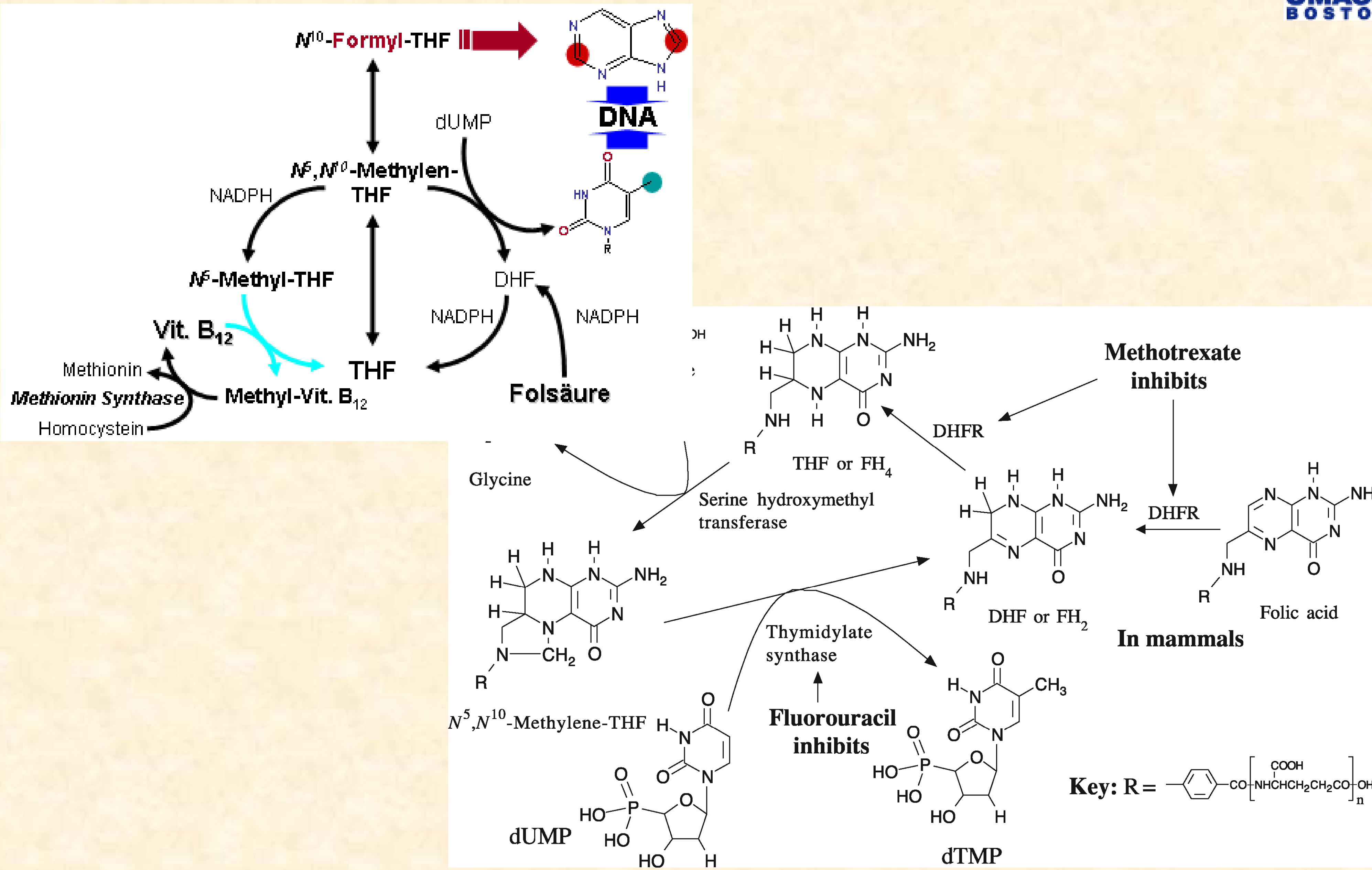
  pernicious anemia

Water-Soluble Vitamins

- Folic acid, folates (also known as vitamin B_9)
  - nucleotide synthesis
  - Lucy Wills, 1931 (prevention of anemia during pregnancy)



Water-Soluble Vitamins



Water-Soluble Vitamins

- folates
  - deficiency
    malnutrition

  megaloblastic anemia (with B_{12})
  spina bifida

Water-Soluble Vitamins

- Biotin (vitamin H or B_7)
  - transfer of CO_2, citric acid cycle

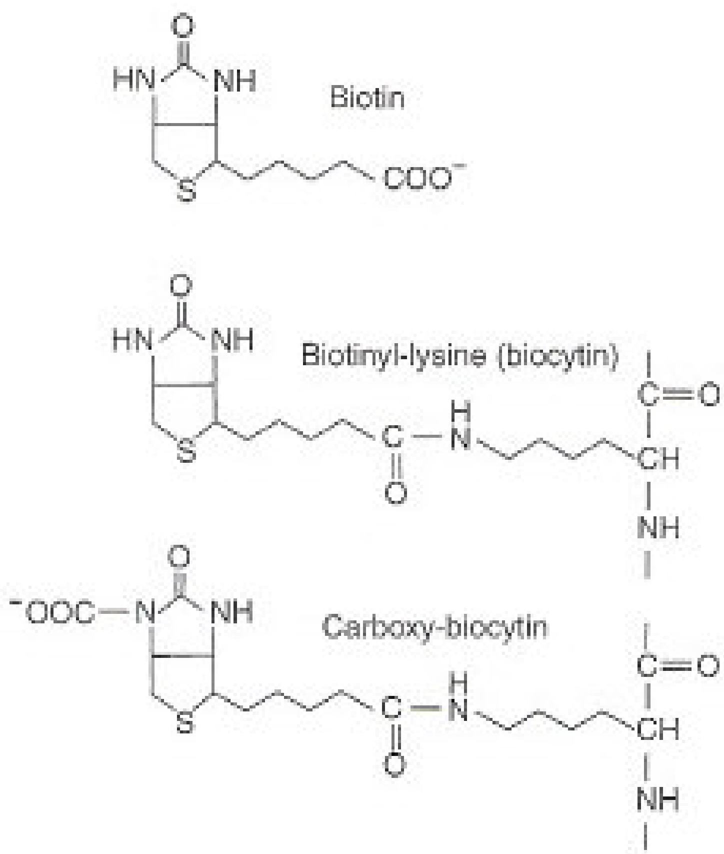


Figure 44–17. Biotin, biocytin, and carboxy-biocytin.

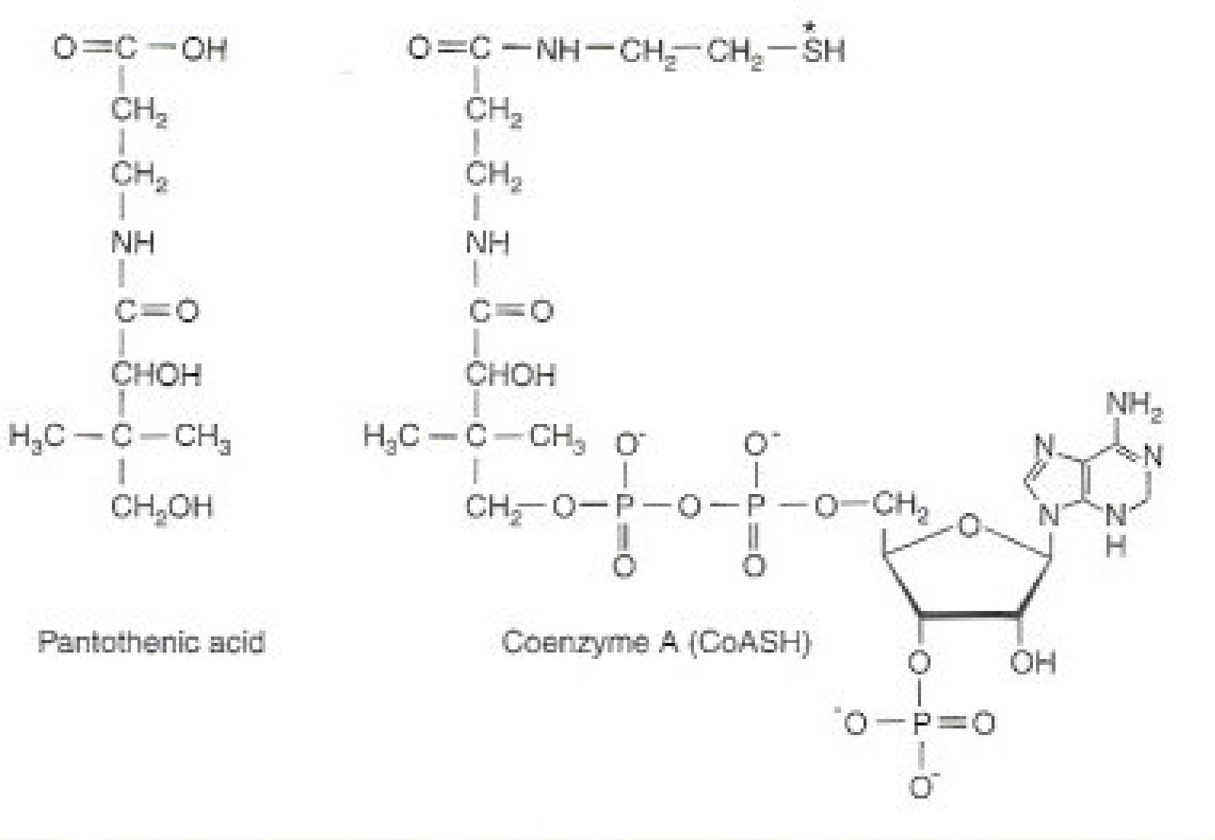
Water-Soluble Vitamins

- biotin
  - deficiency
    - hair loss
    - sebhorreic dermatitis

Water-Soluble Vitamins

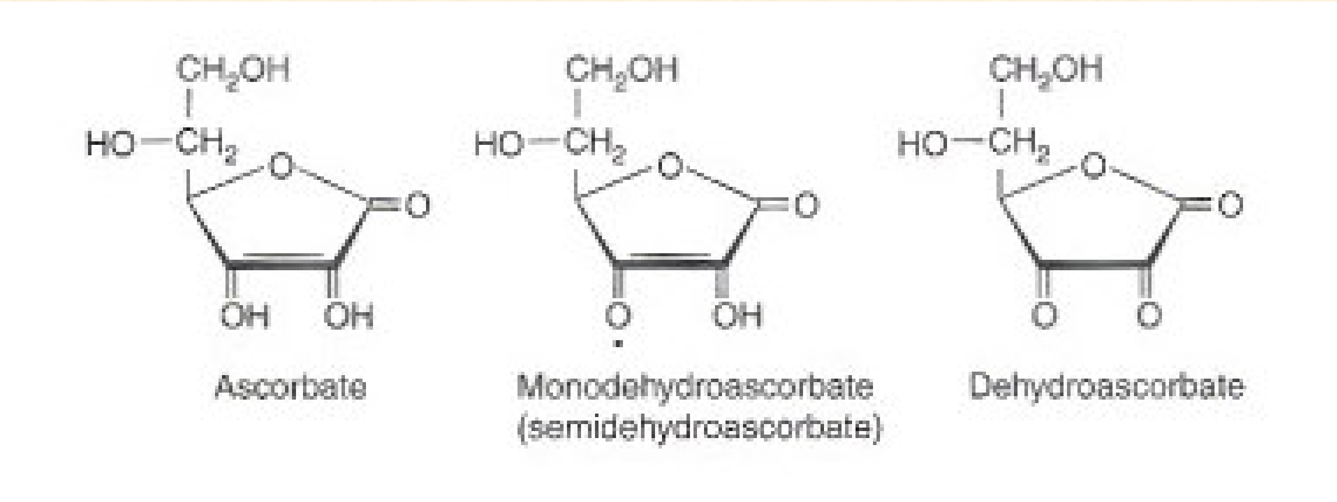
- Panthotenic acid (also known as vitamin B_5)

  - carrier of acetyl radical



Water-Soluble Vitamins

- Ascorbic acid (also known as vitamin C)
  - a sugar acid
  - antioxidative properties
  - Walter Haworth , Albert Szentgyorgyi, 1920s
  - coenzyme for two group of hydrolases:
    - dopamine β-hydroxylase
    - peptidylglycin hydroxylase
    - lysin hydroxylases



Water-Soluble Vitamins

- Vitamin C

  - deficiency

    scurvy

    deficiency in collagen synthesis

    fragility of blood capillaries

  - excess vitamin C

    potential benefits

Minerals

Table 44–2. Classification of minerals according to their function.

Function	Mineral
Structural function	Calcium, magnesium, phosphate
Involved in membrane function	Sodium, potassium
Function as prosthetic groups in enzymes	Cobalt, copper, iron, molybdenum, selenium, zinc
Regulatory role or role in hormone action	Calcium, chromium, iodine, magnesium, manganese, sodium, potassium
Known to be essential, but function unknown	Silicon, vanadium, nickel, tin
Have effects in the body, but essentiality is not established	Fluoride, lithium
May occur in foods and known to be toxic in excess	Aluminum, arsenic, antimony, boron, bromine, cadmium, cesium, germanium, lead, mercury, silver, strontium