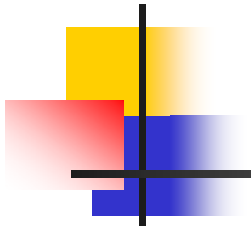
Vitamins



- Polish biochemist Casimir Funk discovered vitamin B1 in 1912 in rice bran.
- He proposed the complex be named "Vitamin" (vital amines).
- By the time it was shown that not all vitamins were *amines*, the word was already universal.

Vitamin - definition

- An organic compound required as a nutrient in tiny amounts by an organisms.
- It cannot be synthesized in sufficient quantities by an organism, and must be obtained from the diet.
- Vitamins have diverse biological function:
  - hormone-like functions as regulators of mineral metabolism (vit. D),
  - regulators of cell and tissue growth and differentiation (some forms of vit. A)
  - antioxidants (vit. E, C)
  - enzyme cofactors (tightly bound to enzyme as a part of prosthetic group, coenzymes)

Vitamin classification

Lipid-soluble vitamins (A, D, E and K)

- hydrophobic compounds, absorbed efficiently with lipids,
- transport in the blood in lipoproteins or attached to *specific binding proteins,*
- more likely to accumulate in the body,
- more likely to lead to *hypervitaminosis*

Vitamin classification

Water-soluble vitamins - 8 B vitamins and vitamin C

- Function: mainly as enzyme cofactors,
- hydrophilic compounds dissolve easily in water,
- not readily stored, excreted from the body,
- their consistent daily intake is important.

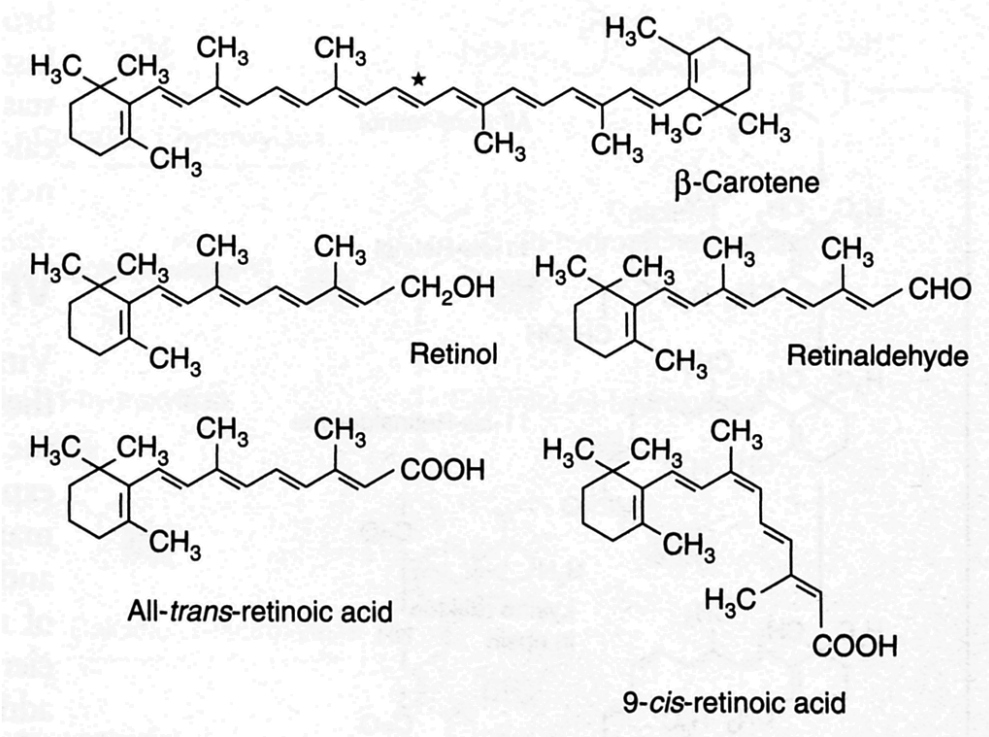
Many types of water-soluble vitamins are synthesized by bacteria.

Lipid-soluble vitamins
Vitamin A

Retinol

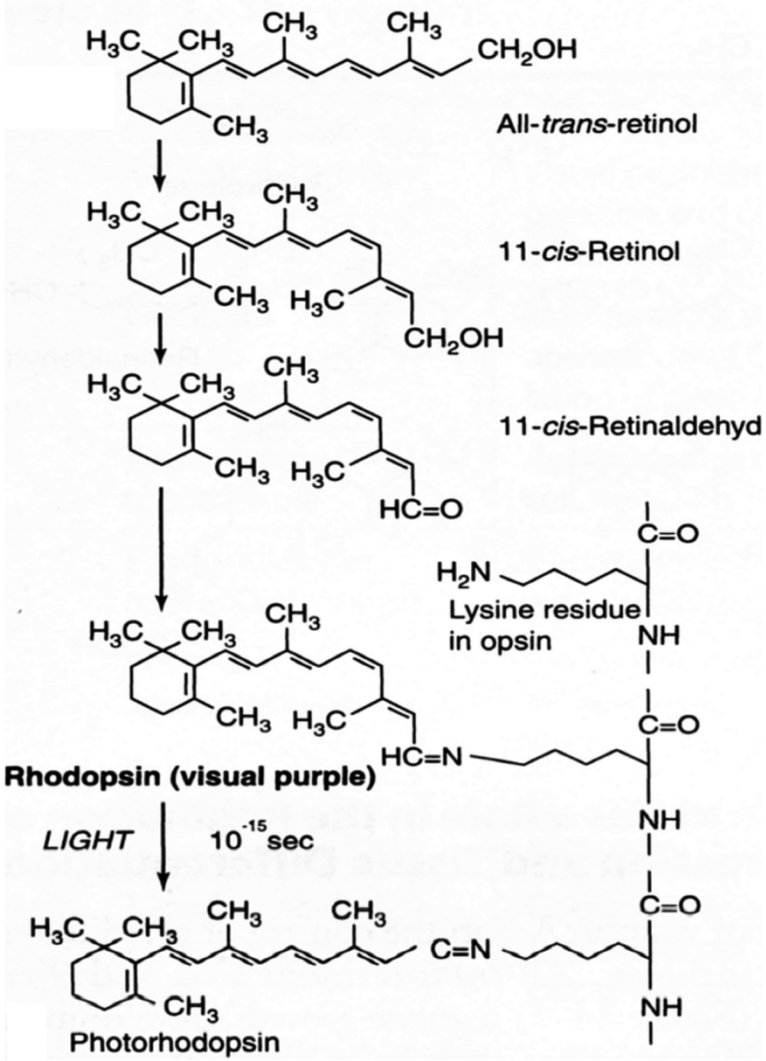
- Biologically active forms - *retinoids*: retinol, retinal, retinoid acid.
- Major vit. A precursors (provitamins) → plants *carotenoids*.
- Foodstaf of animals origin contain most of vit. A in the form of esters (retinylpalmi-tates) – *retinol* and *long fatty acid*

Cyklohexan ring and isoprenoid chain



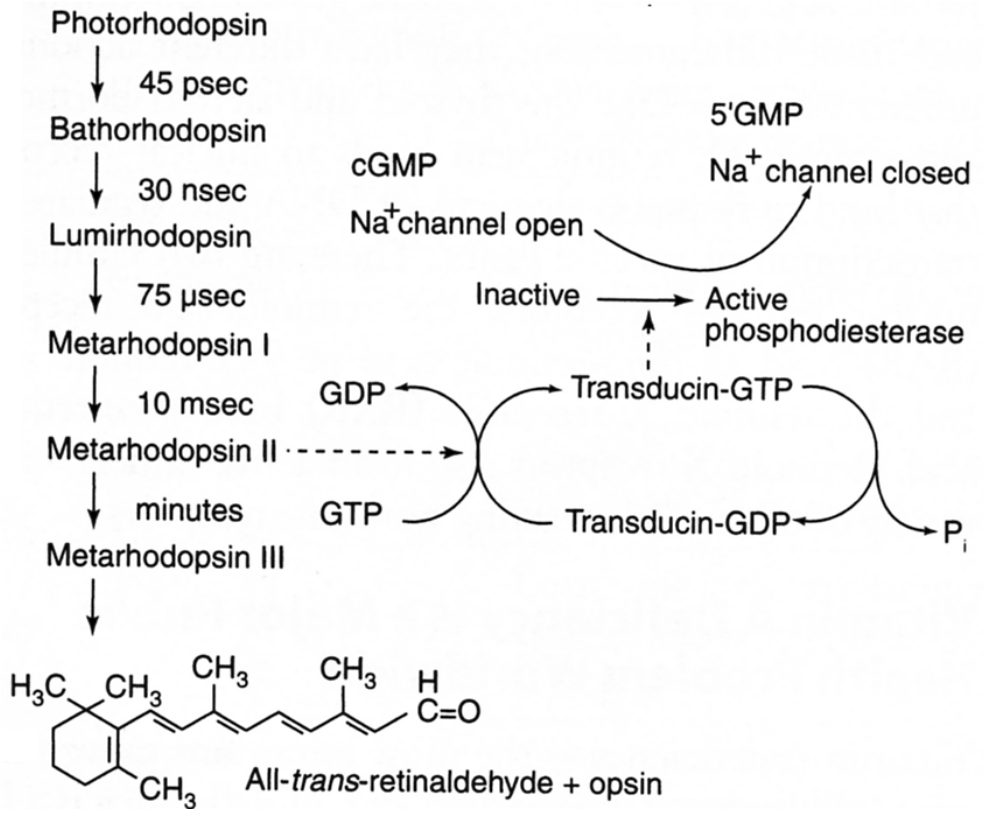
Vitamin A and vision

- Vit. A is necessary to form **rhodopsin** (*in rodes, night vision*) and **iodopsins** (**photopsins**, *in cones – color vision*) - visual pigment.
- Retinaldehyd is a prosthetic group of light-sensitive opsin protein.
- In the retina, all-*trans*-retinol is isomerized to 11-*cis*-retinol → oxidized to 11-*cis*-retinaldehyd, this reacts with opsin (Lys) → to form the holoprotein *rhodopsin*.
- Absorption of light → conformation changes of opsin → photorhodopsin.



Vitamin A and vision

- The following is a series of izomerisation→ initiation of nerve impulse.
- The final step is hydrolysis to release all-*trans*-retinaldehyde and opsin.
- Deficiency of vit. A leads to night blindness.
- Vitamin A is an important antioxidant.



Vitamin A and other functions

Transcription and cell differentiation

- Retinoic acid regulates the transcription of genes - acts through nuclear receptors (steroid-like receptors).

- By binding to various nuclear receptors, vit. A stimulates (RAR – retinoid acid receptor) or inhibits (RXR- retinoid „X" receptor) transcription of genes transcription. All-*trans*-retinoic acid binds to RAR and 9-*cis*-retinoic acid binds to RXR.
- Retinoic acid is necessary for the function and maintenance of epithelial tissues.

Vitamin A - deficiency

- The early sign → a loss of sensitivity to green light,
  - prolonged deficiency → impairment to adapt to dim light
  - more prolonged deficiency leads to night blindness

- Ever escalated deficiency leads to ***squamous metaplasia*** - columnar epithelia are transformed into heavily keratinized squamous epithelia.

- The conjunctiva loses mucus-secreting cells → glykoprotein content of the tears is reduced → ***xeroftalmia*** („dry eyes")
  - Often complication - bacterial or chlamidial infection which results in perforation of the cornea and blindness

Vitamin A - deficiency

- Transformation of respiratory epithelium – *loss of protective airway function* (antibacterial properties) → bronchitis.
- Conversion of the urinary tract epithelium → *higher frequency of urinary stone formation*

- Immunosuppression
- Impairment of reproductive function (both in men and women).

- Worldwide deficiency of vit. A
- 3 – 10 mil. children become xerophtalmic every year
  - 250 000 to 500 000 go to blindness
  - 1 million die from infections

Vitamin A - toxicity

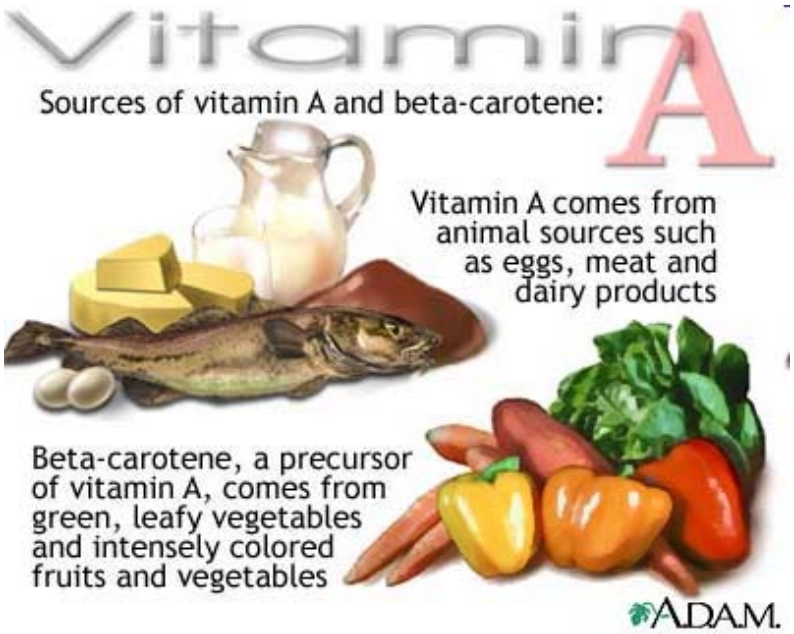
- Toxic dose:
  - single dose of more than 200 mg
  - more than 40 mg per day
- Acute symptoms - headache, vomiting, impaired consciousness.
- Chronic intoxication – weight loss, vomiting, pain in joints, muscles, blurred vision, hair loss, excessive bone growth.
- Both vit. A excess and deficiency in pregnancy are *teratogenic* – retinoic acid is gene regulator during early fetal development
- *Carotenoids* are non toxic - accumulation in tissues rich in lipids (the skin of babies overdosed with carrot juice may be orange).

Metabolic functions of vitamin A

- Vision
- Gene transcription
- Immune function
- Embryonic development and reproduction
- Bone metabolism
- Haematopoieis
- Skin health
- Antioxidant activity

Sources of vitamin A

- cod liver oil
- meat
- egg
- milk
- dairy products
- carrot
- broccoli
- spinach
- papaya
- apricots



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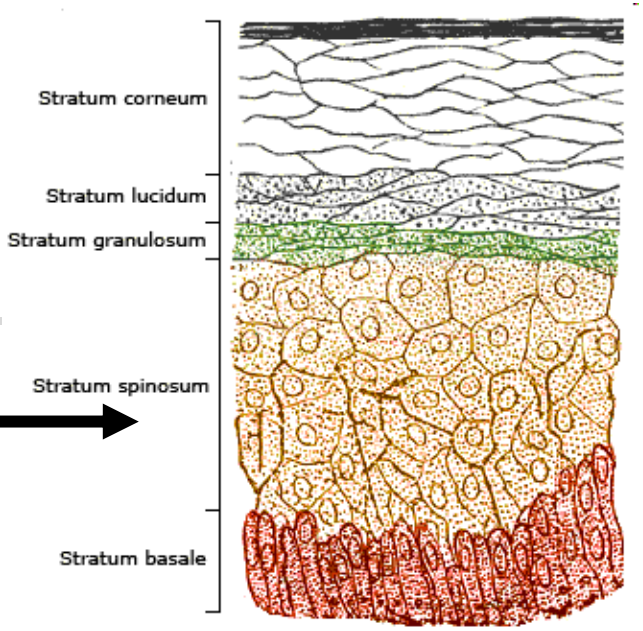
Vitamin D

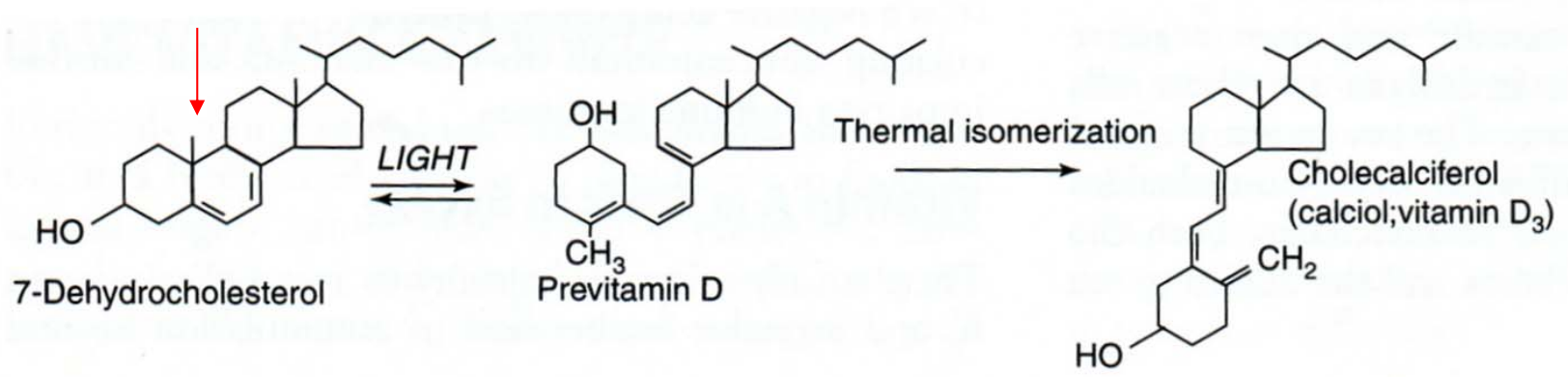
- Calciol, vitamin D_2 (cholecalciferol) → precursor of calcitriol, D_3 (1,25-dihydroxycalciferol).
- Regulates with PTH calcium and phosphate level (absorption, reabsorption, excretion).
- Synthesis in the skin (7-dehydrocholesterol) UV → further transformation in the liver and kidneys .

Synthesis

UV irradiation 270 – 300 nm

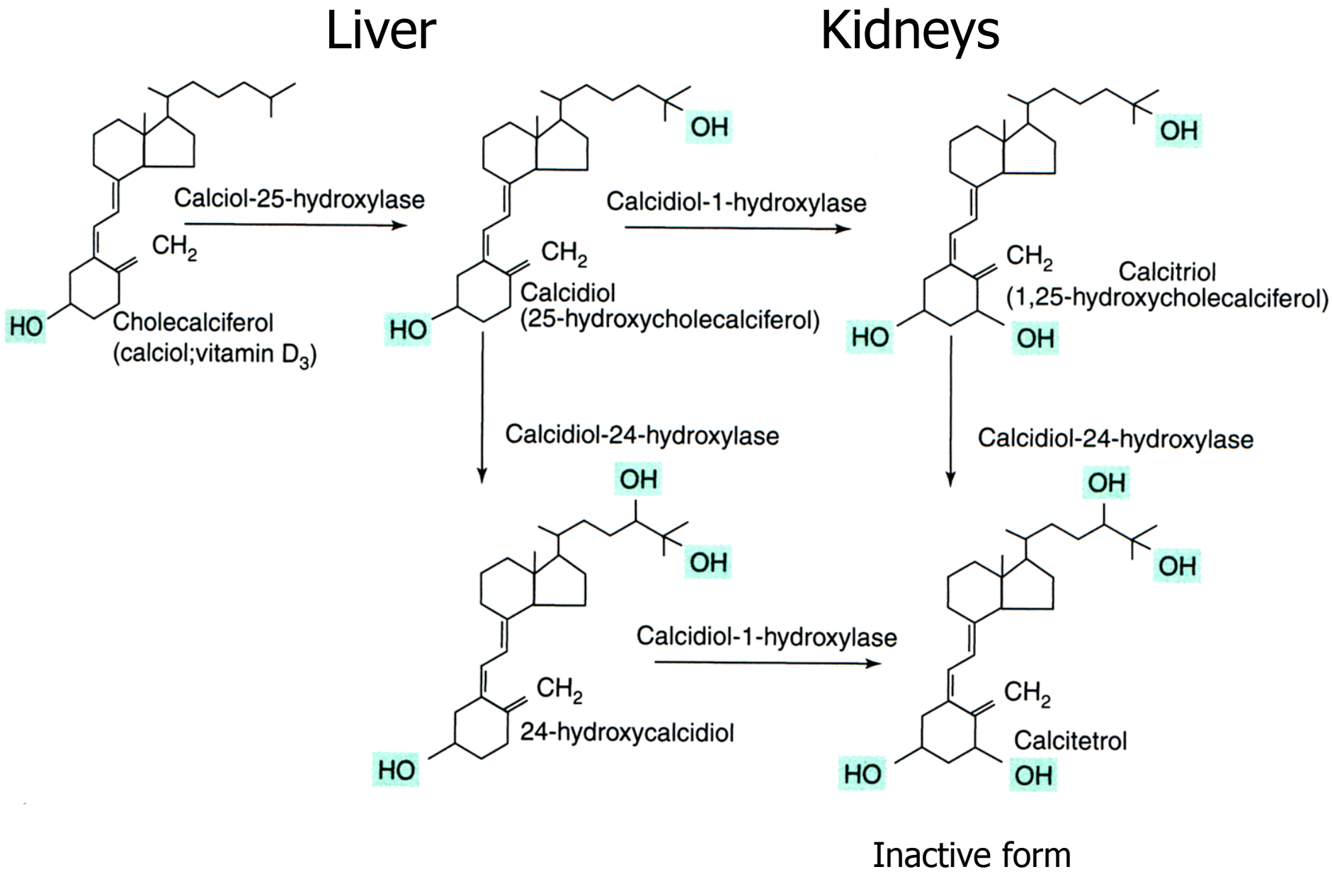


Photolysis



Non-enzymatic reaction in the skin

Transport to the liver


Liver
Kidneys
Calciol-25-hydroxylase
Calcidiol-1-hydroxylase
Calcidiol-24-hydroxylase
Calcidiol-24-hydroxylase
Calcidiol-1-hydroxylase
HO
CH2
Cholecalciferol
(calciol;vitamin D3)
OH
Calcidiol
(25-hydroxycholecalciferol)
Calcitriol
(1,25-hydroxycholecalciferol)
24-hydroxycalcidiol
Calcitetrol
Inactive form

Effects of vitamin D

- Transported in the blood on a carrier (vitamin-D binding protein, VDBP).
- $1,25(OH)_2D$ binds to intracellular receptors (intestine, bone, kidney).
- The main function is to maintain plasma levels of calcium (essential for neuromuscular activity) and phosphate levels:
  - increase Ca absorption in the intestine,
  - reduce the excretion of calcium (stimulates parathyroid hormone-dependent Ca reabsorption in the distal tubule),
  - mobilizing bone mineral, together with parathyroid hormone

Vitamin D - deficincy

- Failure of absorption in the intestine.
- The lack of the liver and the renal hydroxylation of vit. D (congenital deficiency of 1-hydroxylase).
- The lack of UV irradiation.
- The main manifestation - impaired ossification of the newly created osteiod, abundance of non mineralized matrix.
- Vit. D is necessary for the prevention of skeletal changes (rickets in growing individuals, osteomalacia in adults).

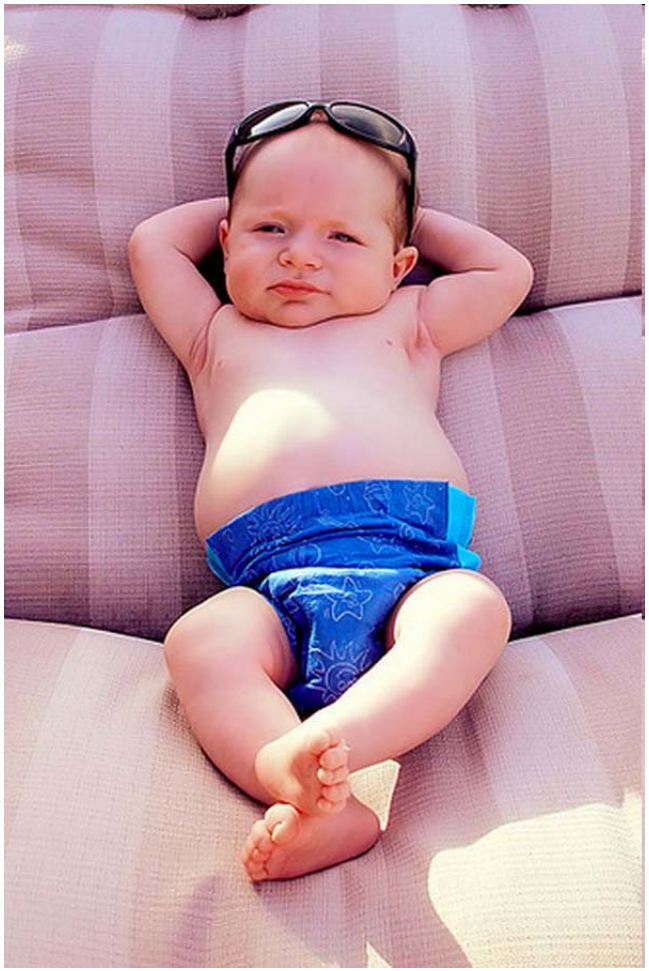
Vitamin D and imunity

- It increases the activity of natural killer cells (cytotoxic lymphocytes).
- Increases the phagocytic ability of macrophages .
- Reduces the risk of virus diseases (colds, flu).
- Reduces the risk of many cancers (colon, breast and ovarian cancer).
- Reduces the risk of cardiovascular disease → have a positive impact on the composition of plasma lipids.

Sources of vitamin D

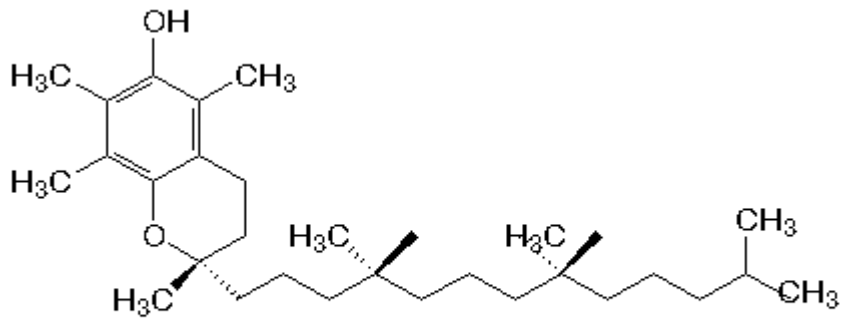
- In addition to sunbathing:
- various fish species (salmon, sardines and mackerel, tuna, catfish, eel), fish oil, cod liver

- eggs, beef liver, mushrooms



Vitamin E

- Vitamin E is a family of α–, β–, γ–, δ– tocopherols and corresponding tocotrienols izomers.
- They are formed from chroman ring and hydrofobic fytyl side chain.
- The highest biological activity has α-tokoferol.



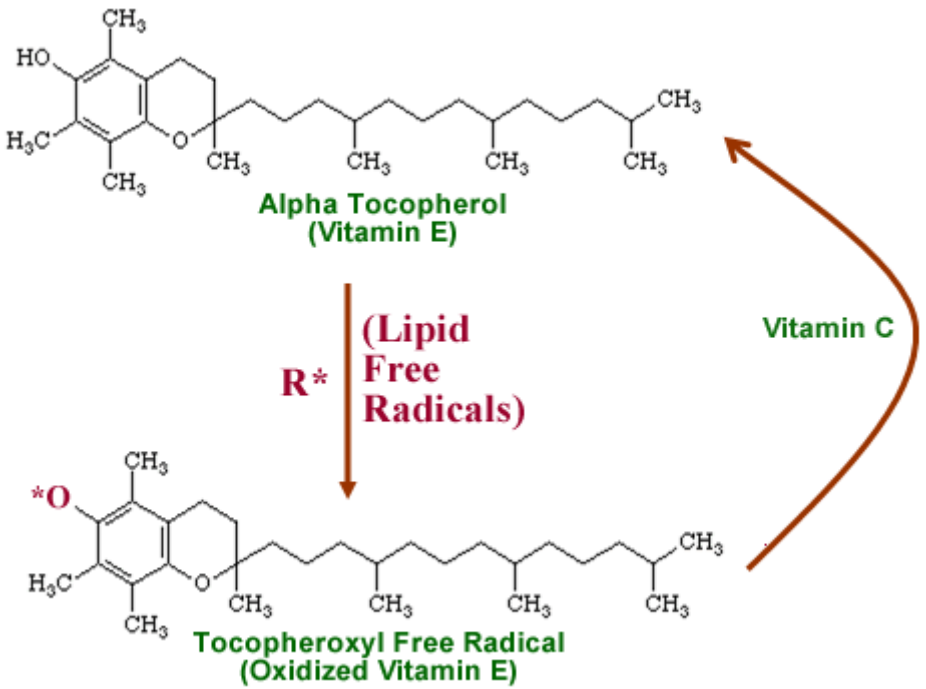
Vitamin E (α-tocopherol)

Vitamin E

- Adsorbtion from the small intestine.
- Its absorption is dependent on the presence of lipids in the diet.
- Associated with plasma lipoproteins → liver uptake through receptors for apolipoprotein E.
- α–tocopherol is bind to *α-tocopherol transport protein* (α-TTP) → transported to the target organs (the excess is stored in adipocytes, in muscle, liver).
- β–, γ– a δ–tocopherols are transferred into the bile and degraded.

Vitamin E as antioxidant

- Stops free radical reactions (peroxyl radicals $ROO^{\bullet}$, oxygen radicals $HO^{\bullet}$, lipoperoxid radicals $LOO^{\bullet}$). Chroman ring with OH group → uptake radicals.



Vitamin E as enzyme cofactor

- *α-tocopherol quinon* generated by oxidation of *α-tocopherol* can acts as a cofactor of mitochondrial unsaturated fatty acids .

- α-tocopherol quinon + cytochrom B_5 + $NADH+H^+$ initiate formation of double bonds in FA – temporarily changes to α-tocopherol-hydroquinon (in the presence of O_2 changes back to α-tocopherol quinon).

Vitamin E – deficiency and toxicity

- The lack of α-tocopherol in plasma is often associated with impaired fat absorption or distribution (in patients with cystic fibrosis, in patients with intestine resection)
- deficit of vit. D exhibit - neurological problems, impaired vision, eye muscle paralysis, platelet aggregation, impairment of fertility in men, impaired immunity.
- Toxicity is relatively small.

Sources of vitamin E

- fortified cereals
- seeds and seed oils, like sunflower
- nuts and nut oils, like almonds and hazelnuts
- green leafy vegetables,
- broccoli
- cabbage
- celery

Vitamin E is found in corn, nuts, olives, green, leafy vegetables, vegetable oils and wheat germ

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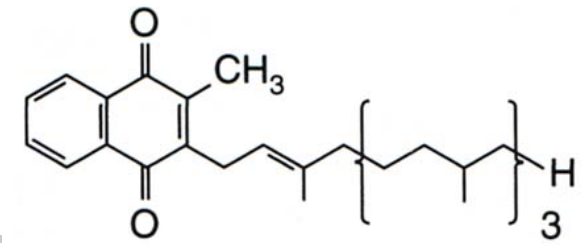
Vitamin K

- **Vitamin K** is a group of lipophilic, hydrophobic vitamins.
- They are needed for the postranslation modification of proteins required for blood coagulation,
- They are involved in metabolism pathways, in bone mineralisation, cell growth, metabolism of blood vessel wall.

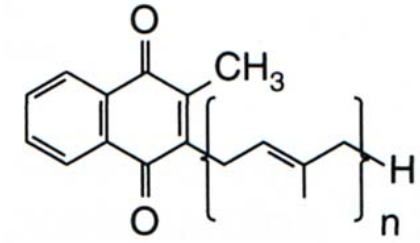
Vitamin K

- Vitamin K_1 (phylloquinon) – plant origin
- Vitamin K_2 (menaquinon) – normally produced by bacteria in the large intestine
- K_1 a K_2 are used differently in the body
  - K_1 – used mainly for blood clothing
  - K_2 – important in non-coagulation actions - as in metabolism and bone mineralization, in cell growth, metabolism of blood vessel walls cells.



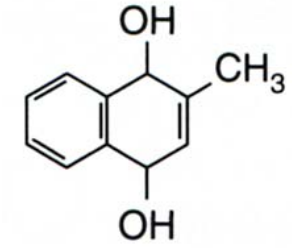
Fylochinon

Vitamin K_1

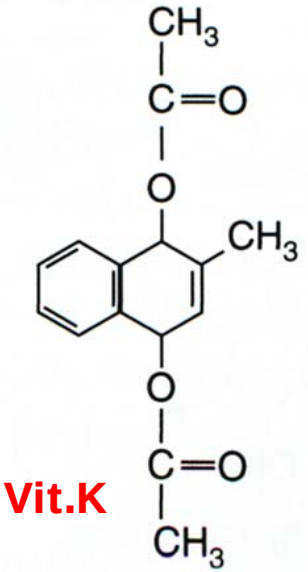


Menachinon

Vitamin K_2



Menadiol



Menadiondiacetát

Synthetic derivatives of Vit.K

Vitamin K - function

- Cofactor of liver microsomal *carboxylase* which carboxylates glutamate residues to γ-carboxyglutamate during synthesis of prothrombin and coagulation factors VII, IX a X (posttranslation reaction).
- Carboxylated glutamate chelates Ca^{2+} ions, permitting the binding of blood clotting proteins to membranes.
- Forms the binding site for Ca^{2+} also in other proteins – osteocalcin.

Vitamin K - deficiency

- Deficiency is caused by fat malabsorption or by the liver failure.
- Blood clotting disorders – dangerous in newborns, life-threatening bleeding (*hemorrhagic disease of the newborn).*
- Osteoporosis due to failed carboxylation of osteokalcin and decreased activity of osteoblasts.
- Under normal circumstances there is not a shortage, vit. K is abundant in the diet.

Sources of vitamin K

- Green leafy vegetables
- vegetable oil
- broccoli
- cereals

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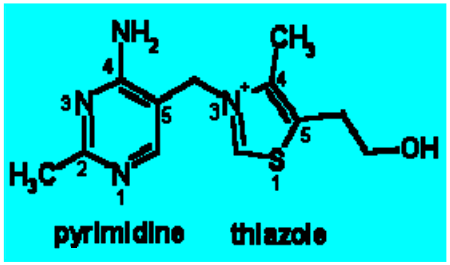
Water soluble vitamins

- Vitamin B_1 (thiamine)
- Vitamin B_2 (riboflavin)
- Vitamin B_3 or Vitamin P or Vitamin PP (niacin)
- Vitamin B_5 (panthotenic acid)
- Vitamin B_6 (pyridoxine and pyridoxamine)
- Vitamin B_7 or Vitamin H (biotin)
- Vitamin B_9 or Vitamin M and Vitamin B-c (folic acid)
- Vitamin B_{12} (cobalamin)

Vitamin B_1 (thiamine)



- Thiamin has a central role in energy-yielding metabolism.
- Composed of a substituted pyridine and thiazole ring.
- Active form is thiamine diphosphate (thiamin pyrophosphate, TPP), a coenzyme for three multi-enzyme complex →
- This complex catalyses oxidative decarboxylation of α-ketoacids →
  - *pyruvate dehydrogenase* in carbohydrate metabolism,
  - *α-ketoglutarate dehydrogenase* → cytric acid cycle,
  - *Branched-chain keto-acid dehydrogenase .*
  - TPP is coenzyme for *transketolase* – pentose phosphate pathway.

Vitamin B_1 - deficiency

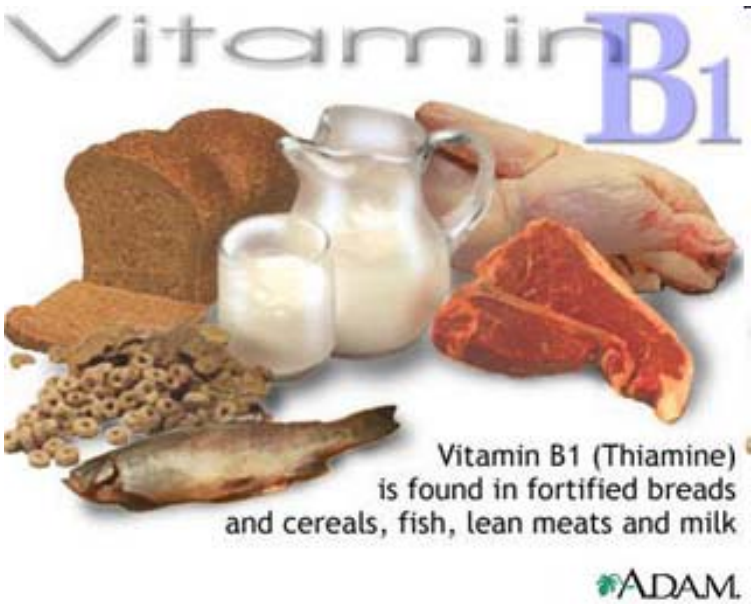
1. Mild deficiency – leads to gastrointestinal complients, weakness
2. Moderate deficiency - peripheral neuropathy, mental abnormalities, ataxia
3. Full-blown deficiency - *beri-beri* – characterized with severe muscle weakness, muscle wasting and delirium, paresis of the eye muscles, memory loss.

- Degeneration of the cardiovascular system. .

- Beri-beri causes long-term consumption of foods rich in carbohydrates but poor in thiamine - husked rice, white flour and refined sugar.

Source of vitamin B_1

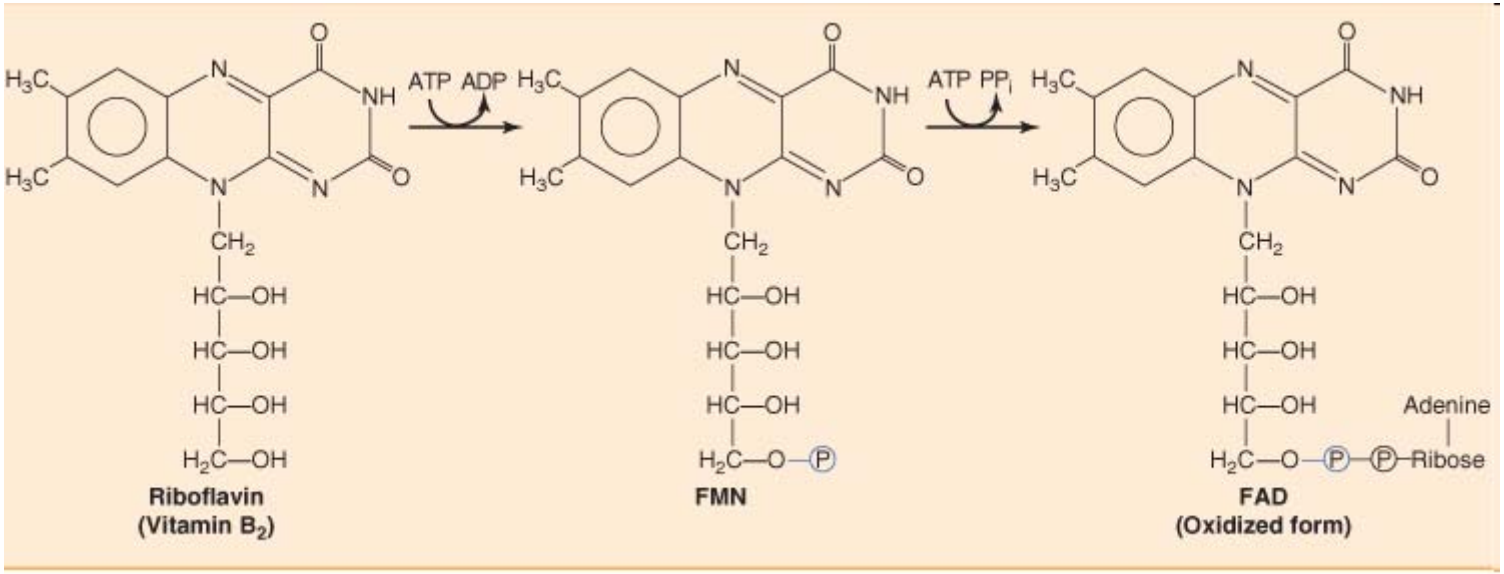
- paddy grains, cereals
  meat
  yeast
  honey
  nuts



Vitamin B_2 (riboflavin)

- Yellow to orange-yellow natural dye slightly soluble in water.
- Has a central role in energy-yielding metabolism.
- Provides the reactive moieties of the coenzymes *flavin mononucleotide (FMN)* and *flavin adenine dinucleotid (FAD).*
- Flavin coenzymes are electron carries in oxidoreduction reaction.

Vitamin B_2



FMN → ATP-dependent phosphorylation of riboflavin
FAD → further reaction with ATP in which its AMP moiety is transferred to FMN.

FMN a FAD function

FMN and FAD act as prosthetic groups of many oxidoreduction enzymes, flavoprotein:

- *oxydase* of *α-amino acids* – degradation of amino acids
- *xantinoxidase* – degradation of purines
- *aldehyde dehydrogenas*
- mitochondrial *glycerol-3-phosphate dehydrogenase* – transport of reducing unit (H^+) from mitochondra to cytosol
- *succinate dehydrogenas* – citric acid cycle
- *succinyl CoA-dehydrogenase* – β-oxidation of FA
- *NADH-dehydrogenase* – part of respiratory chain in mitochondria
- coenzymes in hydrogen transfer – formation of reducing forms - $FMNH_2$ a $FADH_2$

Vitamin B_2 absorption

- Riboflavin is absorbed in the proximal intestine.
- Riboflavin is stored mainly in the liver, kidney and heart in the form of FAD (70- 90%) or FMN.

Causes of vitamin B_2 deficiency

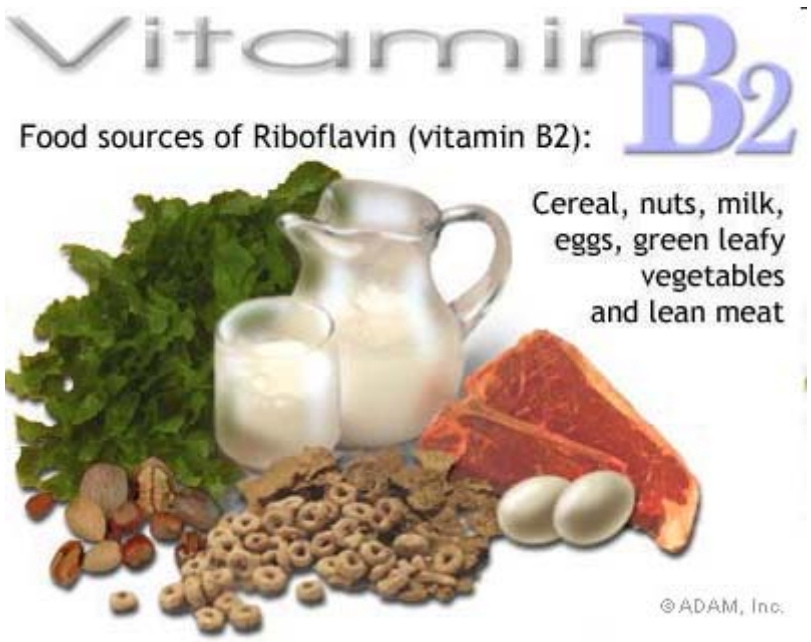
- Lack of dietary vitamin B.
- A result of conditions that affect absorption in the intestine.
- The body not being able to use the vitamin.
- An increase in the excretion of the vitamin from the body.

Vitamin B_2 – symptoms of deficiency

- Cracked and red lips.
- Inflammation of the lining of mouth and tongue.
- Dry and scaling skin- keratitis, dermatitis and iron-deficiency anemia

Sources of vitamin B_2

- foods of animal origin (liver, pork and beef, milk, dairy products, fish eggs)
- cocoa,
- nuts,
- yeast,
- of smaller quantities in cereals.



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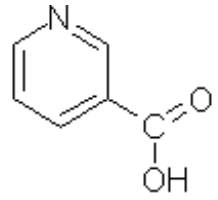
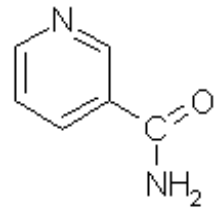
Vitamin B_3 - niacin

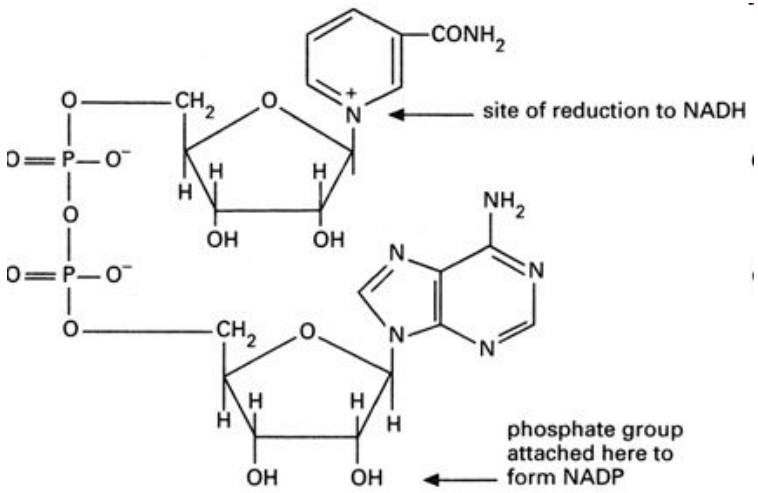
- Active form – nikotinic acid and nikotinamid.
- NAD a NADP → key components of the metabolic pathways of carbohydrates, lipids, amino acids.
- Nicotinic acid prevents the release of fatty acids from adipose tissue, decreases lipoproteins VLDL, IDL a LDL.
- High dose of niacin dilates blood vessels .



Nicotinic Acid



Nicotinamide



Vitamin B_3 - niacin

- Absorption:
  - At low concentration by active transport.
  - At high concentration by passive diffusion.
- Transportation:
  - Both nicotinic acid (NA) and nicotinamide (NAm) bind to plasma proteins for transportation.
- Biosynthesis:
  - The liver can synthesize *Niacin* from the essential amino acid **tryptophan**, but the synthesis is extremely slow and requires vitamin B_6 (60 mg of Tryptophan= 1mg of niacin). Bacteria in the gut may also perform the conversion but are inefficient.

Vitamin B_3 - deficiency

- Pellagra: A serious deficiency of niacin.
- The main results of pellagra can easily be remembered as "the four D's": diarrhea, dermatitis, dementia, and death.
- Pelagra is very rare now, except in alcoholics, strict vegetarians, and people in areas of the world with very poor nutrition.

- Milder deficiencies of niacin can cause dermatitis around the mouth and rashes, fatigue, irritability, poor appetite, indigestion, diarrhea, headache.

Sources of vitamin B_3

- foods of animal origin
- yeast
- sunflower seeds, beans, peas
- green leafy vegetable
- broccoli, carrots

Food sources of Niacin (vitamin B3) include dairy, poultry, fish, lean meat, nuts and eggs

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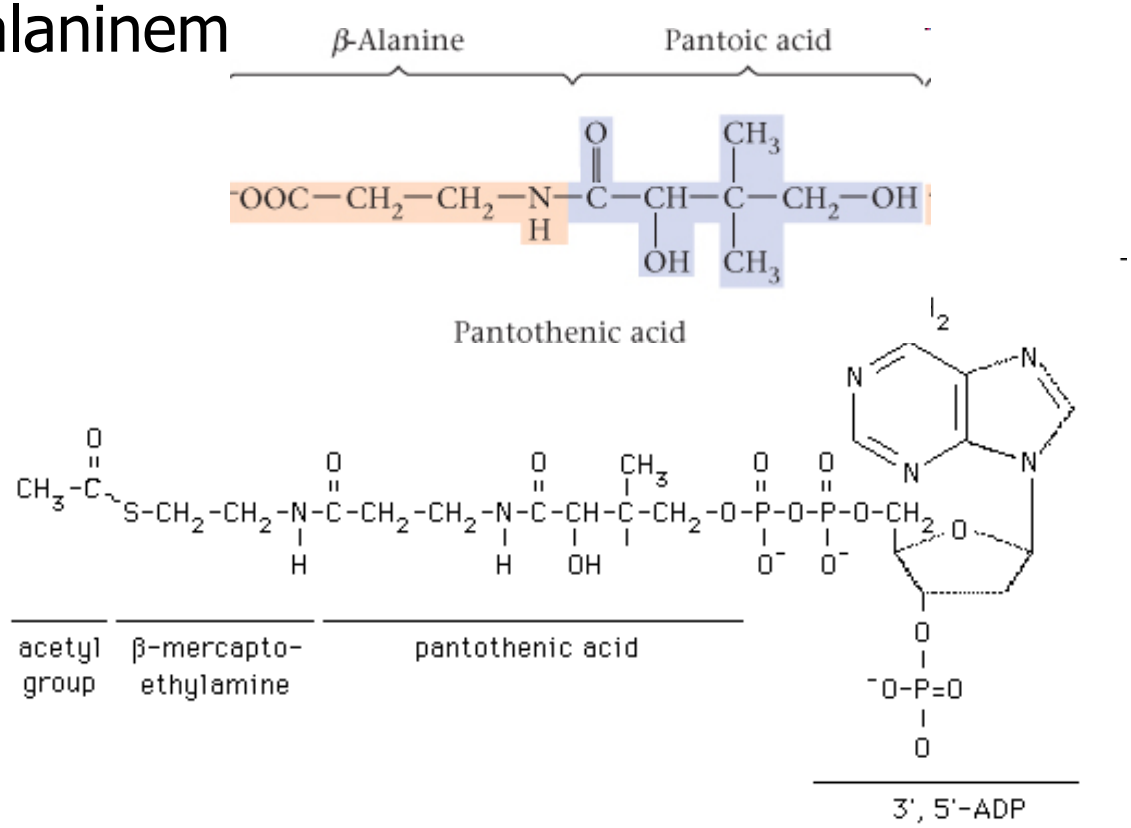
Vitamin B_5 – panthotenic acid

- Part of acetyl-CoA – consists of pantoic acid and β-alaninem



Acetyl coenzyme A, showing its constituents

Vitamin B_5 – panthotenic acid

- Co-enzyme A assists the following reactions:
  - formation of sterols (cholesterol and 7-dehydrocholesterol).
  - formation of fatty acids.
  - formation of keto acids such as pyruvic acid.

  Other reactions are acylation, acetylation, signal transduction deamination

Vitamin B_5 - deficiency

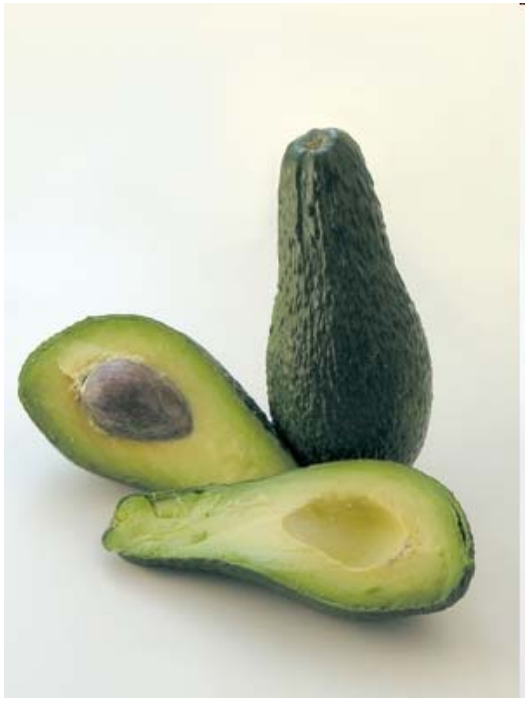
Rare to occur.

- When occur it leads to paresthesias.

- Disorders of the synthesis of acetylcholine – neurological symptoms (parestesie).

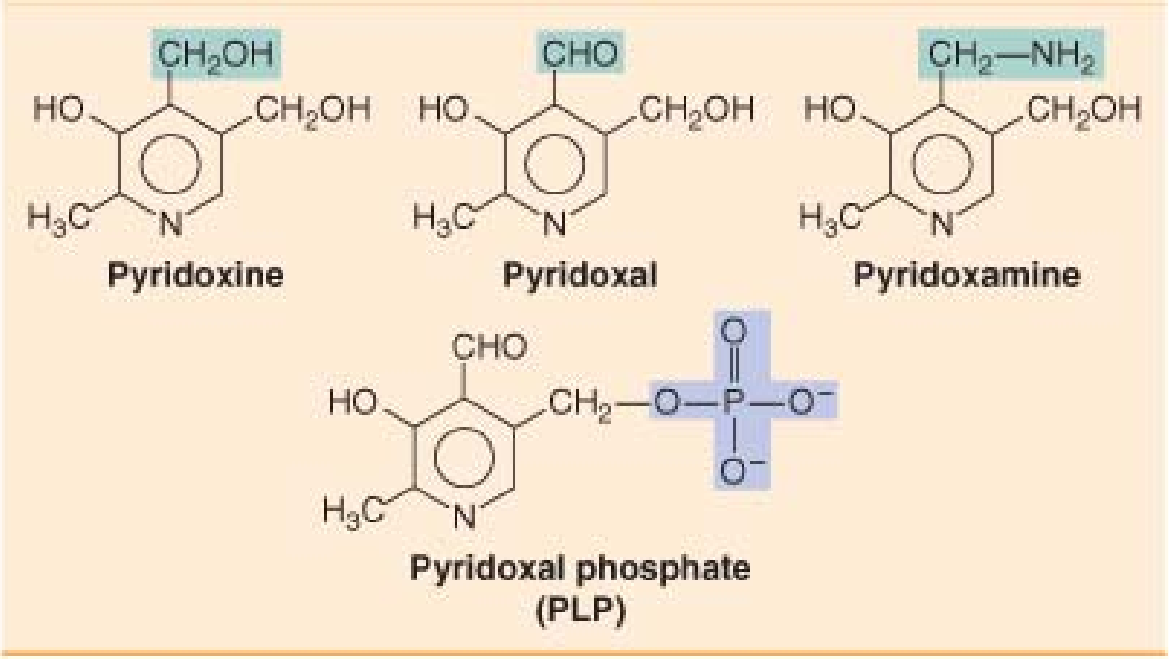
Sources of vitamin B_5

- meat, foods of animal origin,
- yeast,
- wholemeal bread,
- broccoli, avocado
- royal gelly



Vitamin B_6

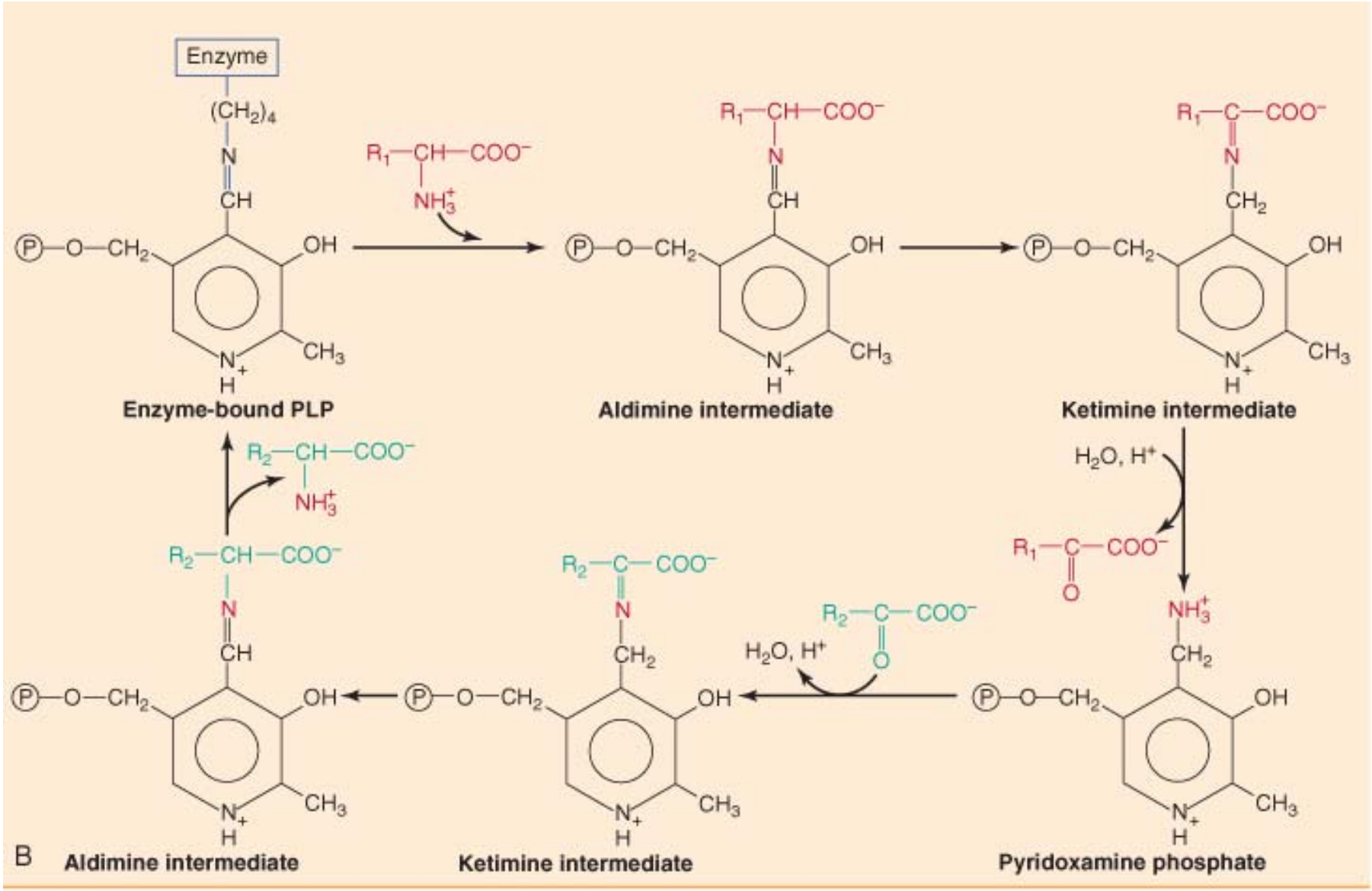
- Prekursor of active coenzyme pyridoxalphosphate – PPL.



Vitamin B_6

- Vitamin B_6 is needed for more than 100 enzymes involved in protein metabolism.
- It is also essential for red blood cell metabolism and hemoglobin formation.
- The nervous and immune systems need vitamin B_6 to function efficiently.
- It is also needed for the conversion of tryptophan to niacin (vitamin B_3).
- Vitamin B_6 also helps maintain blood glucose within a normal range. When caloric intake is low, vitamin B_6 helps to convert stored carbohydrate or other nutrients to glucose to maintain normal blood sugar levels.

Transamination reaction



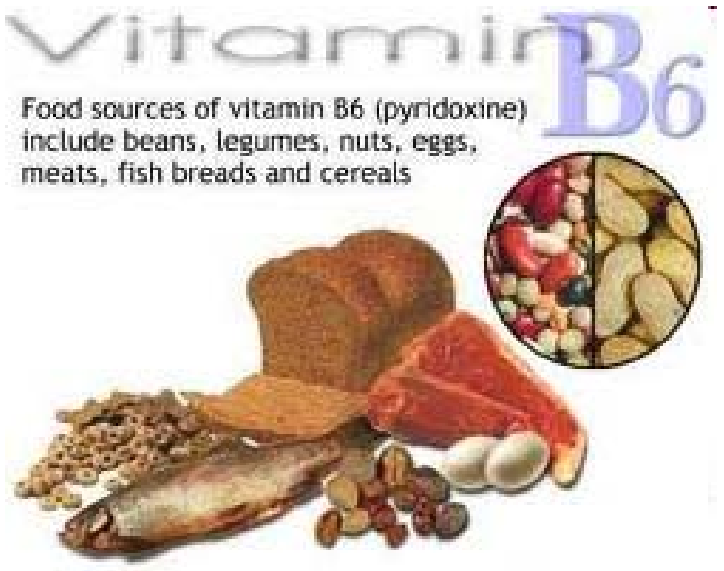
Vitamin B_6 deficiency

Signs of vitamin B_6 deficiency include:

- Skin: *dermatitis* (skin inflammation), *stomatitis* (inflammation of the mucous lining of any of the structures in the mouth), *glossitis* (inflammation or infection of the tongue).
- Neurological abnormalities: Depression, confusion, and convulsions.
- Vitamin B_6 deficiency also can cause anemia.

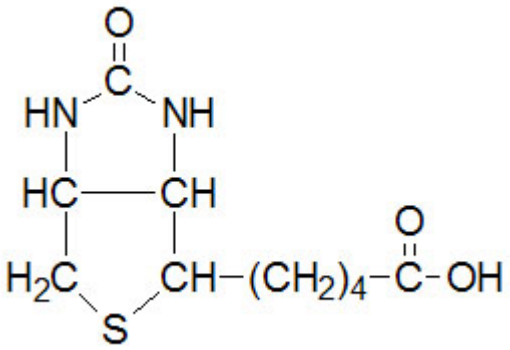
Vitamin B_6 – narural sources

- cereals,
- beans,
- meat,
- liver,
- fish,
- yeast,
- nuts and some fruits as banana
- potatoes.
- It is also produced by bacterial flora in the colon.



Vitamin B_7 - biotin

- Prosthetic group of *pyruvate carboxylase, acetyl-CoA carboxylase* and other *ATP-dependent carboxylases*.

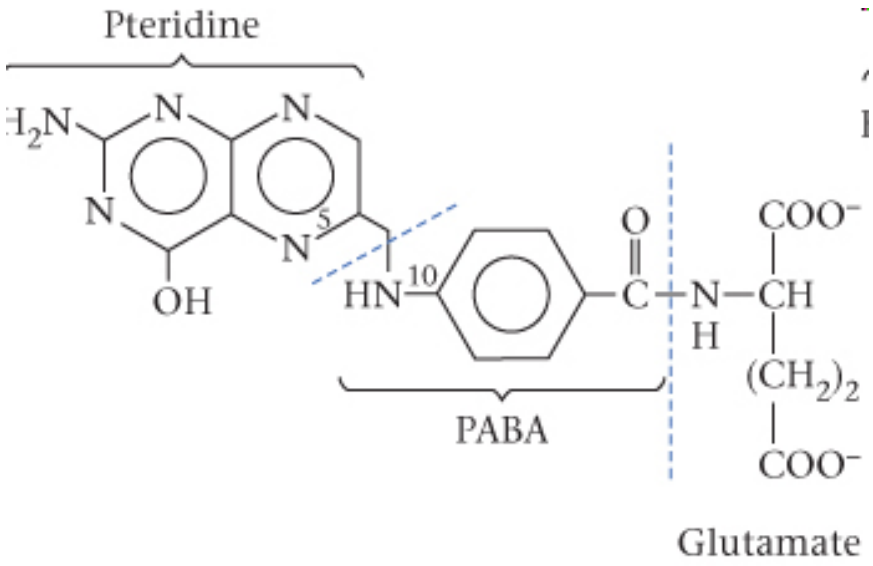


Biotin – natural source

- liver
- meat
- kidney
- yeast
- egg yolk
- mushrooms
- milk and diary products.

Vitamin B_9 – folic acid

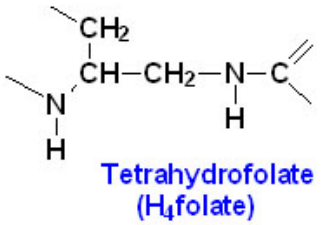
- Consist of pteroic acid - pteridine + paraaminobenzoic acid (PABA) + glutamic acid

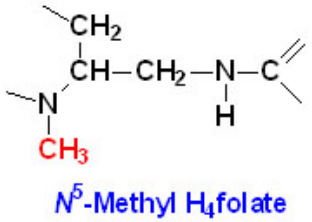


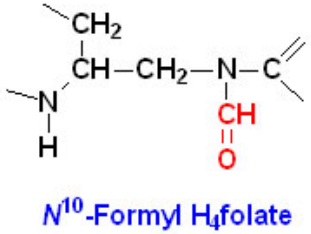
Pteroyl-monoglutamate
(the absorbed form of folic acid)

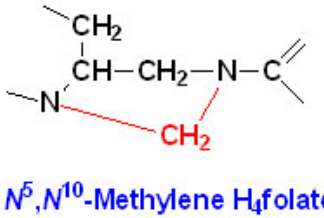
Vitamin B_9 – folic acid

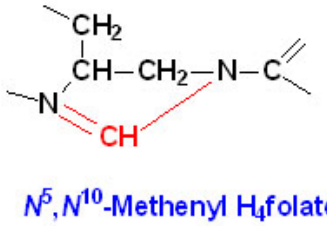
- Active metabolit of folic acid is tetrahydrofolate (THF) .
- THF is coenzym of transferases carrying one carbon units.
- This reaction participate in nucleotide and nucleic acid synthesis
- N^5,N^{10}-THF carries one carbon units (methylen or methenyl).











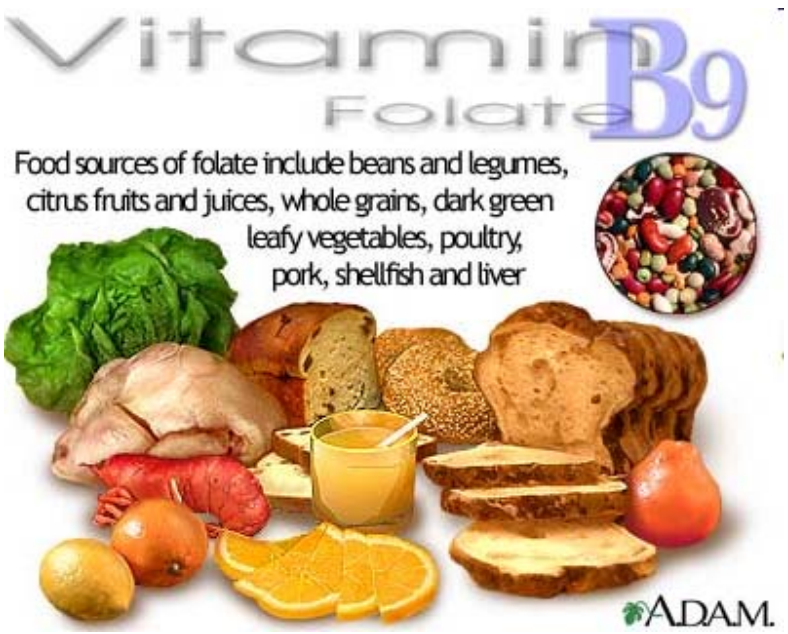
Folic acid deficiency

Deficiency results in elevated levels of homocystein.

Deficiency in pregnant women can lead to birth defects.

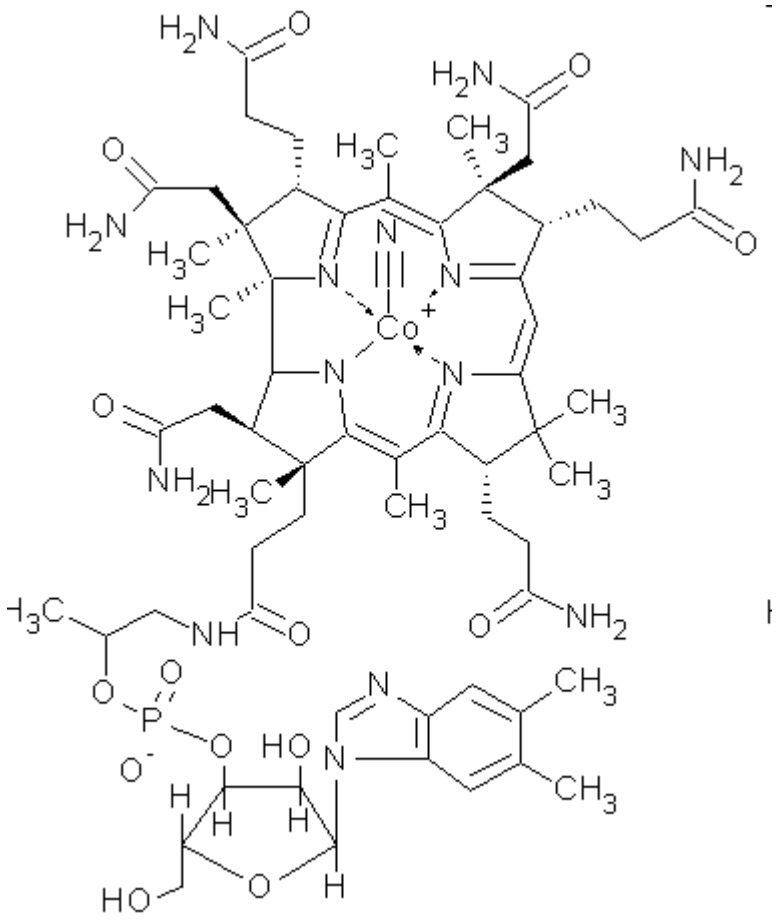
Sources of vitamin B_9

- sources of animal origin
- milk and milk products
- yeast
- greens



Vitamin B_{12} - cobalamin

- Chemically most complex vitamin
- Complex of organic compounds atom within the molecule is Co, similar to the heme.
- In man there are two metabolically active forms: methylkobalamin a adenosylkobalamin.



Vitamin B_{12} - cobalamin

- Cobalamin catalyses two reactions
  - Cytoplasmic *methylation of homocystein* to *methionin*.
  - Mitochondrial *methylmalonyl-CoA mutase* (methylmalonyl-CoA → sukcynyl-CoA) needs *deoxy adenosylkobalamin.*

Vitamin B_{12} – cobalamin

- Essential for the maturation of erythrocytes.
- Protects against pernicious anemia.
- Essential for cell growth and reproduction.
- Essential for the formation of myelin and nucleoproteins.

Vitamin B_{12} – cobalamin

- Vitamin B_{12} in food is bound to the protein.
- Hydrochloric acid in the stomach releases free vitamin B_{12}.
- Once released vitamin B_{12} combines with a substance called intrinsic factor (IF). This complex can then be absorbed by the intestinal tract.

Sources of vitamin B_{12}

- fish and shellfish,
- meat (especially liver),
- poultry,
- eggs,
- milk, and
- milk products

while lacto-ovo vegetarians usually get enough B_{12} through consuming diary products, vegan will lack B_{12}

Vitamin C

- Vitamin C is a water-soluble vitamin.
- Almost all animals and plants synthesize their own vitamin C, not man.
- Vitamin C was first isolated in 1928 and in 1932 it was proved to be the agent which prevents scurvy.

Vitamin C

- Vitamin C is a weak acid, called ascorbic acid or its salts “ascorbates”.
- It is the L-enantiomer of ascorbic acid.
- The D-enantiomer shows no biological activity.

The role of vitaminC

- Cofactor in the synthesis of norepinephrine from dopamine.
- Involved in a variety of metabolic processes (oxidation-reduction reactions and cellular respiration, carbohydrate metabolism, synthesis of lipids and proteins).
- antioxidant and free radical scavenger → maintain proper immune system.

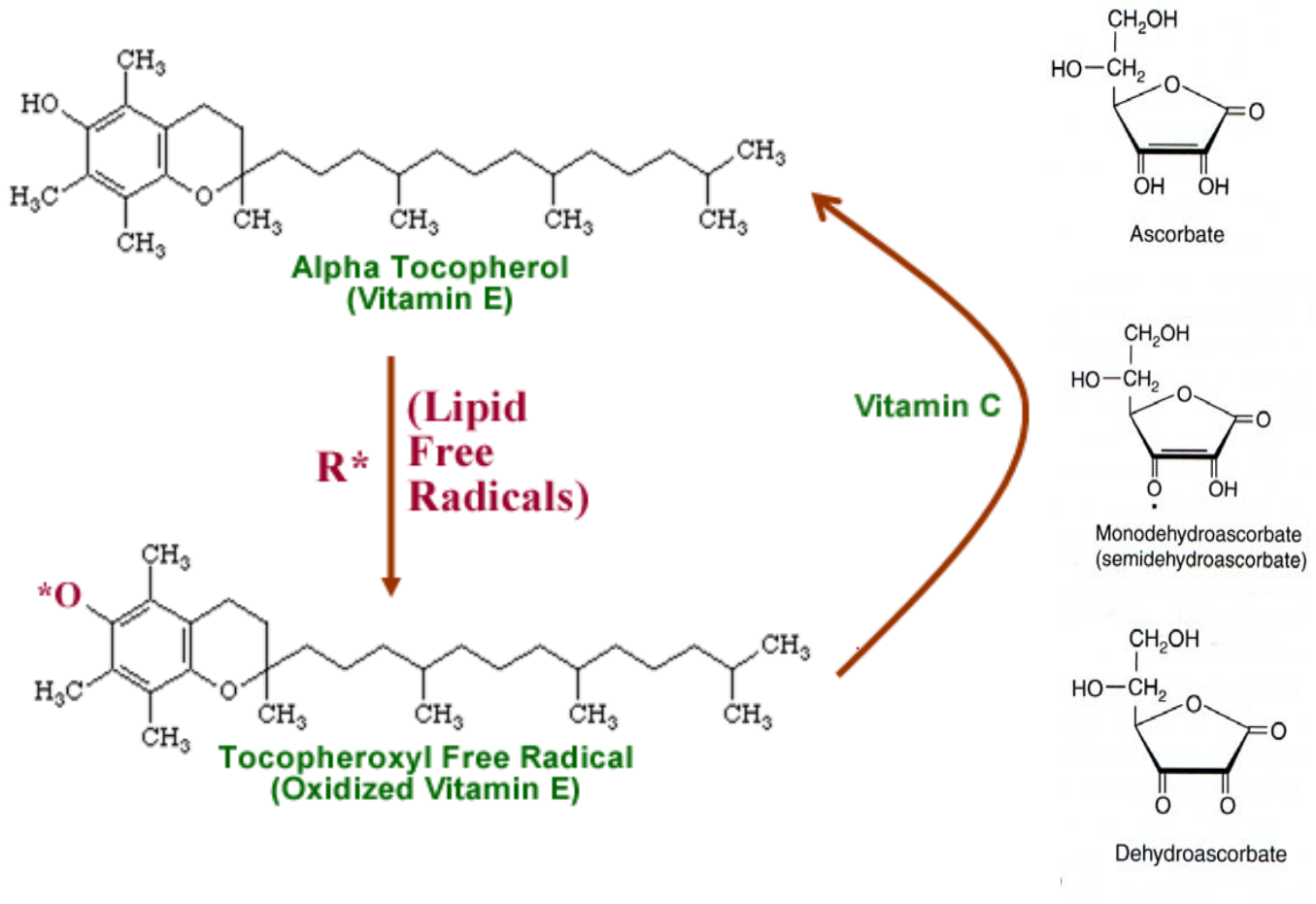
The role of vitaminC

- T-lymphocyte activity, phagocyte function, leukocyte mobility, and possibly antibody and interferon production seem to be increased by vitamin C.
- Involved in the synthesis of collagen, the major component of ligaments, tendons, cartilages and skin.
- Involved in tyrosine metabolism.

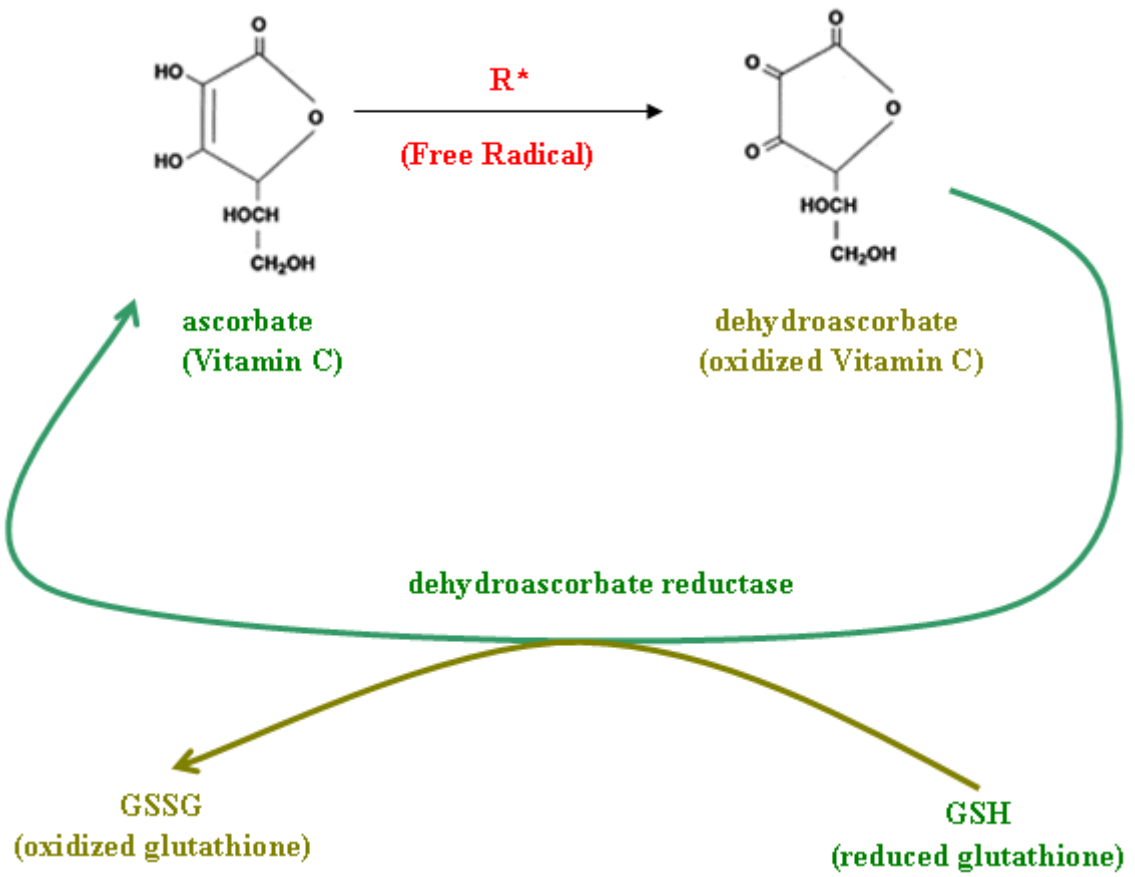
Deficiency of vitaminC

- Fatigue, personality changes, decline in psychomotor performance and motivation.
- Vitamin C deficiency over 3-5 months results in *symptomatic scurvy.*
- Scurvy leads to the formation of liver spots on the skin, spongy gums, and bleeding from all mucous membranes.
- In advanced scurvy there are open, suppurating wounds and loss of teeth. Severe scurvy may progress to neuritis, jaundice, fever, dyspnea, and death.

Vitamin C as antioxidant



Vitamin C as antioxidant



Vitamin C as pro-oxidant

- Ascorbic acid reduces transition metals - Cu^{2+}, to Cu^{+}, and Fe^{3+} to Fe^{2+} during conversion from ascorbate to dehydroascorbate. This reaction can generate superoxide and other ROS:
- Fenton´s reaction:
- (1) $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH\cdot + OH^{-}$
- (2) $Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + OOH\cdot + H^{+}$

$2\ Fe^{2+} + 2\ H_2O_2 \rightarrow 2\ Fe^{3+} + 2\ OH\cdot + 2\ OH^{-}$

$2\ Fe^{3+}$ + ascorbate $\rightarrow 2\ Fe^{2+}$ + dehydroascorbate