VITAMIN K

**History**

- Existence – first suggested by Henrik Dam in 1929
  - Observed: ‘Hemorrhagic disease’ of cattle fed on synthetic diets
- 1939: Dam & co-workers isolated ‘Vitamin K’ from the plant ‘Alfalfa’
- Edward Doisy & associates: isolated another factor in the same year from fish – ‘Vitamin K₂’
  - Different in structure but similar in properties
- Both Dam & Doisy were awarded Nobel prize in the year 1943
Nomenclature

- Vitamin K was originally named as ‘Koagulation factor’ - important role in ‘coagulation process’
  - Later abbreviated as ‘K’
- Different compounds with Vitamin K activity were isolated from different sources
  - Vitamin \( K_1 \) : Phylloquinone
    - present in most edible vegetables
  - Vitamin \( K_2 \) : Menaquinone
    - present in fish & produced by intestinal bacteria
  - Vitamin \( K_3 \) : Menadione
    - All compounds are structurally related to this simpler compound.
Chemistry

- All the three compounds are ‘Naphthoquinone’ derivatives

- Vitamin K₁ : 2 – methyl 3– phytyl 1,4 – naphthoquinone
  with a 20 carbon isoprenoid side chain
  - also called as ‘Mephyton’

- Vitamin K₂ : 2 – methyl 3 – phytyl 1,4 – naphthoquinone
  with 30 / 35 / 45 carbon isoprenoid side chain
  - also called as ‘Farnoquinone’

- Vitamin K₃ : 2 – methyl 3 – phytyl 1,4– naphthoquinone
- All the three are stable to heat.
- Their activity is lost by-
  - oxidizing agents
  - irradiation,
  - strong acids & alkalis.
Absorption, Storage, Transport & Excretion

- Vitamin K is absorbed along with other fats in the presence of bile salts.
- It is transported as chylomicrons.
- Unabsorbed Vitamin K may be acted upon by the intestinal bacteria and forms ‘Menadione’.
- Menadione is absorbed directly from the large intestine & is later converted in the body to ‘menaquinone’.
- Absorbed Vitamin K is stored in liver and is transported in plasma along with β-lipoproteins.
Sources

🌟 Vitamin K₁ – Green leafy vegetables, alfalfa, spinach, cauliflower, cabbage, soybeans & tomatoes
🌟 Vitamin K₂ – fish, egg yolk, meat, liver & product of normal intestinal flora
🌟 Cow’s milk contains good amount of Vitamin K as compared to Breast milk
Recommended Dietary Allowance

1 µg / Kg body weight

Adults: 50 – 100 µg / day

- Dietary requirement is not of much importance in adults
- Under normal circumstances, Vitamin K is provided by the intestinal flora itself
Functions

1. Coagulation of blood

Main function: Promotion of coagulation of blood by helping in post-translational modification of clotting factors

Vitamin K dependent clotting factors: II(prothrombin), VII(SPCA), IX(Christmas factor) & X(Stuart-Prower factor)

Vitamin K acts at the ribosomal level, combining with a regulatory protein → helps in synthesis of clotting factors
Coagulation function (Contd)

Mechanism of action:

- Vitamin K acts as a co-enzyme in the $\gamma$-carboxy glutamic acid synthesis
- Vitamin K undergoes a cycle in the process of $\gamma$-carboxy glutamic acid formation
- Vitamin K is first converted to its ‘Hydroquinone’ form (Reduced) in the liver microsomes by the enzyme ‘Vitamin K reductase’ requiring NADPH
Mechanism of action (Contd)

- Reduced Vitamin K utilises CO₂ and incorporates it as an additional COOH group at the γ - carbon of glutamic acid in presence of O₂ forming ‘γ - carboxy glutamic acid’

- Meanwhile, Hydroquinone form gets transformed into ‘2,3-epoxide’

- 2,3 – epoxide is then oxidised back to Vitamin K by the microsomal enzyme ‘Epoxide reductase’
- Lipoic acid is converted into dehydrolipoic acid
- Reaction is inhibited by anticoagulants ‘Dicumoral’ & ‘Warfarin’
Polypeptide

Precursors of clotting factors II, VII, IX, X

Glutamyl residue

O₂

CO₂

Vitamin K

Warfarin

Mature clotting factors II, VII, IX, X

γ-Carboxyglutamyl (Gla) residue
(Protein)-Glu \rightarrow \text{Carboxylase} \rightarrow (Protein)-Gla

Vitamin K (hydroquinone form) \rightarrow \text{Reductase} \rightarrow \text{Dicumarol, warfarin}

2, 3-Epoxide form \rightarrow \text{Reductase} \rightarrow \text{Quinone form}
Functions (Contd)

γ-carboxyl residues formed allows chelation of calcium in a specific protein-calcium-phospholipid interaction, thus enhancing blood coagulation

2. Formation of other calcium binding proteins
   - Vitamin K similarly γ-carboxylates specific glutamate residues of calcium binding proteins such as c-reactive protein, osteocalcin of bone & structural proteins of kidney, spleen, lungs & placenta

3. Role in oxidative phosphorylation
   - Vitamin K is necessary as a cofactor in oxidative phosphorylation being associated with mitochondrial lipids
Deficiency Manifestations

Normal Adults – Vitamin K deficiency is rarely seen
- Intestinal bacteria provides sufficient Vitamin K needed to the body

Vitamin K deficiency occurs due to –
- Malabsorption of fats due to bile salt deficiency
- GI infections like tropical sprue & chronic diarrhea
- Use of antimicrobial drugs which temporarily eliminates intestinal flora
- Anticoagulant agents such as dicumoral & warfarin
- New born infants, esp preterm infants
Deficiency (Contd)

Vitamin K deficiency causes ‘Hemorrhagic disease of the newborn’

Newborn infants are susceptible to Vitamin K deficiency because of –
- low levels of several clotting factors
- minimal stores of Vitamin K
- lack of established intestinal flora
- limited dietary intake

Symptoms include: easy bruising, echymotic patches, mucosal hemorrhage, profuse post-traumatic bleeding & gastro-intestinal bleeding
Deficiency (Contd)

Star Prolonged prothrombin time & delayed clotting time is characteristic of Vitamin K deficiency

Star All newborn infants should receive Vitamin K prophylactically irrespective of deficiency present or not

- A single dose of 0.5 – 1.0 mg of water miscible form of Vitamin K1 is given intramuscularly at birth

Star Vitamin K1 is free from adverse effects, safe in pregnancy & neonates and more effective than other Vitamin K active compounds
Hypervitaminosis K

- Hypervitaminosis K can be produced by administration of large doses of Vitamin K
- Symptoms include hemolysis, hyperbilirubinemia, kernicterus & brain damage
- Treatment includes carefully monitored use of anticoagulants with fresh blood transfusion
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