Nafith Abu Tarboush
DDS, MSc, PhD
natarboush@ju.edu.jo
www.facebook.com/natarboush

Vitamins

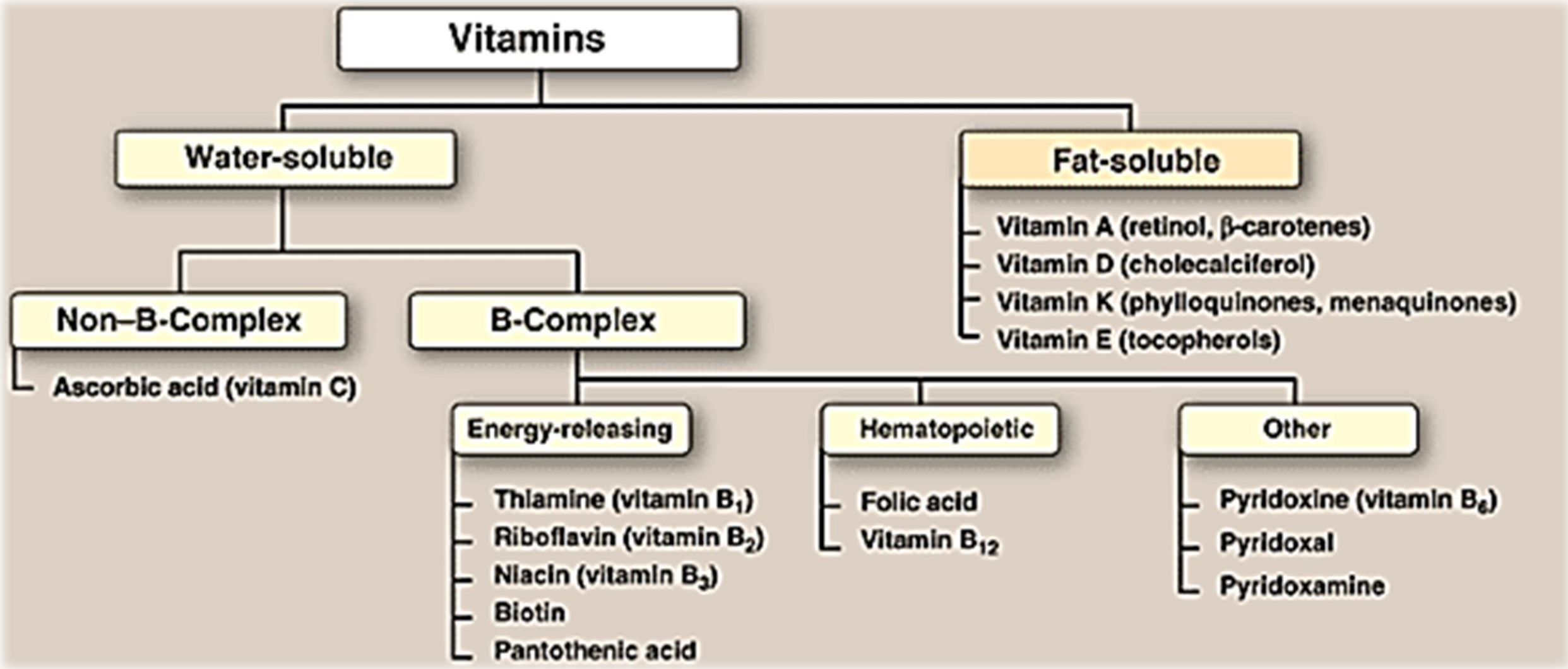
Vitamins

- Organic compounds required by an organism in tiny amounts as a vital nutrient
- Cannot be synthesized in sufficient quantities, & must be obtained from diet
- The term is conditional both on the circumstances & on the particular organism (ascorbic acid, humans, other animals) (vitamin D, human diet)
- Thirteen vitamins are universally recognized at present

Vitamins

- Vitamins have diverse biochemical functions:
  - Hormone-like functions (regulators): regulators of mineral metabolism (e.g., vitamin D), or regulators of cell & tissue growth & differentiation (e.g., vitamin A)
  - Anti-oxidants (e.g., vitamins E & C)
  - Precursors for enzyme cofactors (vitamin B subclasses)

Classification

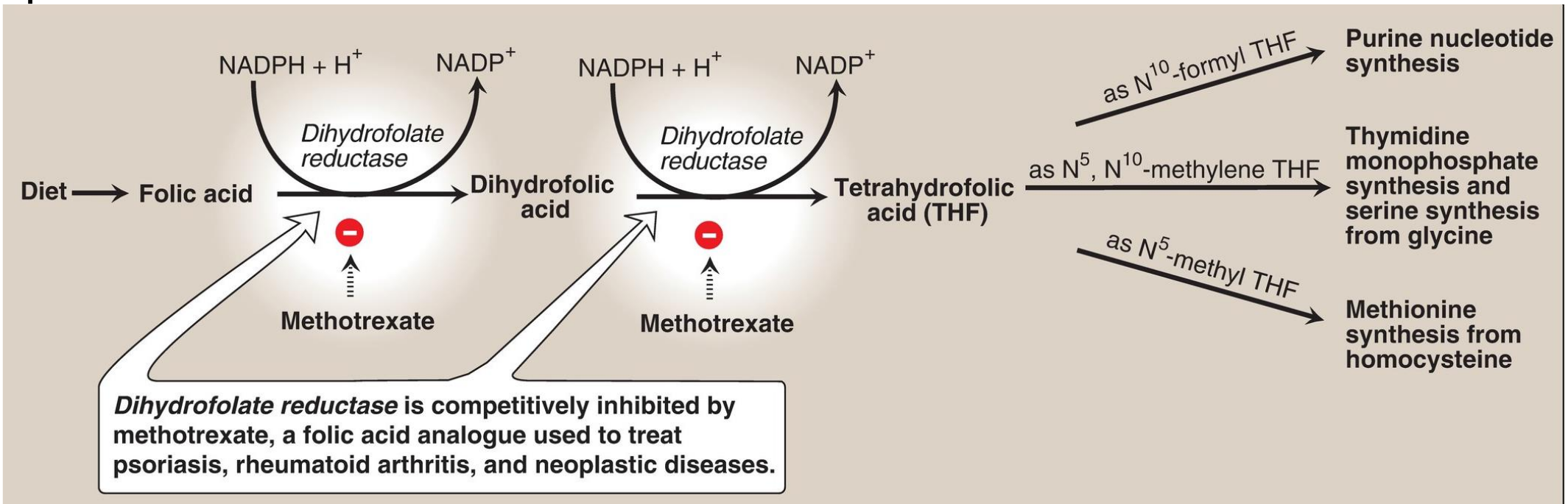


FOLIC ACID (VITAMIN B9) – Folate

- Plays a key role in one-carbon metabolism
- Folic acid deficiency is probably the most common vitamin deficiency, particularly among pregnant women and individuals with alcoholism
- Leafy, dark green vegetables are a good source of folic acid

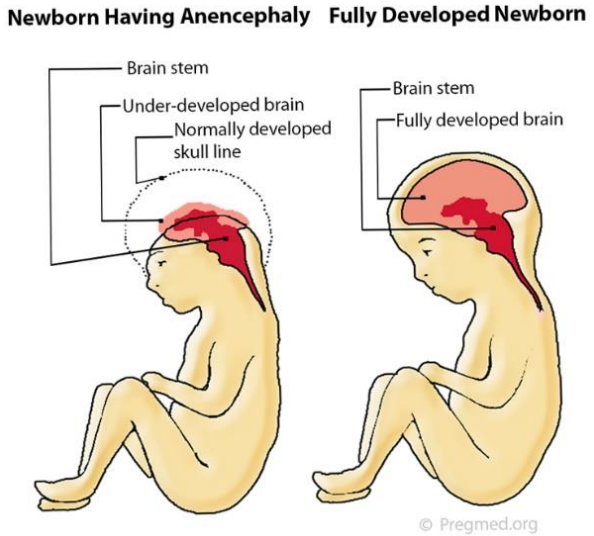
Function

- Tetrahydrofolate (THF), the reduced, coenzyme form of folate
- Receives one-carbon fragments from donors as serine, glycine, and histidine
- Transfers them to intermediates in the synthesis of amino acids, purine nucleotides, and thymidine monophosphate (TMP), a pyrimidine nucleotide incorporated into DNA.



Folate and anemia

- Causes of deficiency:
  - Increased demand (pregnancy and lactation)
  - Poor absorption (pathology or alcoholism)
  - Drugs (methotrexate)
  - Folate-free diet (few weeks)



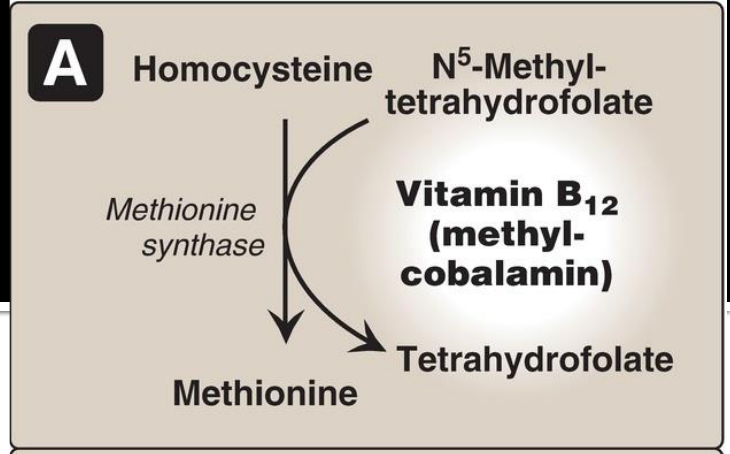
- Might result in:
  - Neural tube defects (NTD): Spina bifida and anencephaly
  - affect ~3,000 pregnancies in the US annually

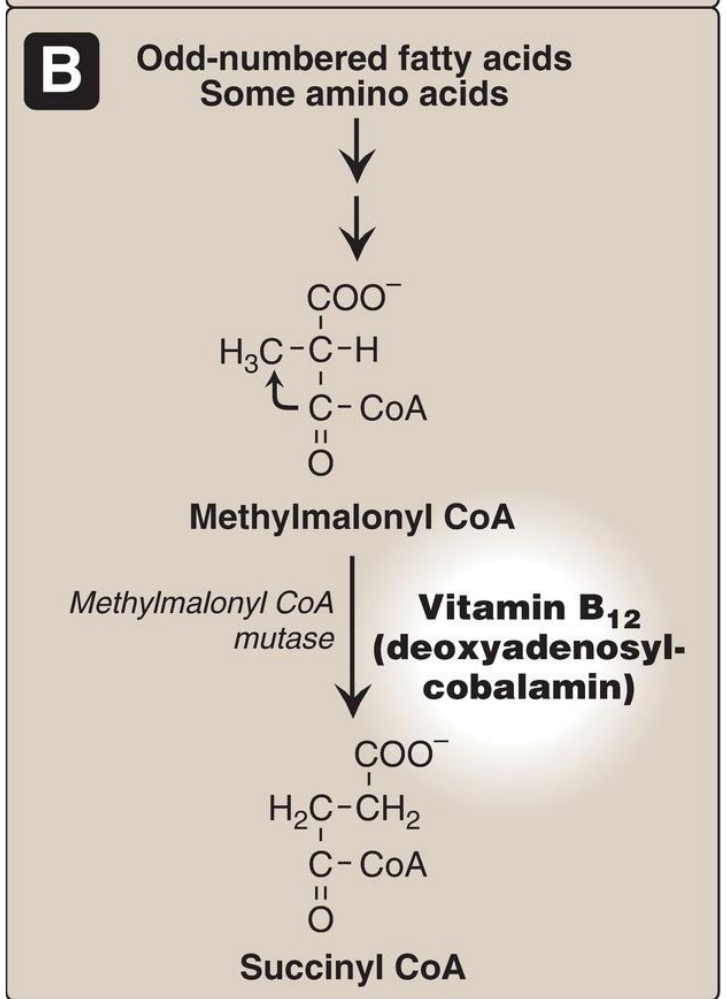
Accordingly

- Folic acid supplementation before conception and during the first trimester
- All women of childbearing age (400 µg/day) of folic acid to reduce the risk, 10 times if a previous pregnancy was affected
- In the U.S., addition of folic acid to wheat flour and enriched grain products, resulting in a dietary supplementation of ~0.1 mg/day
- This supplementation allows ~50% of all reproductive-aged women to receive 0.4 mg of folate from all sources

COBALAMIN (VITAMIN B12)

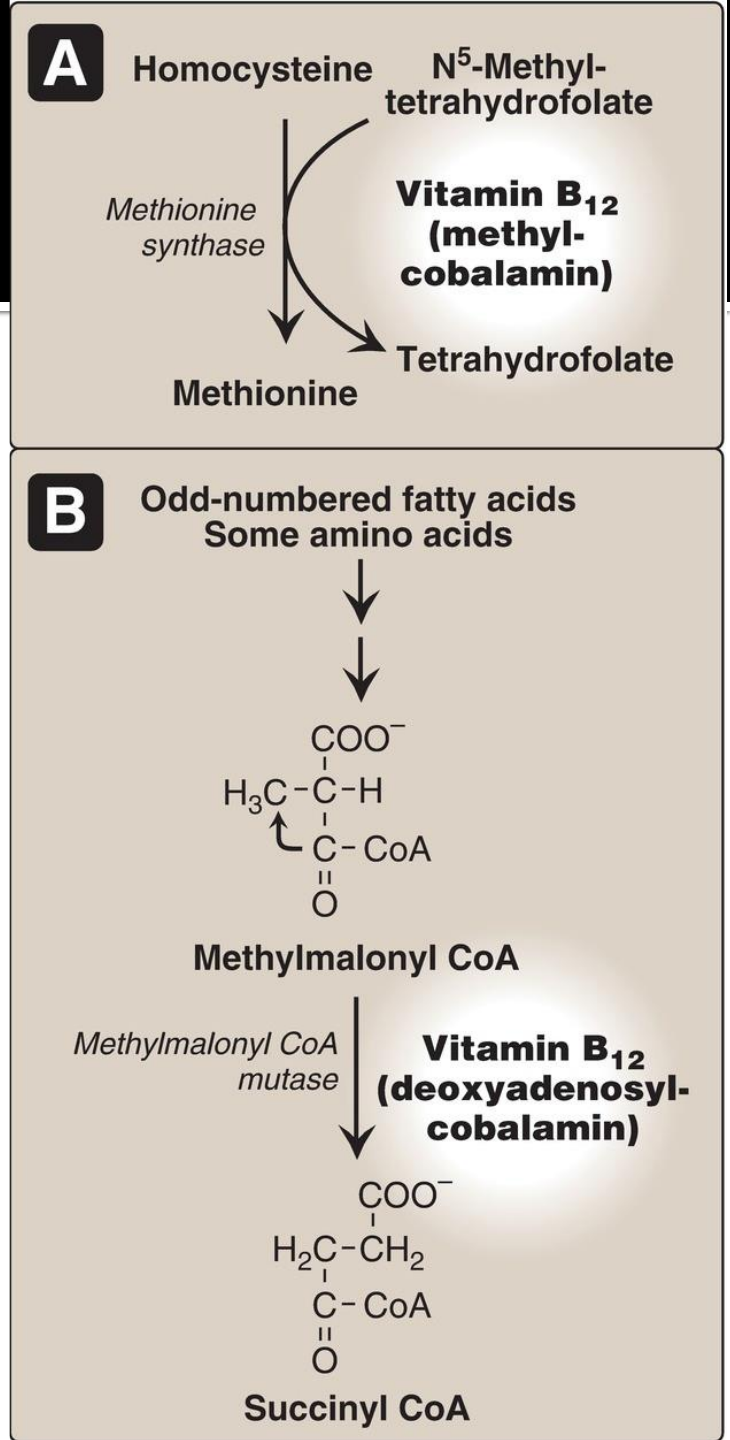
- Required for two essential enzymatic reactions
  - Remethylation of homocysteine (Hcy) to methionine
  - Isomerization of methylmalonyl coenzyme A (CoA), which is produced during the degradation of some amino acids (isoleucine, valine, threonine, and methionine) and fatty acids (FA) with odd numbers of carbon atoms





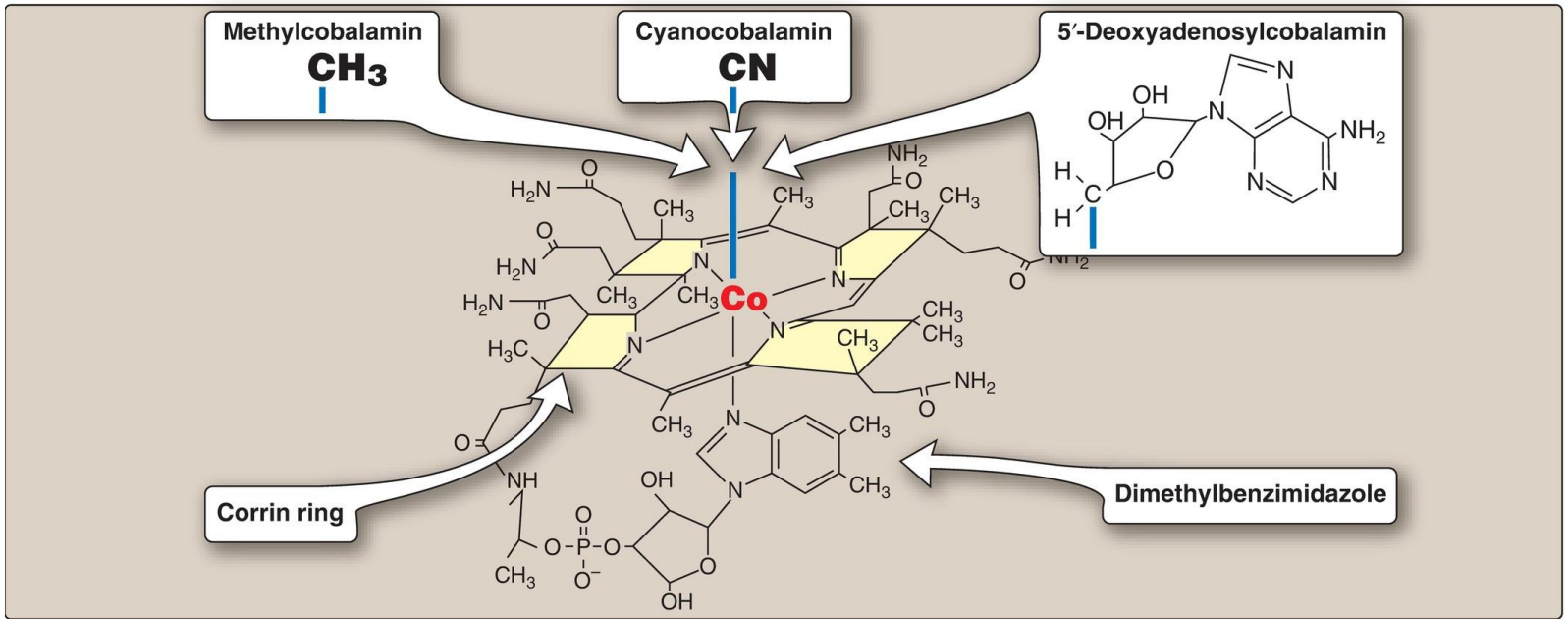
COBALAMIN (VITAMIN B12)

- When cobalamin is deficient, unusual (branched) FA accumulate and become incorporated into cell membranes, including those of the central nervous system (CNS)
- This may account for some of the neurologic manifestations of vitamin B12 deficiency
- Folic acid (as N5-methyl THF) is also required in the remethylation of Hcy. Therefore, deficiency of B12 or folate results in elevated Hcy levels



Structure and coenzyme forms

- A "corrin" ring system vs. Porphyrin (Cobalt)
- The remaining coordination: nitrogen of 5,6-dimethylbenzimidazole and with cyanide in commercial preparations (cyanocobalamin)
- The physiologic coenzyme are:
  - 5′-deoxyadenosylcobalamin
  - Methylcobalamin

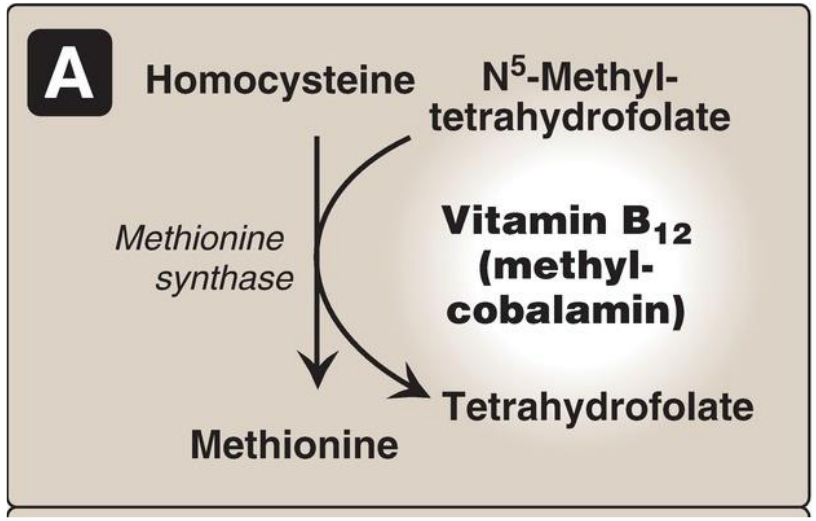


Distribution

- Vitamin B12 is synthesized only by microorganisms, and it is not present in plants
- Animals obtain the vitamin preformed from their intestinal microbiota or by eating foods derived from other animals
- Cobalamin is present in appreciable amounts in liver, red meat, fish, eggs, dairy products, and fortified cereals

Folate trap hypothesis

- Effects of cobalamin deficiency are most pronounced in rapidly dividing cells, such as the erythropoietic tissue of bone marrow and the mucosal cells of the intestine
- Such tissues need both the N5,N10-methylene and N10-formyl forms of THF for the synthesis of nucleotides required for DNA replication
- However, in vitamin B12 deficiency, the utilization of the N5-methyl form of THF is impaired - accumulates
- Deficiency of THF forms needed in purine and TMP synthesis, resulting in megaloblastic anemia

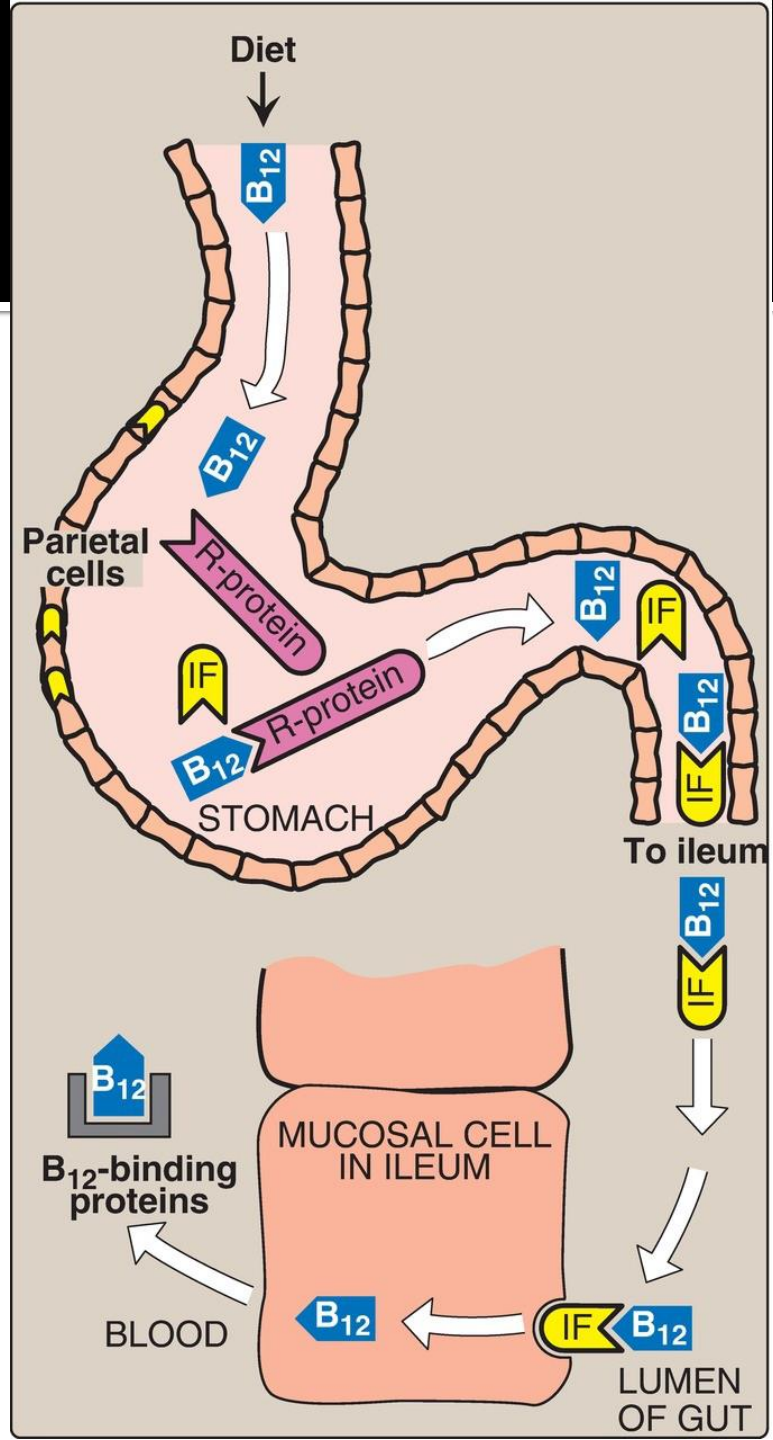


Clinical indications for cobalamin

- In contrast to WS vitamins, significant amounts (2–5 mg) of vitamin B12 are stored in the body
- May take several years for clinical symptoms to develop
- Deficiency happens much more quickly (in months) if absorption is impaired

Pernicious anemia

- Severe malabsorption of vitamin B12 leads to pernicious anemia
- Most commonly a result of an autoimmune destruction of the gastric parietal cells that are responsible for the synthesis of IF
- Impaired absorption
- Intestine ⟶ complexed to intrinsic factor (IF, a glycoprotein) ⟶ cubilin (receptor) ⟶ circulation (transcobalamin)
- Malabsorption in the elderly (achlorhydria)
- Individuals with cobalamin deficiency are usually anemic (folate recycling is impaired)

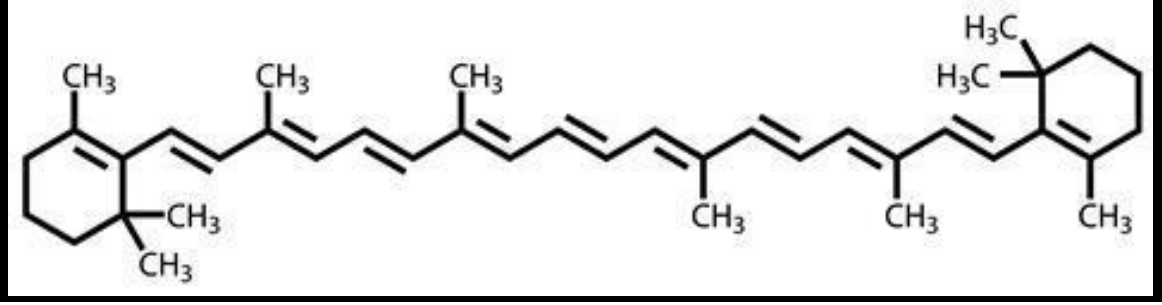


Fat soluble vitamins

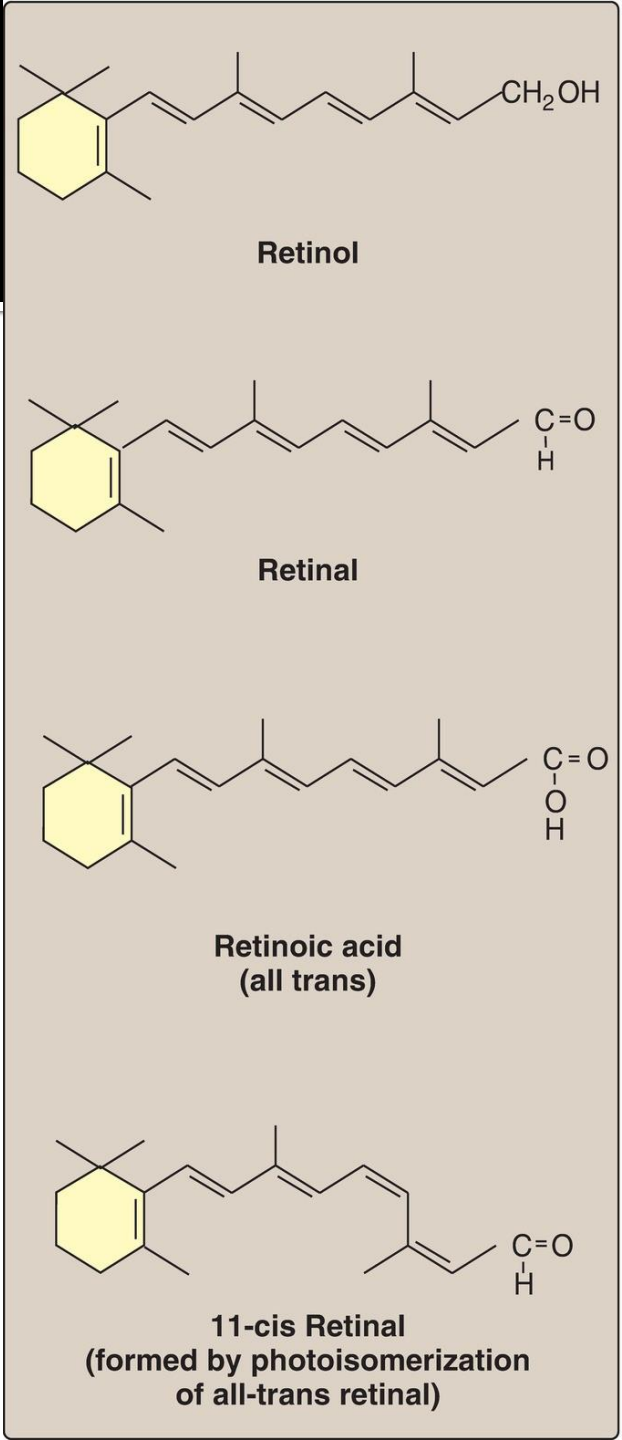
Vitamin	Main function	Deficiency
A	Roles in vision, growth, reproduction	Night blindness, cornea damage
D	Regulation of Ca^{+2} & phosphate metabolism	Rickets (children), Osteomalacia (adults)
E	Antioxidant	RBCs fragility
K	Blood coagulation	Subdermal hemorrhaging

All fat-soluble vitamins are groups and carried in chylomicrons

Vitamin A

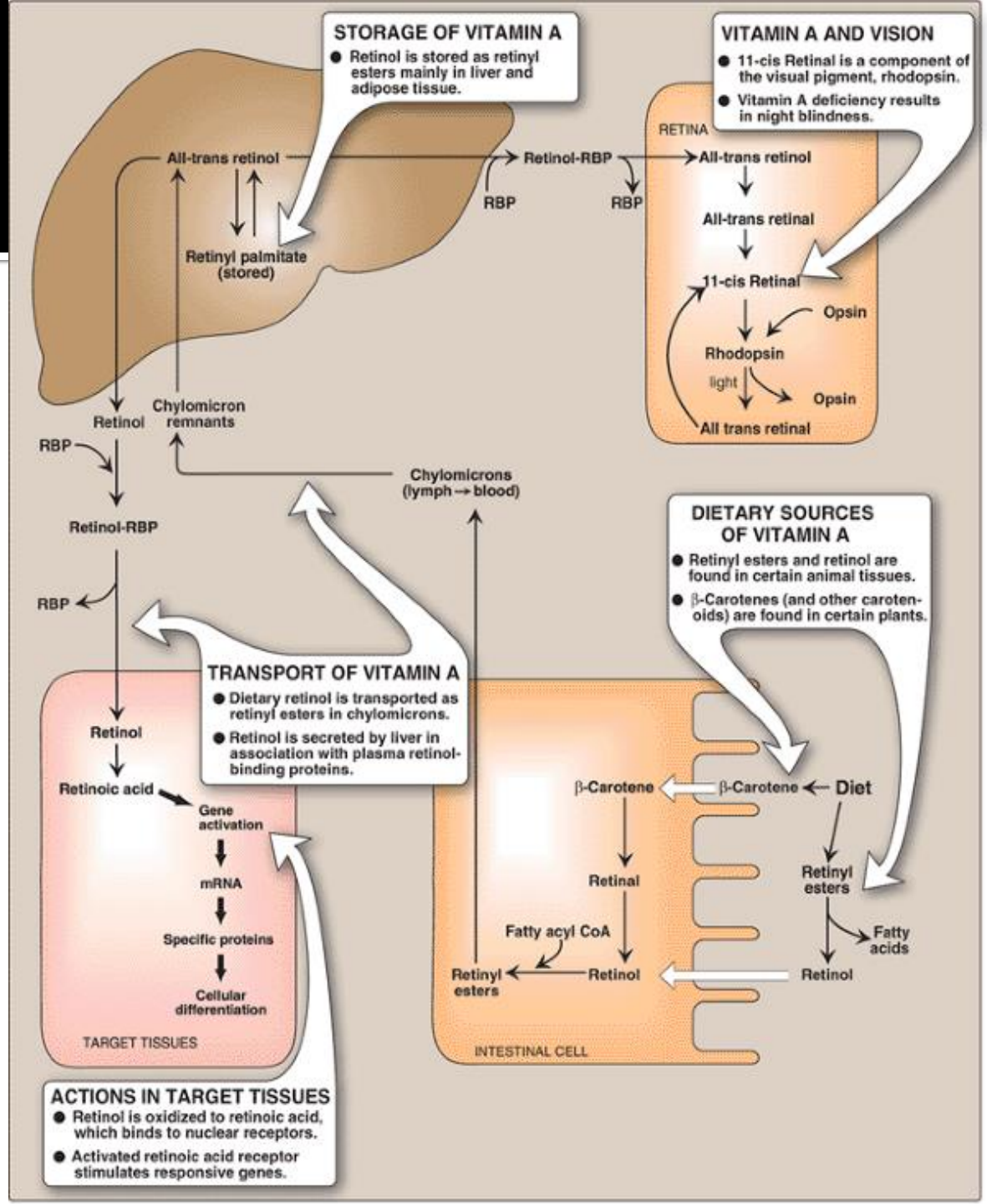


- The retinoids, a family of molecules essential for vision, growth, reproduction, & maintenance of epithelial tissues
- Retinal and retinol are inter-convertible
- β-Carotene: oxidatively cleaved in the intestines to yield 2 molecules of retinal
- Retinoic acid, mediates most of the actions of the retinoids, except for vision and spermatogenesis



Absorption & transport

- ✓ Retinyl esters, intestinal mucosa, retinol
- ✓ Carotenes, retinal, retinol
- ✓ Chylomicrons, lymphatic system, liver (storage)
- ✓ Release from the liver: retinol binds the plasma retinol-binding protein (RBP) complexed with transthyretin
- ✓ Cellular RBP → nuclear receptors (steroids), RNA, proteins (keratin expression)



Visual cycle

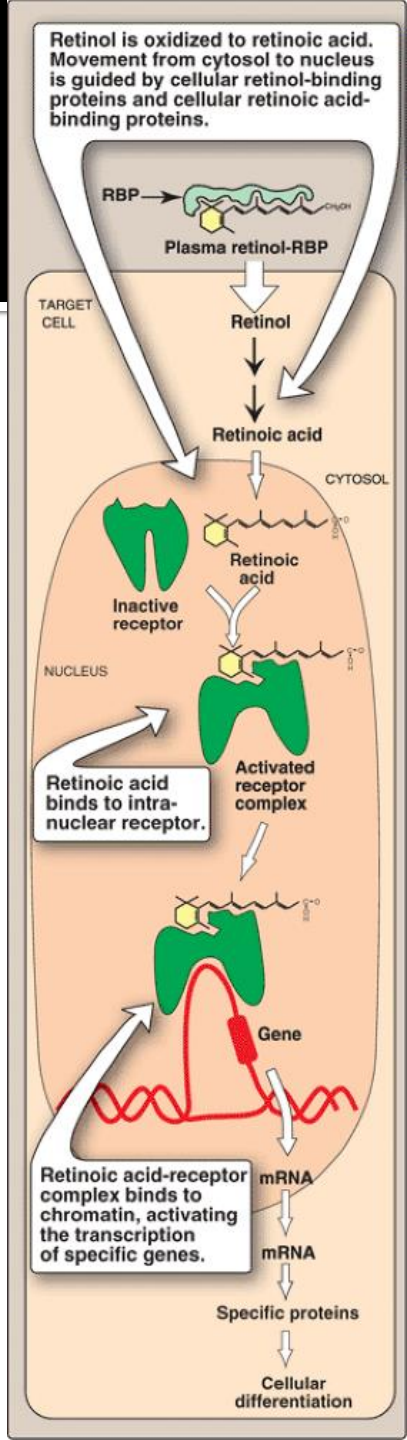
- When rhodopsin, a G protein–coupled receptor, is exposed to light, a series of photochemical isomerizations occurs, which results in the bleaching of rhodopsin and release of all-trans retinal and opsin
- This process activates the G protein transducin, triggering a nerve impulse that is transmitted by the optic nerve

Functions of vitamin A

- ✓ Reproduction: Retinol and retinal (not retinoic acid) are essential for spermatogenesis in the male and preventing fetal resorption in the female
- ✓ Growth (retinoic acid): Vitamin A deficiency results in a decreased (growth rate & bone development) in children
- ✓ Maintenance of epithelial cells (retinoic acid): Vitamin A is essential for normal differentiation of epithelial tissues & mucus secretion
- ✓ Animals given vitamin A only as retinoic acid from birth are blind and sterile

Retinoic acid mechanism of action

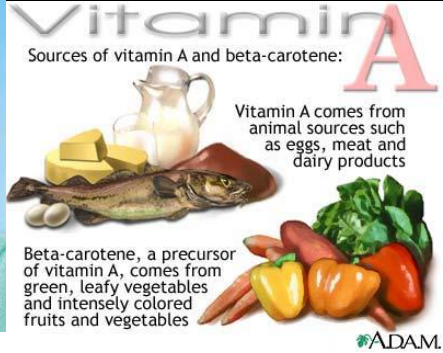
- Binds with high affinity [RAR] - nucleus of target tissues such as epithelial cells
- Activated complex binds to response elements on DNA and recruits activators or repressors to regulate retinoid-specific RNA synthesis
- Retinoids control the expression of the gene for keratin in most epithelial tissues of the body
- RAR proteins are part of the superfamily of transcriptional regulators that includes the nuclear receptors for steroid and thyroid hormones and vitamin D (similar way of function)



Distribution & Requirements

- Liver, kidney, cream, butter, and egg yolk are good sources of preformed vitamin A
- Yellow, orange, and dark-green vegetables and fruits are good sources of the carotenes (provitamin A)
- RDA for adults is 900 retinol activity equivalents (RAE) for males and 700 RAE for females. In comparison, 1 RAE = 1 µg of retinol or 12 µg of β-carotene

Sources & indications



- ✓ Sources: excess cause <u>hypervitaminosis A</u>
- ✓ Clinical indications:
  - ✓ <u>Dietary deficiency</u>: mild (night blindness, nyctalopia), prolonged (irreversible loss for some visual cells), severe (<u>xerophthalmia</u>)
    - ✓ Xerophthalmia: ulceration & dryness of conjunctiva & cornea, followed by scar & blindness (affecting over 500,000 children worldwide every year)
  - ✓ Acne and psoriasis: effectively treated with retinoic acid

Toxicity - Hypervitaminosis A

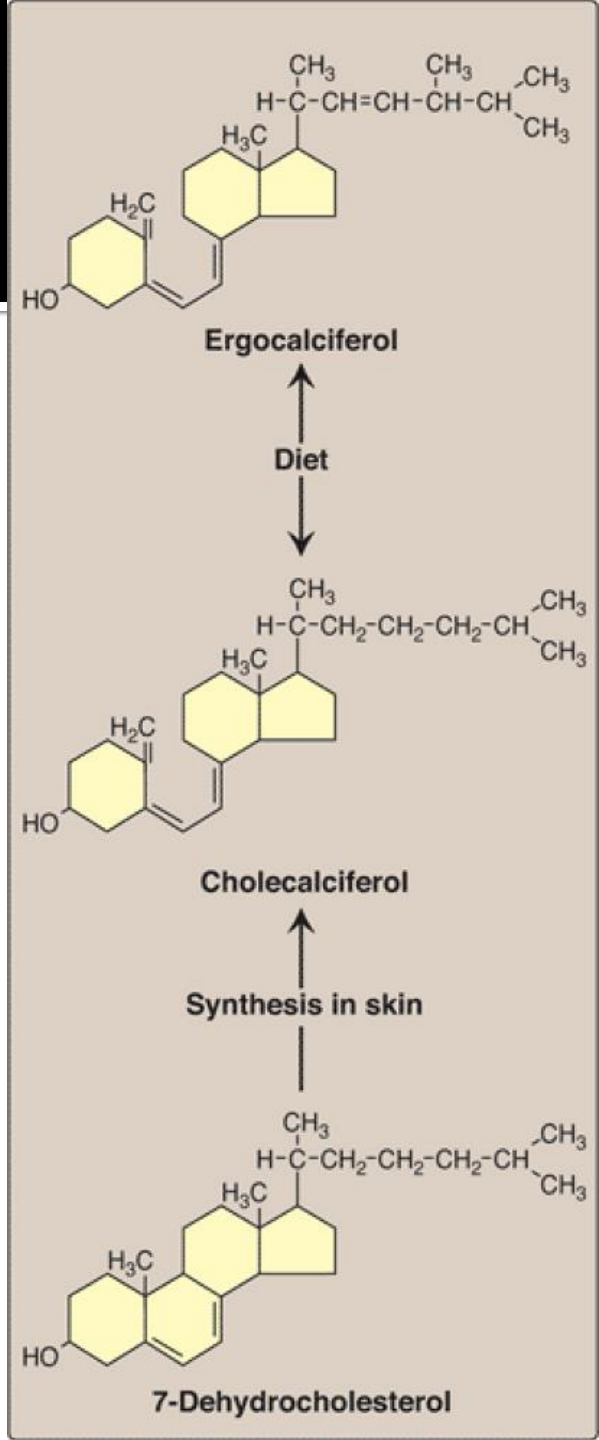
- Amounts exceeding 7.5 mg/day of retinol should be avoided
- Pregnant women: potential for teratogenesis
- UL is 3,000 µg of preformed vitamin A/day
- Prolonged treatment with isotretinoin can result in an increase in TAG and cholesterol, providing some concern for an increased risk of CVD

VITAMIN D

- A group of sterols that have a hormone-like function
- Active molecule, 1,25-dihydroxycholecalciferol ([1,25-diOH-D3], or calcitriol), binds to intracellular receptor proteins
- The 1,25-diOH-D3–receptor complex interacts with response elements in the nuclear DNA of target cells (vitamin A) - selectively stimulates or represses gene transcription
- The most prominent actions of calcitriol are to regulate the serum levels of calcium and phosphorus

Distribution

- 1. Endogenous vitamin precursor: 7-Dehydrocholesterol
  - Converted to cholecalciferol and transported to liver bound to vitamin D–binding protein
- 2. Diet: Ergocalciferol (vitamin D2), and cholecalciferol (vitamin D3)
- Differ chemically
- Packaged in chylomicrons
- Preformed vitamin D is a dietary requirement only in individuals with limited exposure to sunlight



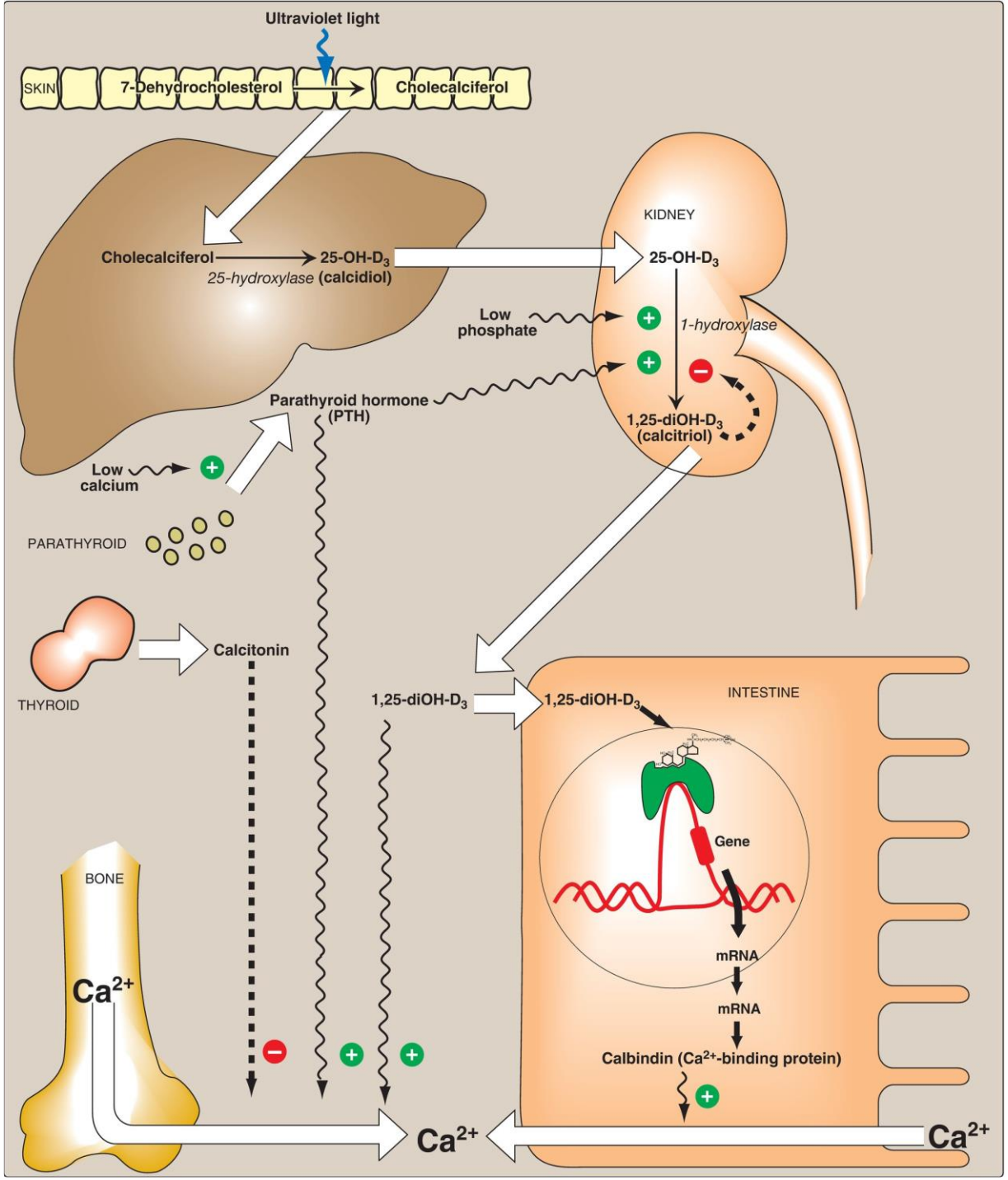
Metabolism

- Vitamins D2 and D3 are not biologically active
- Converted in vivo to calcitriol, the active form of vitamin D
- The first hydroxylation (calcidiol)
  - 25 position – liver - 25-hydroxylase
  - The predominant form in serum and the major storage form
- Further hydroxylated
  - 1 position – kidney - 25-hydroxycholecalciferol 1-hydroxylase
  - Formation of 1,25-diOH-D3 (calcitriol)

Hydroxylation regulation

- Formation of Calcitriol is tightly regulated by the level of serum phosphate (PO_4^{3-}) and calcium ions (Ca^{2+})
- *25-Hydroxycholecalciferol 1-hydroxylase* activity is increased
  - Directly by low serum PO_4^{3-}
  - Indirectly by low serum Ca^{2+} (through PTH)
- Thus, hypocalcemia caused by insufficient dietary Ca^{2+} results in elevated levels of serum 1,25-diOH-D3
- 1,25-diOH-D3 inhibits expression of PTH, forming a negative feedback loop. It also inhibits activity of the *1-hydroxylase*

Hydroxylation regulation



Function

- To maintain adequate serum levels of Ca2+ (intestine, kidney, and bone)
- Increased expression of the calcium-binding protein calbindin (typical of steroid hormones)

Distribution and requirement

- Naturally in fatty fish, liver, and egg yolk
- Milk, unless it is artificially fortified, is not a good source
- The RDA for individuals ages 1–70 years is 15 µg/day and 20 µg/day if over age 70 years
- 1 µg vitamin D = 40 international units (IU)
- Because breast milk is a poor source of vitamin D, supplementation is recommended for breastfed babies

Toxicity

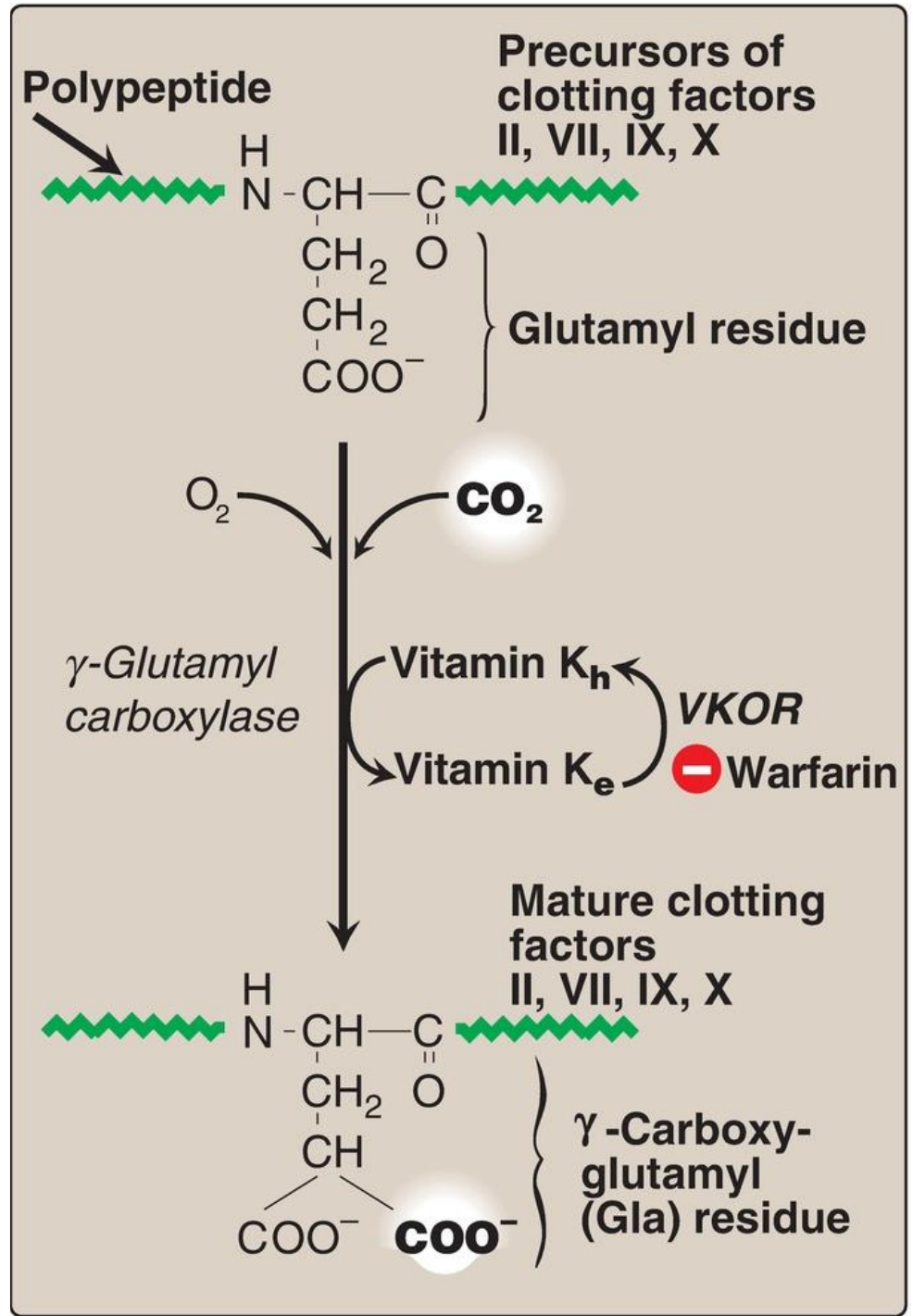
- High doses (100,000 IU for weeks or months) can cause loss of appetite, nausea, thirst, and weakness
- Enhanced Ca^{2+} absorption and bone resorption results in hypercalcemia, which can lead to deposition of calcium salts in soft tissue (metastatic calcification)
- UL is 100 µg/day (4,000 IU/day) for individuals ages 9 years or older, with a lower level for those under age 9 years
- Toxicity is only seen with use of supplements. Excess vitamin D produced in the skin is converted to inactive forms

VITAMIN K

- The principal role is in the posttranslational modification of a number of proteins (most of which are involved with blood clotting), in which it serves as a coenzyme in the carboxylation of certain glutamic acid residues in these proteins
- Vitamin K exists in several active forms
- In plants as phylloquinone (or vitamin K1), and in intestinal bacteria as menaquinone (or vitamin K2).
- A synthetic form of vitamin K, menadione, is able to be converted to K2

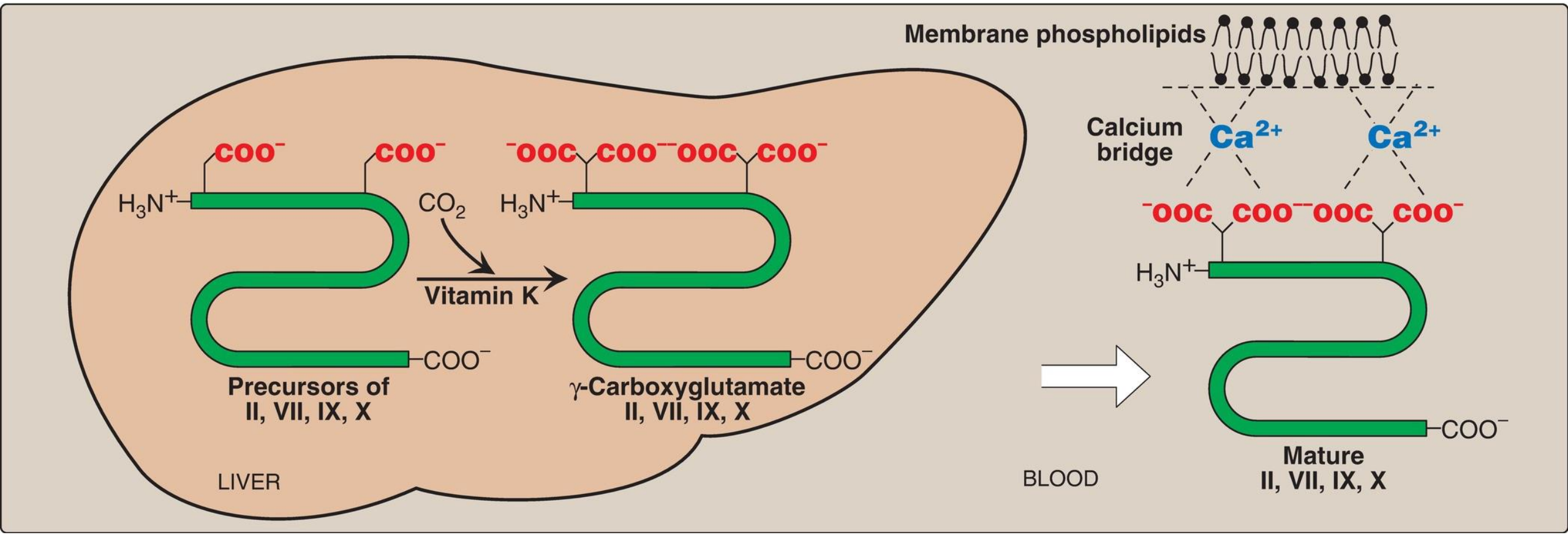
Function

- γ-Carboxyglutamate formation: Vitamin K is required in the hepatic synthesis of the blood clotting proteins, prothrombin (factor [F]II) and FVII, FIX, and FX
- The carboxylation reaction requires γ-glutamyl carboxylase, O_2, CO_2, and the hydroquinone form of vitamin K (which gets oxidized to the epoxide form)
- Formation of Gla residues is sensitive to inhibition by warfarin, a synthetic analog of vitamin K that inhibits vitamin K epoxide reductase (VKOR), the enzyme required to regenerate the functional hydroquinone form of vitamin K


Polypeptide
Precursors of clotting factors II, VII, IX, X
H
N-CH—C
CH2 O
CH2
COO⁻
Glutamyl residue
O2
CO2
γ-Glutamyl carboxylase
Vitamin Kh
Vitamin Ke
VKOR
Warfarin
Mature clotting factors II, VII, IX, X
H
N-CH—C
CH2 O
CH
COO⁻ COO⁻
γ-Carboxy-glutamyl (Gla) residue

Function

- Gla residues are good chelators of positively charged calcium ions, because of their two adjacent, negatively charged carboxylate groups
- Prothrombin–calcium complex is able to bind negatively charged membrane phospholipids on the surface of damaged endothelium and platelets
- Attachment to membrane increases the rate at which the proteolytic conversion of prothrombin to thrombin can occur


Membrane phospholipids
Calcium bridge
Ca2+
Ca2+
COO−
COO−
−OOC
COO−
−OOC
COO−
H3N+
CO2
H3N+
Vitamin K
COO−
COO−
Precursors of
II, VII, IX, X
γ-Carboxyglutamate
II, VII, IX, X
LIVER
BLOOD
−OOC
COO−
−OOC
COO−
H3N+
COO−
Mature
II, VII, IX, X

Distribution and requirement

- Found in cabbage, spinach, egg yolk, and liver
- Adequate intake for vitamin K is 120 µg/day for adult males and 90 µg for adult females
- There is also synthesis of the vitamin by the gut microbiota

Clinical indications for vitamin K

- 1. Deficiency:
- A true vitamin K deficiency is unusual – long antibiotic treatment
- In addition, certain cephalosporin antibiotics (for example, cefamandole) cause hypoprothrombinemia, apparently by a warfarin-like mechanism that inhibits *VKOR*. Consequently, their use in treatment is usually supplemented with vitamin K

Clinical indications for vitamin K

- 2. Deficiency in the newborn: sterile intestines. Human milk provides only about one fifth of the daily requirement for vitamin K, it is recommended that all newborns receive a single intramuscular dose of vitamin K as prophylaxis against hemorrhagic disease of the newborn

Toxicity

- Prolonged administration of large doses of menadione can produce hemolytic anemia and jaundice in the infant, because of toxic effects on the RBC membrane
- Therefore, it is no longer used to treat vitamin K deficiency
- No UL for the natural form has been set

Vitamin E

- ✓ 8 naturally occurring tocopherols
- ✓ α-tocopherol is the most active form
- ✓ The primary function is as an antioxidant
- ✓ Vitamin E deficiency is almost entirely restricted to premature infants
- ✓ When observed in adults, it is usually associated with defective lipid absorption or transport