Biochemistry of Vitamin K

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Objectives

Upon completion of this lecture, the Second Year students will be able to:

- Identify the types and sources of vitamin K
- Understand the role of vitamin K in blood coagulation
- Recognize the importance of g-carboxylation of glutamic acid in coagulation proteins
- Understand the role of anticoagulant drugs in affecting vitamin K function
- Discuss the causes and disorders of vitamin K deficiency

Overview

- Types, chemistry and sources of vitamin K
- Sources and daily requirements
- Functions:
- Synthesis of γ-carboxyglutamate in:
  - Prothrombin and blood clotting factors
  - Interaction of prothrombin with platelets
  - Osteocalcin
  - Protein C and S (anticogaulant proteins)
- Deficiency and disorders
- Clinical manifestations

Types and Sources

Occurs in several forms:

- Vitamin K_1 (Phylloquinone)
- Vitamin K_2 (Menaquinone)
- Vitamin K_3 (Menadione) – synthetic form

Dietary sources:

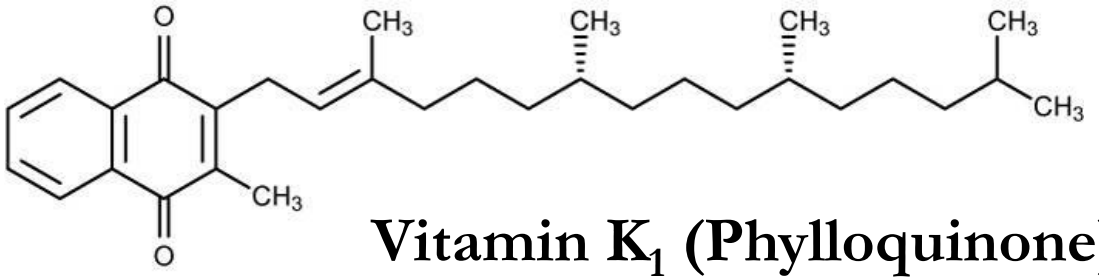
- Cabbage, kale, spinach, egg yolk, liver

Cabbage

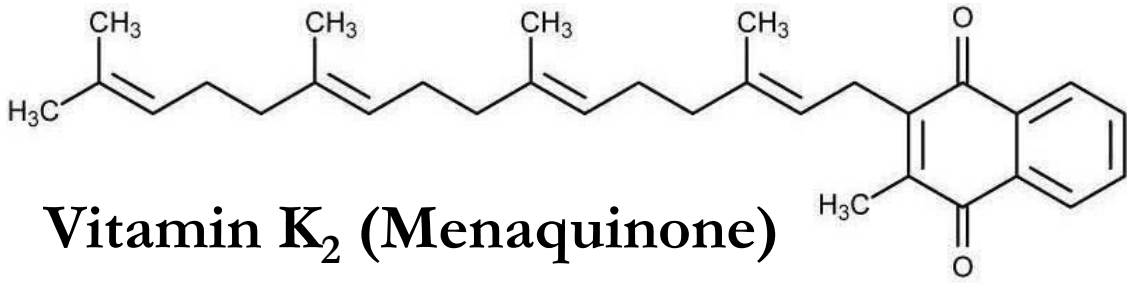
Kale

Spinach

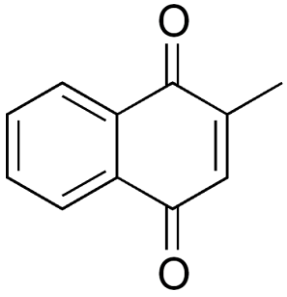
Chemistry of Vitamin K



Vitamin K_1 (Phylloquinone)



Vitamin K_2 (Menaquinone)



Vitamin K_3 (Menadione)

Sources of Vitamin K

- Phylloquinone: Green leafy vegetables
- Menaquinone: Intestinal bacteria
  - Intestinal bacterial synthesis meets the daily requirement of vitamin K even without dietary supplement
- Menadione: synthetic form
  - A precursor of menaquinone

RDA for Vitamin K

(μg/day)

- Infant (0-1 year): 2-2.5
- Children (1-8): 30-55
- Men (19+): 120
- Women (19+): 90
- Pregnancy / lactation: 90 / 90
- UL: Not established

Functions of Vitamin K

- Coenzyme for the synthesis of prothrombin and blood clotting factors in the liver
  - Prothrombin and clotting factors are protein in nature
  - Synthesis of prothrombin, clotting factors II, VII, IX, X require carboxylation of their glutamic acid (Glu) residue

Active form

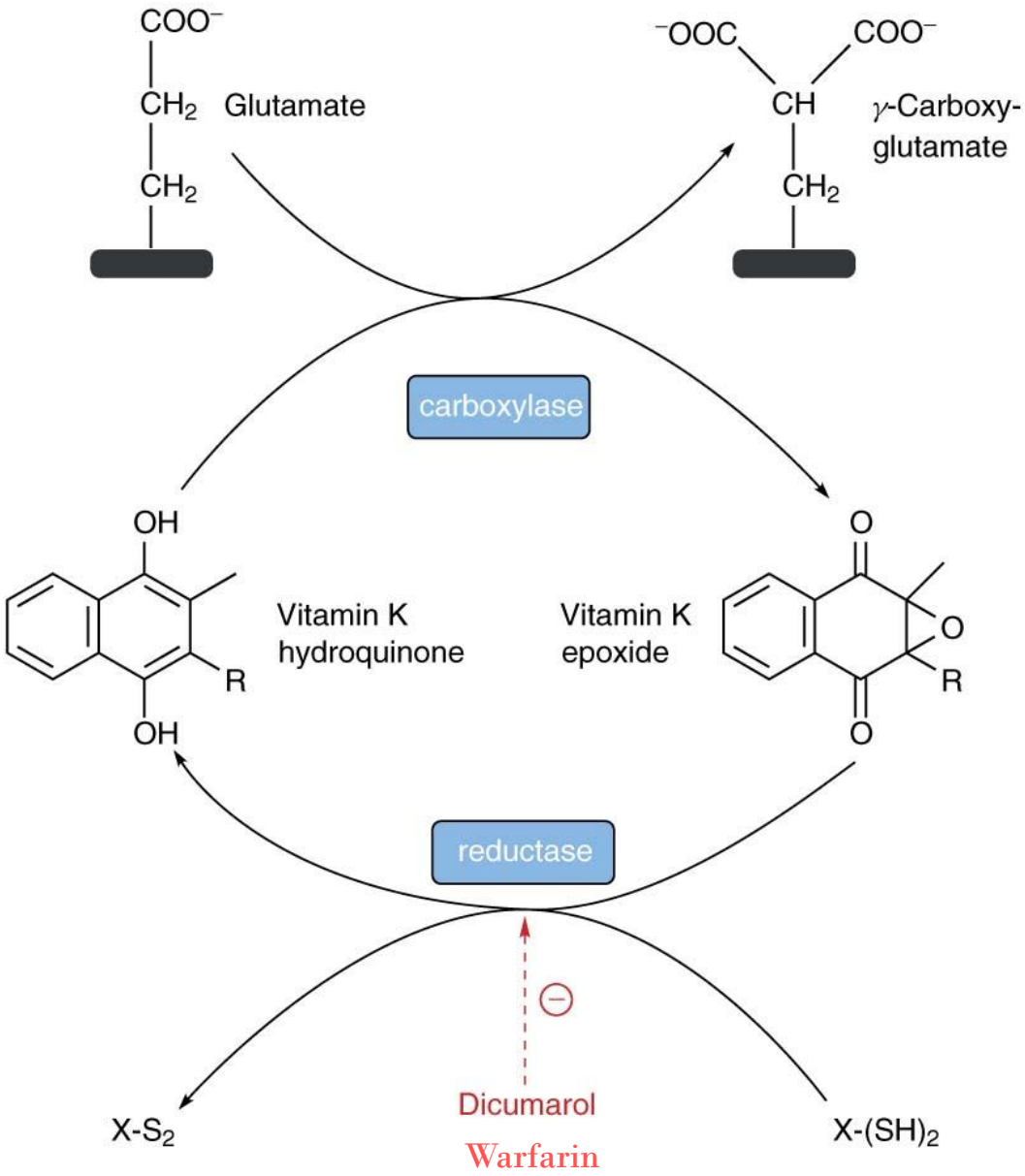


Figure 28.7. Function of Vitamin K.

Functions of Vitamin K

- Mature prothrombin and clotting factors contain γ-carboxyglutamate (Gla) after carboxylation reaction
- Vitamin K is essential for the carboxylase enzyme involved
- Dihydroquinone form of vitamin K is essential for this reaction

Active form

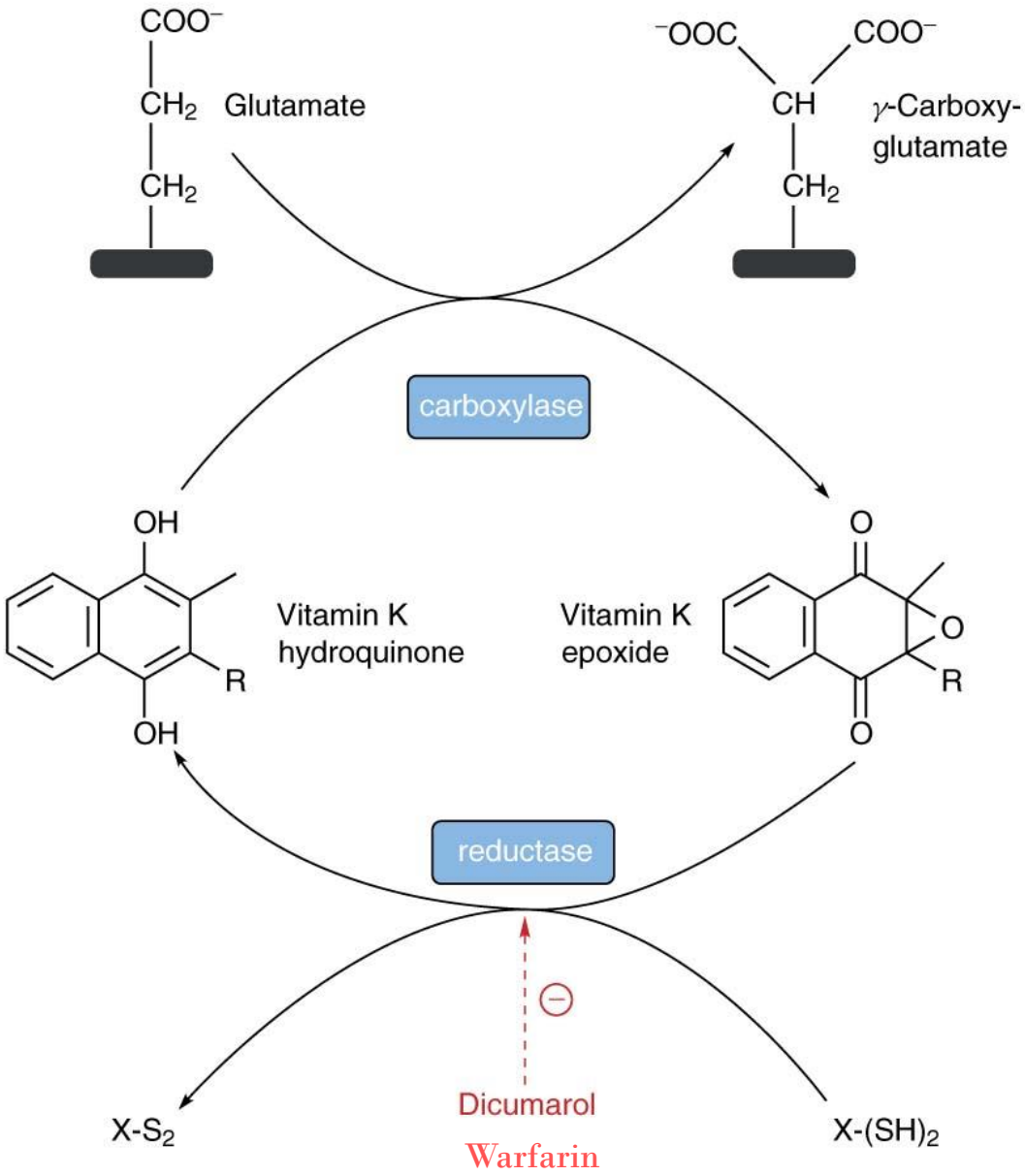
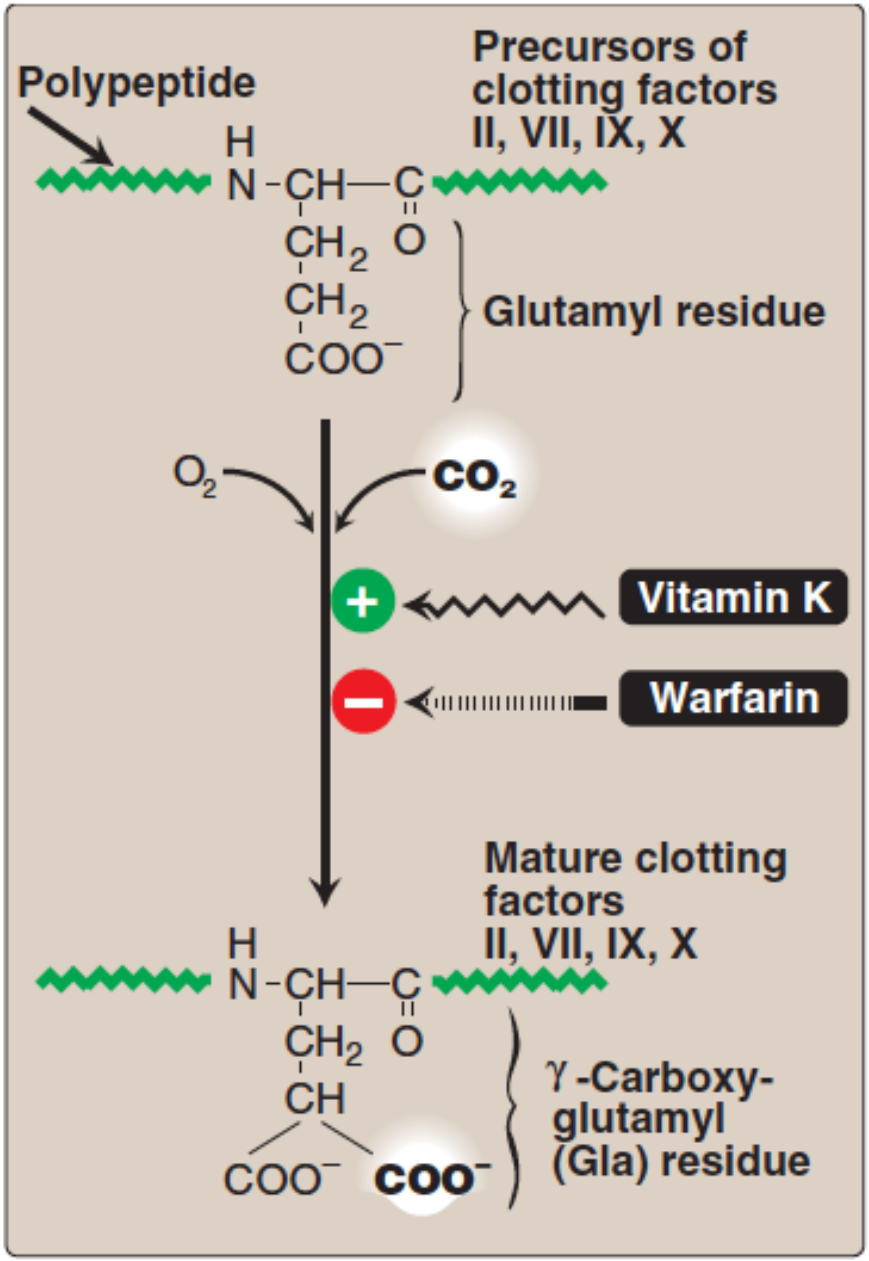


Figure 28.7. Function of Vitamin K.

Analogs of Vitamin K

- Anticoagulant drugs: warfarin and dicoumarol
  - Structural analogs of vitamin K
- They inhibit the activation of vitamin K to hydorquinone form (inhibiting the reductase enzyme)
- Prothrombin and clotting factors are not carboxylated
- Hence blood coagulation time increases upon injury

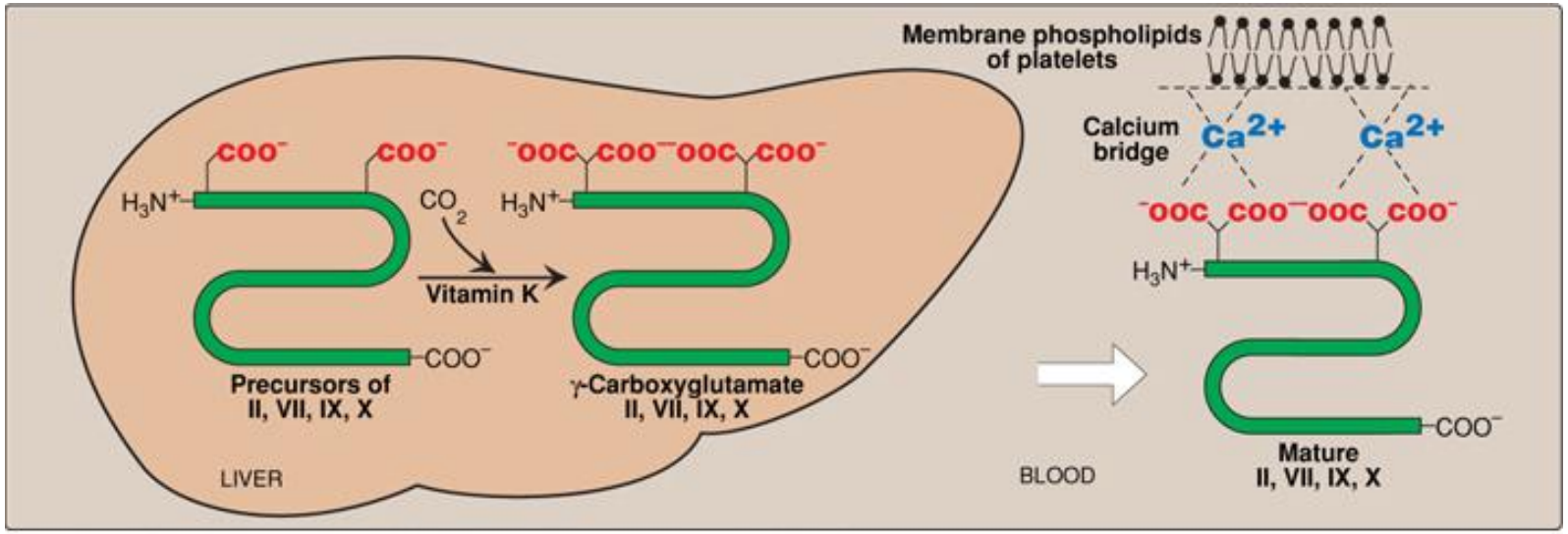
- Carboxylation of glutamate requires vitamin K
- The process is inhibited by **warfarin**

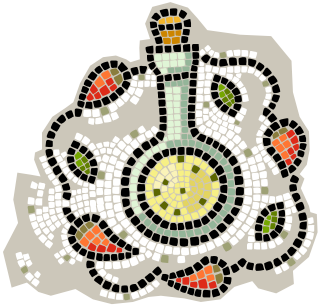


Functions of Vitamin K

- Prothrombin – platelet interaction
  - Carboxylated prothrombin contains two carboxylate groups (COO^-)
  - These groups bind to Ca^{2+}, forming prothrombin-calcium complex
  - The complex then binds to phosholipids on the surface of platelets (important for blood clotting)
  - Converting prothrombin to thrombin and initiating clot formation

Prothrombin – platelet interaction





Functions of Vitamin K

- Synthesis of γ-carboxyglutamate in osteocalcin
  - Osteocalcin is a bone turnover protein
  - Also called Bone Gla Protein (BGP)
  - Involved in bone formation, mineralization and resorption
  - γ-Carboxyglutamate is required for osteocalcin binding to hydroxyapatite (a calcium mineral) in the bone
  - The binding mechanism is similar to that of prothrombin-platelet binding

Deficiency of Vitamin K

- Deficiencies are rare: it is synthesized by intestinal bacteria
- Hypoprothrombinemia: increased blood coagulation time
- Some second-generation cephalosporin drugs cause this condition due to warfarin-like effects (antibiotics given with vit. K)
- May affect bone growth and mineralization
- Lipid malabsorption can lead to vitamin K deficiency

Deficiency of Vitamin K

- Prolonged antibiotic therapy
  - Especially in marginally malnourished individuals (e.g. debilitated geriatric patients)
- Gastrointestinal infections with diarrhea
- Both of the above destroy the bacterial flora leading to vitamin K deficiency

Deficiency of Vitamin K

- Deficiency most common in newborn infants
  - Newborns lack intestinal flora
  - Human milk can provide only 1/5th vitamin K
  - Supplements are given intramuscularly at birth

Clinical Manifestations of the Deficiency

- Hemorrhagic disease of the newborn
- Bruising tendency, ecchymotic patches (bleeding underneath the skin)
- Mucus membrane hemorrhage
- Post-traumatic bleeding / internal bleeding
- Prolonged prothrombin time

Toxicity of Vitamin K

- Prolonged supplementation of large doses of menadione can cause:
  - Hemolytic anemia
  - Jaundice
- Due to toxic effects on RBC membrane

Take home message

- Vitamin K is essential for blood coagulation process
- It mediates the process by γ-carboxylation of glutamic acid residues of prothrombin and coagulation factors

References

- Lippincott's Biochemistry 6th Edition
  Chapter 28, pp. 389-391
  Richard Harvey and Denise Ferrier
  Lippincott Williams & Wilkins, USA

- Textbook of Biochemistry with Clinical Correlations by Thomas M Devlin. 6th Edition
  Chapter 28, pp. 1099-1101