Revised & Approved

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BIOCHEMISTRY TEAM
439

MED439
KING SAUD UNIVERSITY

Biochemistry of vitamin K

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Editing File

Objectives

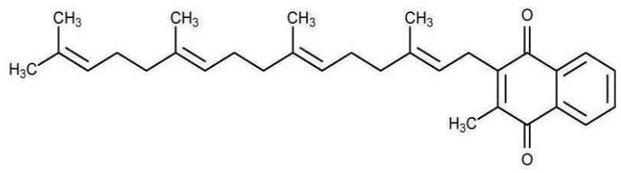
- Identify the types and sources of vitamin K
- Understand the role of vitamin K in blood Coagulation
- Recognize the importance of g-carboxylation of glutamic acid in coagulation proteins
- Understand the role of anticoagulant drugs in affecting vitamin K function
- Discuss the causes and disorders 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 (anticoagulant proteins)
- **Clinical manifestations**
- **Deficiency and disorder**

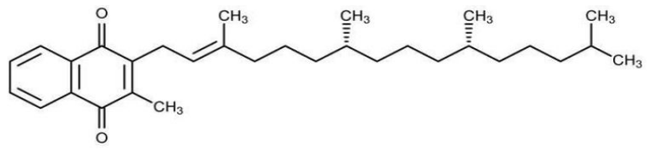
Types & Chemistry of Vitamin K

Occurs in several forms: Same function but different structure



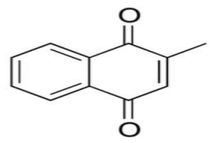
Vitamin K2
(Menaquinone)
Animal sources

1. **Vitamin K1**
(Phylloquinone)
Plant sources

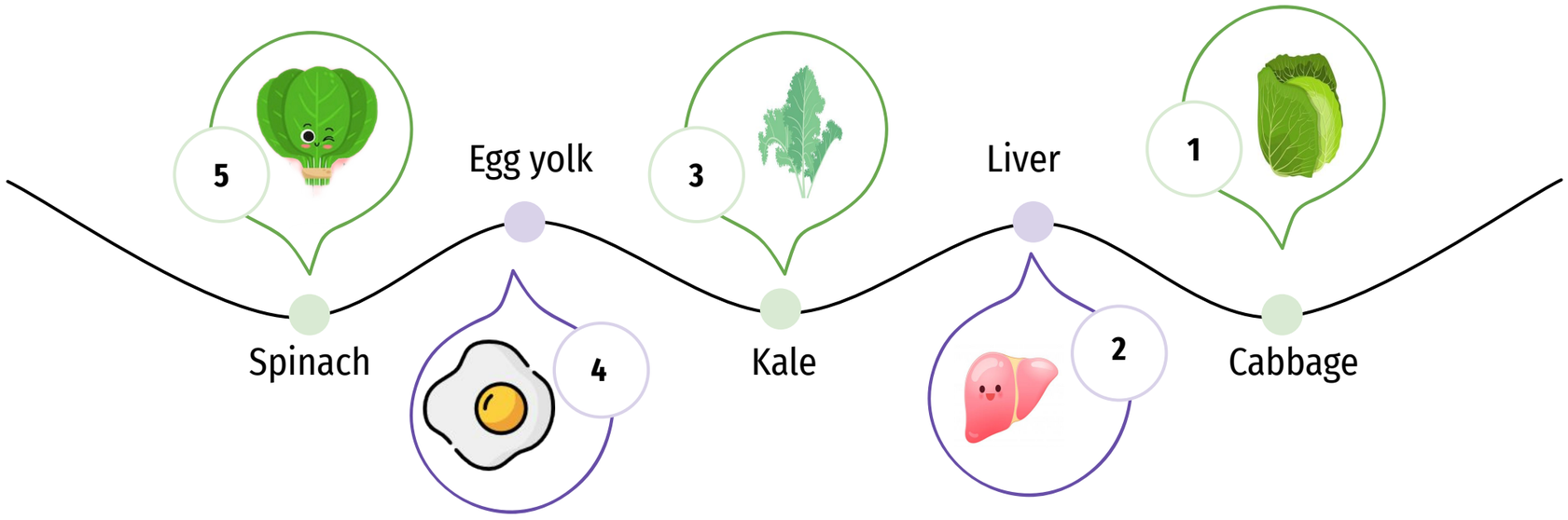


2.

3. **Vitamin K3**
(Menadione)
synthetic form
no long chain !!



Dietary sources



Sources of Vitamin K

Phylloquinone: **Green leafy vegetables**
Phyllo means plant

Menaquinone: **Intestinal bacteria**
Intestinal bacterial synthesis meets the daily requirement of vitamin K even without dietary supplement.

Menadione: **Synthetic form**
A precursor of menaquinone

AI(adequate intake)for Vitamin K (µg/day)

Infant (0-1 year):
(2-2.5)

Children (1-8):
(30-55)

Men (19+):
(120)

Women (19+):
(90)

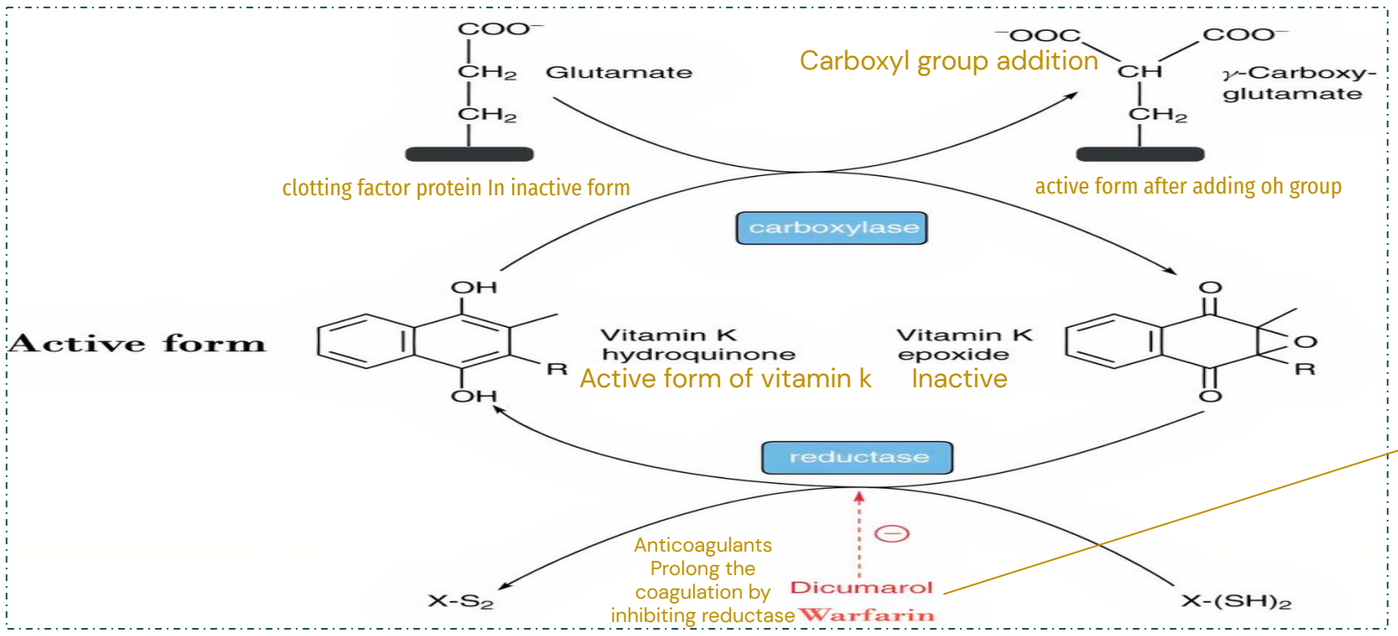
Pregnancy/ lactation:
(90)

Upper limit:
(Not established)

Functions of Vitamin K

- **Coenzyme for the synthesis of prothrombin and blood clotting factors in the liver**
- Prothrombin and other clotting factors are protein in nature
- Synthesis of prothrombin, clotting factors II, VII, IX, X require carboxylation of their glutamic acid (Glu) residue
- Mature prothrombin and clotting factors contain γ-carboxyglutamate (Gla) after carboxylation reaction
- Vitamin K is essential for the carboxylase enzyme involved as coenzyme
- Dihydroquinone form of vitamin K is essential for this reaction

Without carboxylation the clotting factors won't be active



Analogs of Vitamin K

Anticoagulant drugs: warfarin and dicoumarol (Structural analogs of vitamin K)

They inhibit the activation of vitamin K to hydroquinone form (inhibiting the reductase enzyme)

Prothrombin and clotting factors are not carboxylated

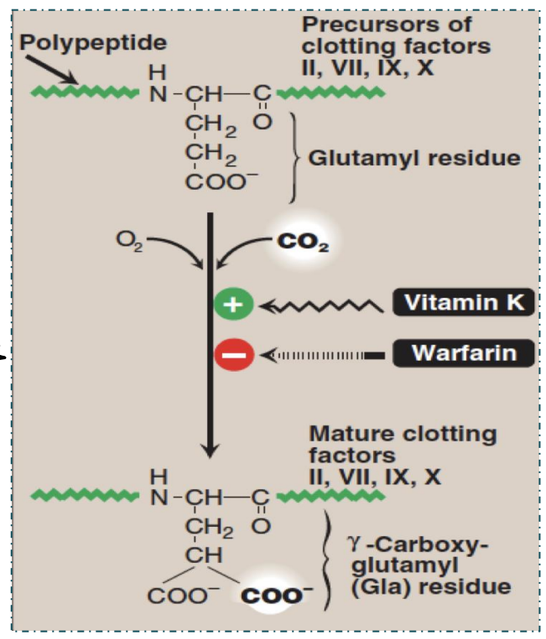
Inactive

Hence blood coagulation time increases upon injury

so bleeding will continue for longer time

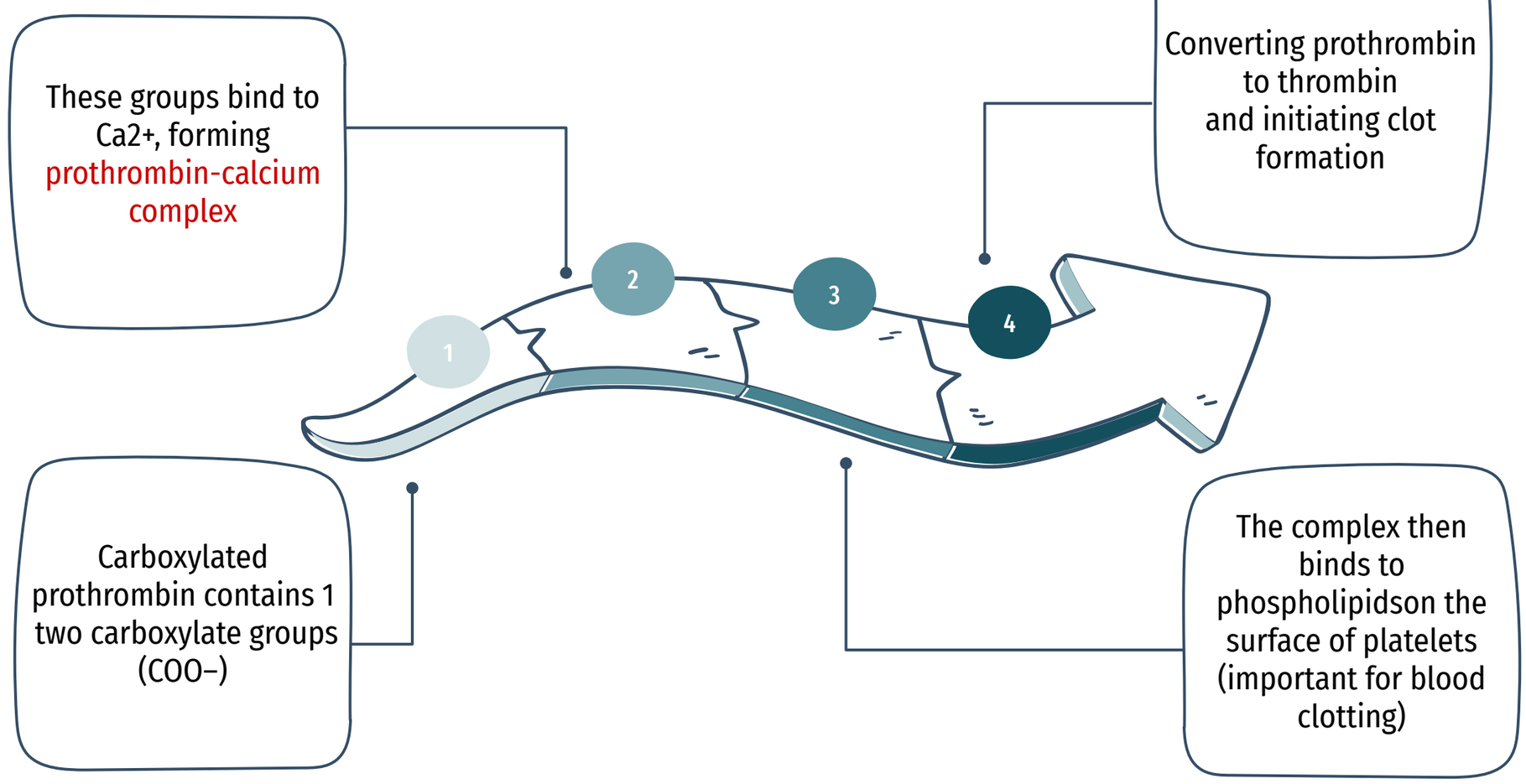
1-Carboxylation of glutamate requires vitamin K

2-The process is inhibited by warfarin



Functions of Vitamin K:

1- Prothrombin – platelet interaction:



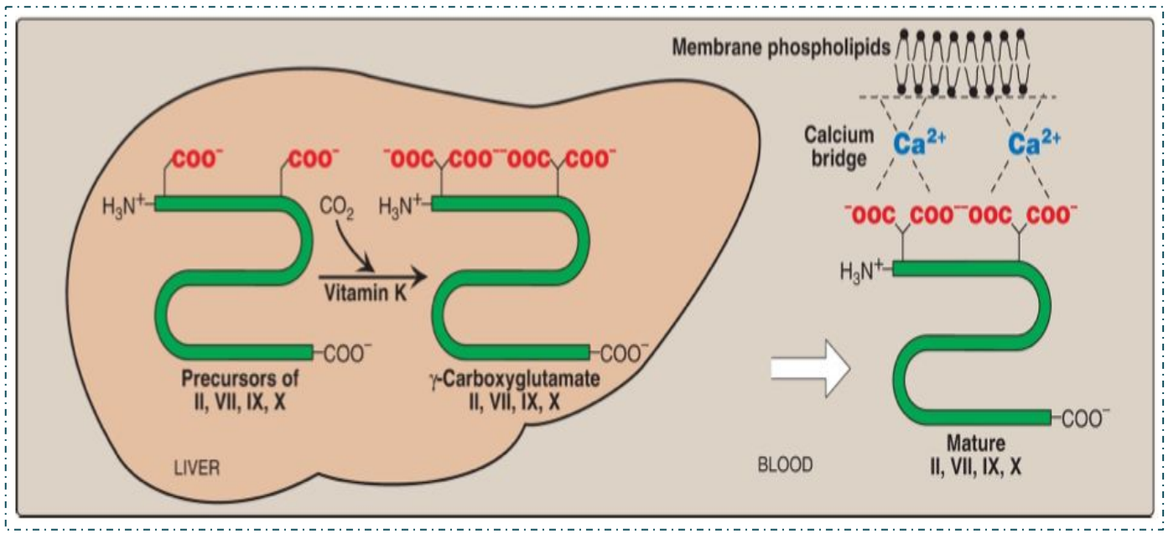
2- Synthesis of γ-carboxyglutamate in osteocalcin:

1- Osteocalcin (Also called Bone Gla Protein “BGP”) is a bone turnover protein

2- Involved in bone formation, mineralization and resorption

3- γ-Carboxyglutamate is required for osteocalcin binding to hydroxyapatite (a calcium mineral) in the bone Details are still unknown but they believe that gamma glu hold ca+ in bone

4- The binding mechanism is similar to that of prothrombin-platelet binding



Dr explanation:

-liver synthesizes all the precursors of prothrombin.
-once the precursors are formed, they’re not in their active form, they contain only one carboxyl group.
-an additional carboxyl group is added by the vitamin k reaction by carboxylase.
-the molecule will have 2 carboxyl groups after the reaction and will go to the circulation and combine with calcium.
-the calcium complex will interact with the membrane phospholipids of the platelets.

Dr question: why add one more carboxyl group? Because the valency of calcium is 2 so it can bind to 2 cooh (to complete the calcium binding)

Deficiency of Vitamin K

◎ Deficiencies are rare: Vitamin k is synthesized by intestinal bacteria and stored in the liver

Causes of vit K deficiency

1-Lipid malabsorption can lead to vitamin K deficiency

2-Some second-generation cephalosporin drugs for long time cause this condition due to warfarin-like effects (antibiotics given with vit. K) They also reduce the normal flora

3-Prolonged antibiotic therapy Especially in marginally malnourished individuals (eg debilitated geriatric patients)

4-Gastrointestinal infections with diarrhea

5- Both of the above destroy the bacterial flora leading to vitamin K deficiency

Deficiency most common in newborn infants

1-Newborns lack intestinal flora There gut is sterile

2-Human milk can provide Newborns lack intestinal flora only 1/5th vitamin K

3-Supplements are given intramuscularly at birth

Effects of Vit K deficiency

1-Hypoprothrombinemia: ↑ blood coagulation time

2-Bone growth and mineralization

Clinical Manifestations of the Deficiency

1-Mucus membrane hemorrhage

2-Hemorrhagic disease of the newborn

3-Post-traumatic bleeding / internal bleeding

4-Bruising tendency, ecchymotic patches (bleeding underneath the skin) cause skin discoloration

5-Prolonged prothrombin time

Toxicity of Vitamin K

Prolonged supplementation of large doses of menadione can cause:
Hemolytic anemia or **Jaundice**

↘

Due to toxic effects on RBC membrane

Take Home Messages

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

Summary

Vitamin K	
Types	K1 (Phylloquinone) K2 (Menaquinone) K3 (Menadione)
Function	Coenzyme for the synthesis of proteins in the liver: Prothrombin and Blood clotting factors by carboxylation of (Glu) into (Gla) which needs dihydroquinone form of Vit K. Warfarin inhibits reductase (no dihydroquinone formation) Synthesis of (Gla) γ-carboxyglutamate for osteocalcin to bind with hydroxyapatite. Carboxylated Prothrombin + Ca2+ > phospholipids on surface of platelets: (Important for clotting)
Deficiency	-Lipid malabsorption - 2nd Gen cephalosporins (given antibiotic + vit k due to warfarin-like effects) - Prolonged antibiotic therapy - GI Infections with diarrhea - last two destroy normal flora → Vit k deficiency because Vit k is synthesized by intestinal bacteria (normal flora)
Clinical Manifestations	1-Mucus membrane hemorrhage. 2-Hemorrhagic disease of the newborn. 3-Post-traumatic bleeding / internal bleeding. 4-Bruising tendency, ecchymotic patches (bleeding underneath the skin) 5-Prolonged prothrombin time.
Toxicity	1-Prolonged supplementation of large doses of menadione can cause: -**Hemolytic anemia or Jaundice.** 2-Due to toxic effects on RBC membrane

MCQs

1- Which ONE of the following is synthetic form of Vitamin K?			
A- Dihydroquinone	B- Phylloquinone	C- Menaquinone	D- Menadione
2- What is the RDA of Vitamin K for children? (µg/day)			
A- (2-2.5)	B- (30-55)	C- (90)	D- (120)
3- Vitamin K is Coenzyme for the synthesis of prothrombin and blood clotting factors in?			
A- Kidney	B- Pancreas	C- Spleen	D- Liver
4-Toxicity of vitamin K cause which one of the following?			
A-iron overload.	B- Hemolytic anemia	C-associated with splenomegaly	D-ankle ulcers.
5- The form of vitamin K that is required for activation of clotting factors is:			
A- diHydroquinone	B-Phylloquinone	C-Menadione	D-Menaquinone
6-Which one of the following required for osteocalcin binding to hydroxyapatite (a calcium mineral) in the bone?			
A-alpha-Carboxyglutamate	B-carboxylase	C-γ-Carboxyglutamate	D-Dihydroquinone

Answers key

1- D 2- B 3- D 4- B 5- A 6- C

SAQs

1- List 4 dietary sources of Vitamin K?

Cabbage, Kale, Spinach, Egg yolk, Liver.

2- Mention the types of Vitamin K?

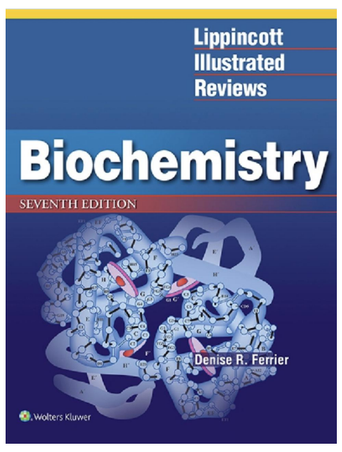
- Vitamin K1 (Phylloquinone)
- Vitamin K2 (Menaquinone)
- Vitamin K3 (Menadione)

3- Write 3 causes of Vit K deficiency

-Prolonged antibiotic therapy , lipid malabsorption , destroy the bacterial flora

Resources

Click on the book to download the resource



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