Fat-soluble vitamins

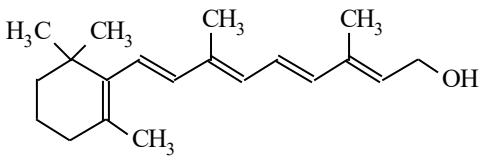
58.1.1. Retinol (vitamin A) and retinoids

Vitamin A is a customary name and refers to compounds of animal origin which show the activity of vitamin A.

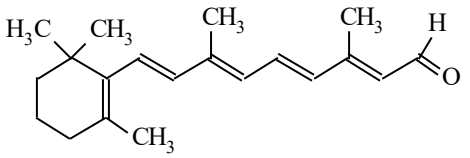
This group comprises retinol, retinal and retinoic acid.

Only retinol demonstrates fully the activity of vitamin A.

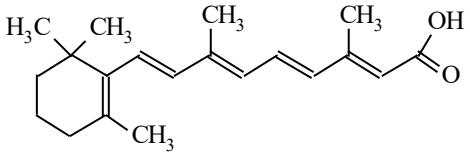
Retinoids are natural or synthetic analogues of retinol.



Retinol

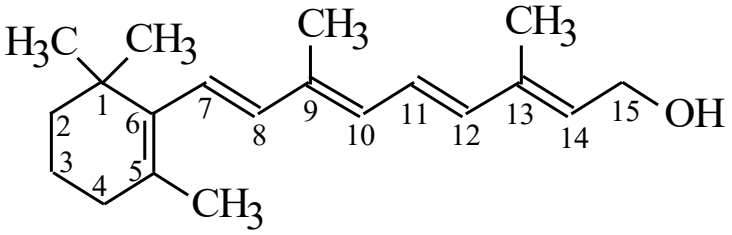


Retinal

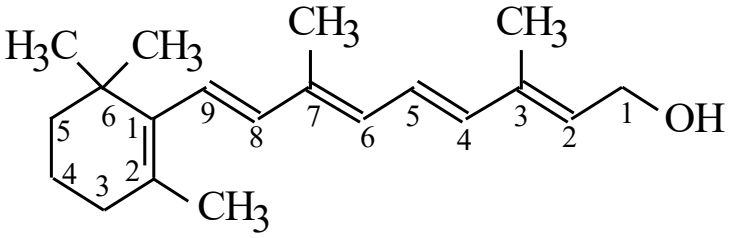


Retinoic acid

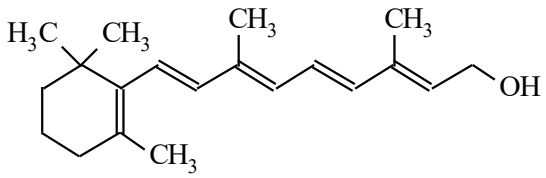
The most important retinoids are esters of retinol, retinal and retinoid acids, such as *all-trans*-retinoic acid (*Tretinoin*), 13-*cis*-retinoic acid (*Isotretinoin*) and 9-*cis*-retinoic acid.
β-Carotene and nonatetraene are the basis of the nomenclature of retinol and retinoids, respectively.



Retinol, *Vitamin A*, *Vitamin A*$_1$
15-*Apo*-β-caroten-15-ol



(*all-E*)-3,7-Dimethyl-9-(2,6,6-trimethyl)-1-cyklohexen-1-yl)-2,4,6,8-nonatetraen-1-ol



The vitamin activity of retinol is determined by the β-ionone structure at the terminal carbon atom of the polyenolic chain.

When a β-ionone is replaced by an α-ionone vitamin activity disappears.

Because there are four double bond in the polyenolic chain, 16 geometric *cis*-*trans* isomers are possible.

All *cis* isomers are less active than *trans* isomers.

For example, 13-*cis*-retinol shows 75-80%, 11-*cis*-retinol 45-50%, 9-*cis*-retinol 22% of the activity of *all*-*trans*-retinol.

The oxidation of the alcohol group of retinol ($\rightarrow$ retinal $\rightarrow$ retinoic acid) decreases the activity of retinal by 5-10% and of retinoic acid by 40-50% in comparison with retinol.

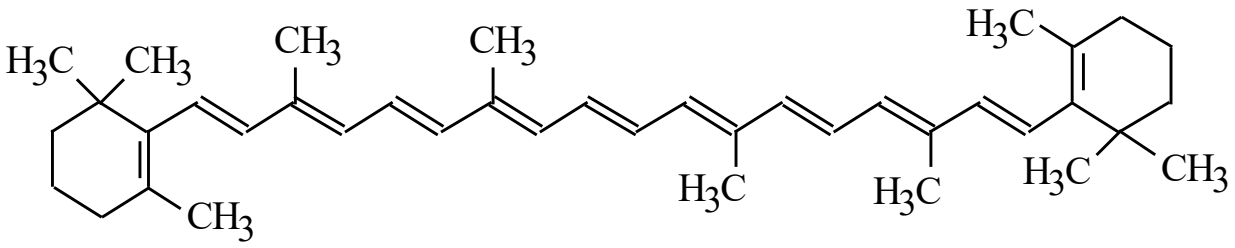
The introduction of an additional double bond into the β-ionone ring creates 3,4-didehydroretinol (vitamin A_2), which shows only 40% of the activity of retinol.

Vitamin A appears only in animals.

In plants pro-vitamin A (β-carotene) is present.

β-Carotene is a yellow pigment.

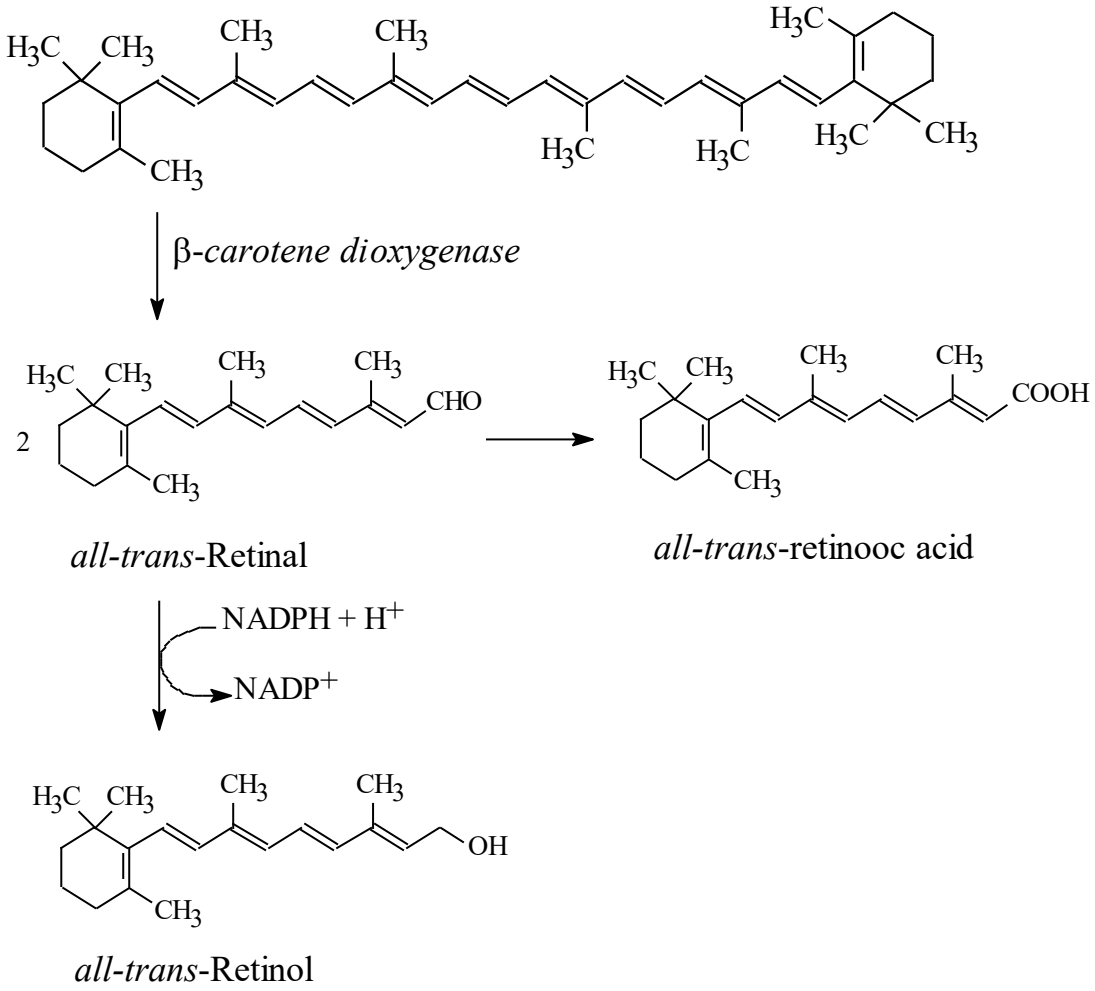
The chain of β-carotene consists of 4 isoprenyl_rests and 2 β-ionone rings at the terminal carbon atom of the polyenolic chain.



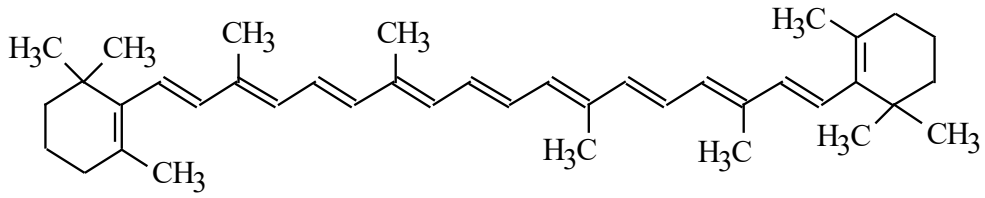
In the human body, in the intestinal mucosa, cleavage of β-carotene to 2 molecules of retinal under the influence of β-carotene dioxygenase is observed. In this reaction molecular oxygen is necessary.
Salts of bile acids intensify this process.

The conversion of β-carotene to retinol is not complete.

β-Carotene demonstrates only 1/6 of retinol's activity, which means that 1 g of retinol is equivalent to 6 g of β-carotene.

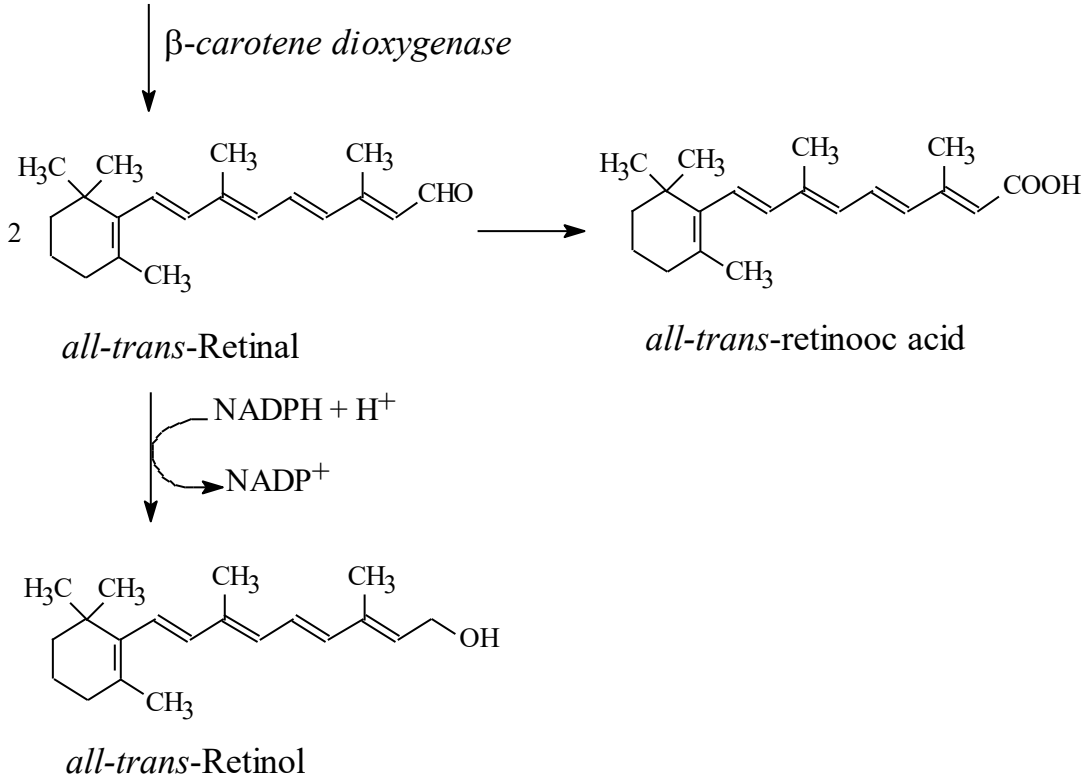


In the intestinal mucosa the reduction of retinal to retinol also takes place. NADPH is a hydrogen electron donor.
A small amount of retinal is oxidated to retinoic acid.



β,β-Carotene = (*all E*)- 1,1'-(3,7,12,16-tetramethyl-1,3,5,7,9,11,13,15,17-octadecanonaen-1,18-diylo)bis[2,6,6-trimethylcyclohexen] =

(*all E*)- 3,7,12,16-tetramethyl-1,18-bis(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5,7,9,11,13,15,17-octadecanonaen



Preparations of β-carotene (BETAVIN, CAROTABEN) are used in therapy as vitamin A precursors. Retinal, produced in the intestinal mucosa, after reduction to retinol, undergoes esterification under the influence of retinol acetyltransferase.

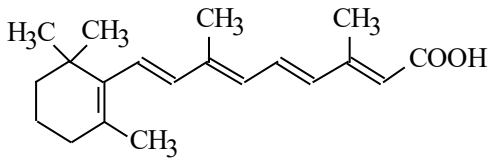
β-Carotene is an effective scavenger of singlet oxygen ($^1O_2$). This property explains why β-carotene is used as a substance preventing the development of certain tumors, especially cutaneous carcinoma under the influence of UV radiation and some chemical substances.

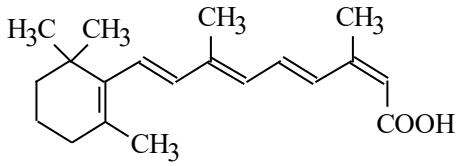
Carotenoids are also used as pigments in the food industry. For example, β-carotene is used as a colouring agents in margarine. Water-soluble derivatives of β-carotene are used as colouring agents in drinks and other products that do not contain fats.

In therapy, in addition to retinol the following are also used:

- esters of retinol (acetate - *Retinol acetate*, palmitate - *Retinol palmitate*, propionate - *Retinol propionate*),

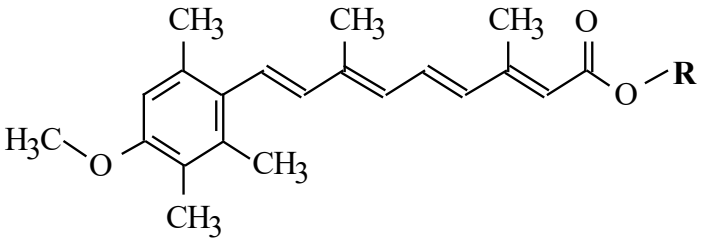
- retinoic acids (*Tretinoin*, *Isotretinoin*) and





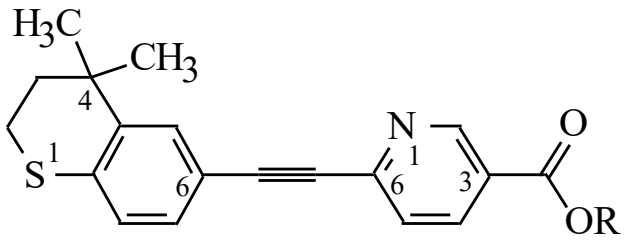
Tretinoin, EPI-ABEREL *Isotretinoin*, ROACCUTAN

- synthetic retinoids, in which the cyclohexene ring was replaced by a benzene ring (*Etretinate*, *Acitretin*, *Tazaroten*), are used.



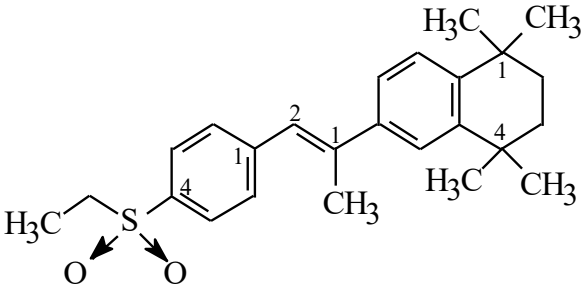
Etretinate, R = -CH_2-CH_3; TIGASON

Acitretin, R = H; NEOTIGASON

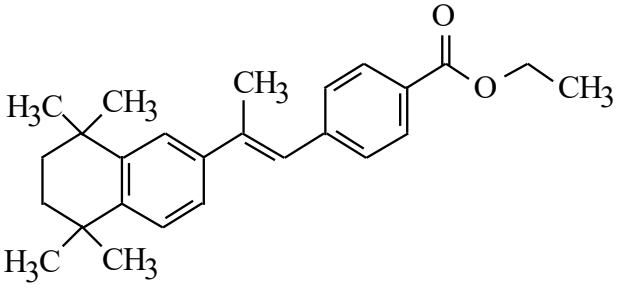


Tazaroten, R = -C_2H_5 (pro-drug); ZORAC

Tazarotenoic acid; R = H



Etarotene

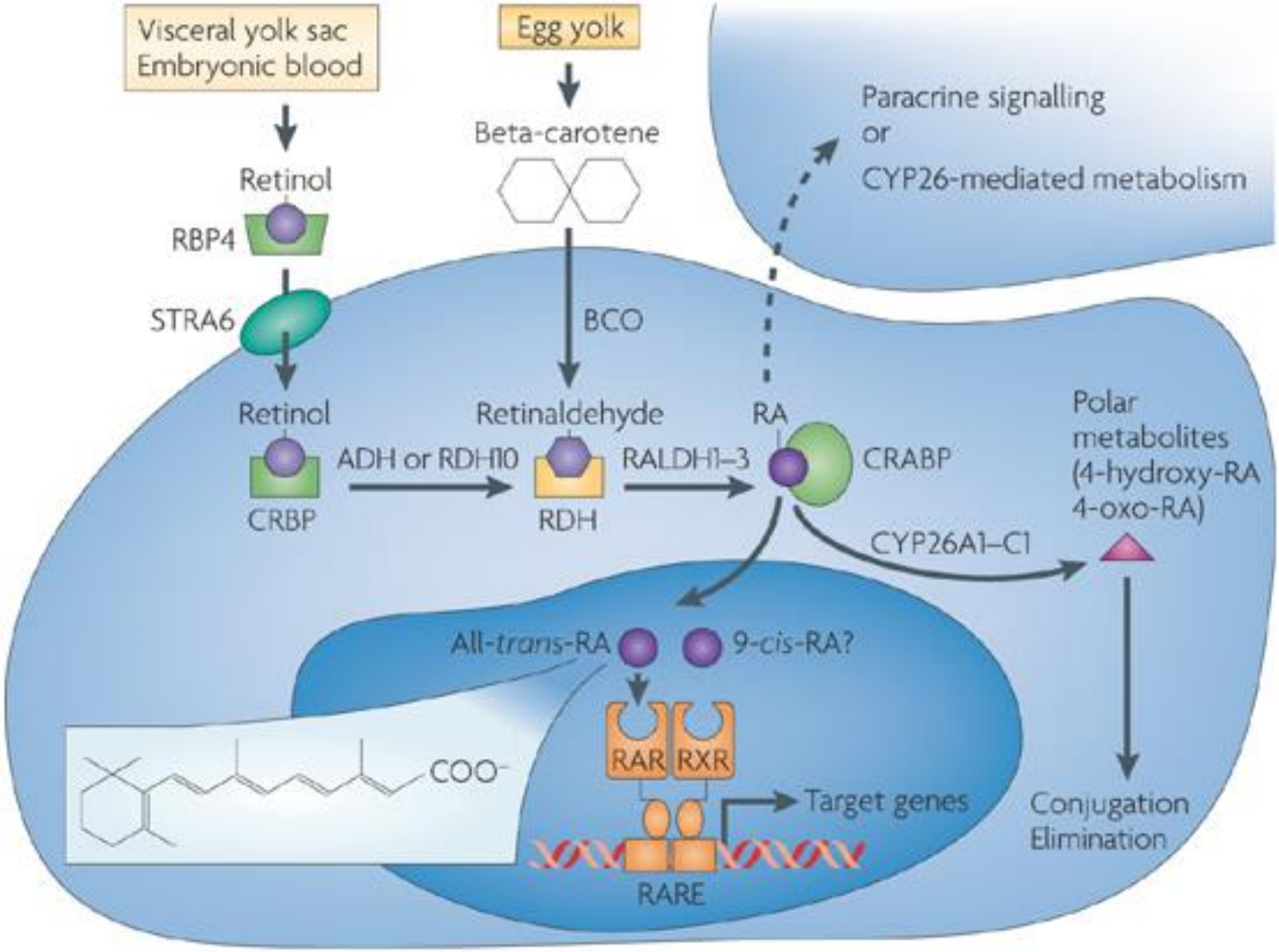


Arotinoide

The activity profile of retinoic acids is different from the activity profile of retinol. Certain polyaromatic retinoids, eg. arotinoids (*Arotinoidethylester*, *Arotinoid acid*, *Etarotene)* are in clinical trials.

Retinol esters are hydrolyzed in the intestinal mucosa, releasing retinol and free fatty acids. Retinol derived from esters and from the cleavage and reduction of carotenes is reesterfied to long-chain fatty acids in the intestinal mucosa and secreted as a component of chylomicrons into the lymphatic system. Retinol esters contained in chylomicrons are taken up by and stored in the liver.

Retinol is released from the liver and transported to extrahepatic tissue by the plasma retinol-binding protein (RBP). This complex attaches to specific receptors on the surface of the cells of peripherial tissues, permitting retinol to enter. Many tissues contain a cellular retinol-binding protein that carries retinol to sites in the nucleus where the vitamin acts in the manner analogous to steroid hormones.



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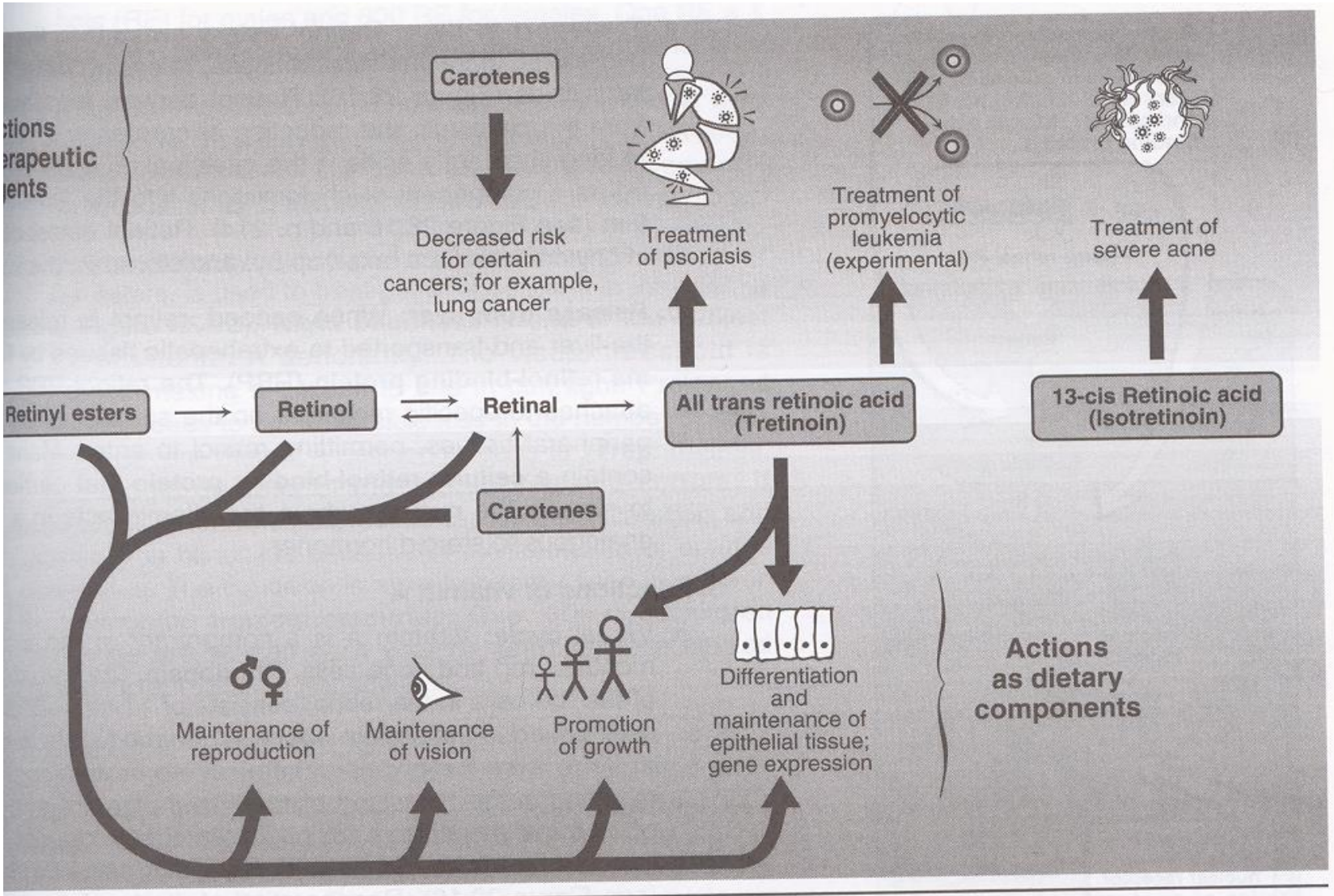
Vitamin A:

- participates in the visual cycle and is important for correct vision
- stimulates the growth of young bodies
- is vital for the reproduction process
- is essential for normal differentiation of epithelial tissues and mucus secretion
- demonstrates antioxidant properties.

Vitamin A deficiency may result from long-term starvation, an inappropriate diet, the mal absorption syndrome or liver damage. Night blindness is one of the earliest signs of vitamin A deficiency. Severe vitamin A deficiency leads to xerophthalmia, a pathologic dryness of the conjunctiva and cornea. If untreated, xerophthalmia results in corneal ulceration and ultimately in blindness because of the formation of opaque scar tissue. Dietary deficiency in children may cause anemia and growth inhibition.



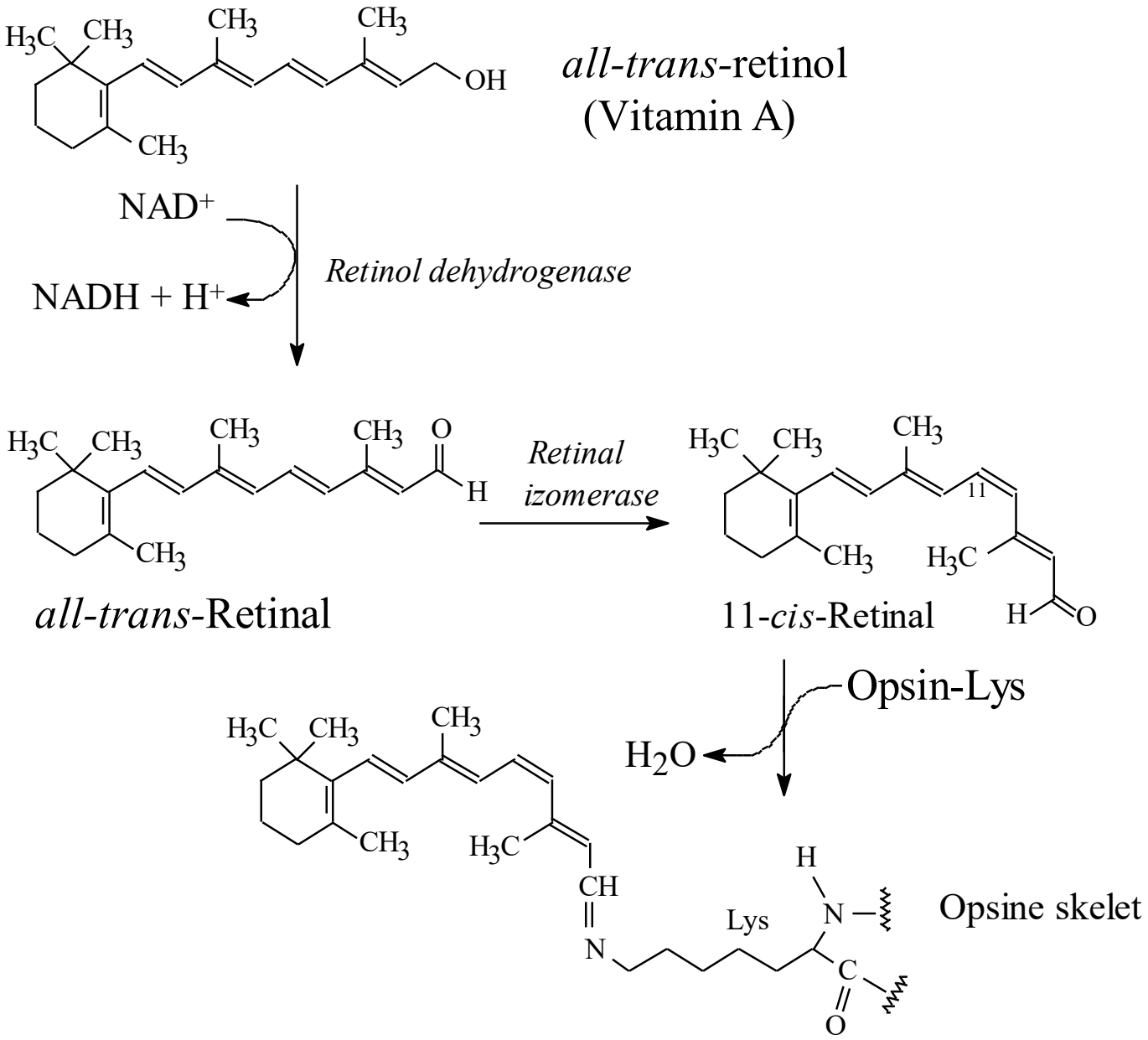
re 28.13
mary of actions of retinoids. Compounds in boxes are available as dietary components or as pharmaco-
agents.

An excessive intake of vitamin A produces a toxic syndrome called hypervitaminosis A.

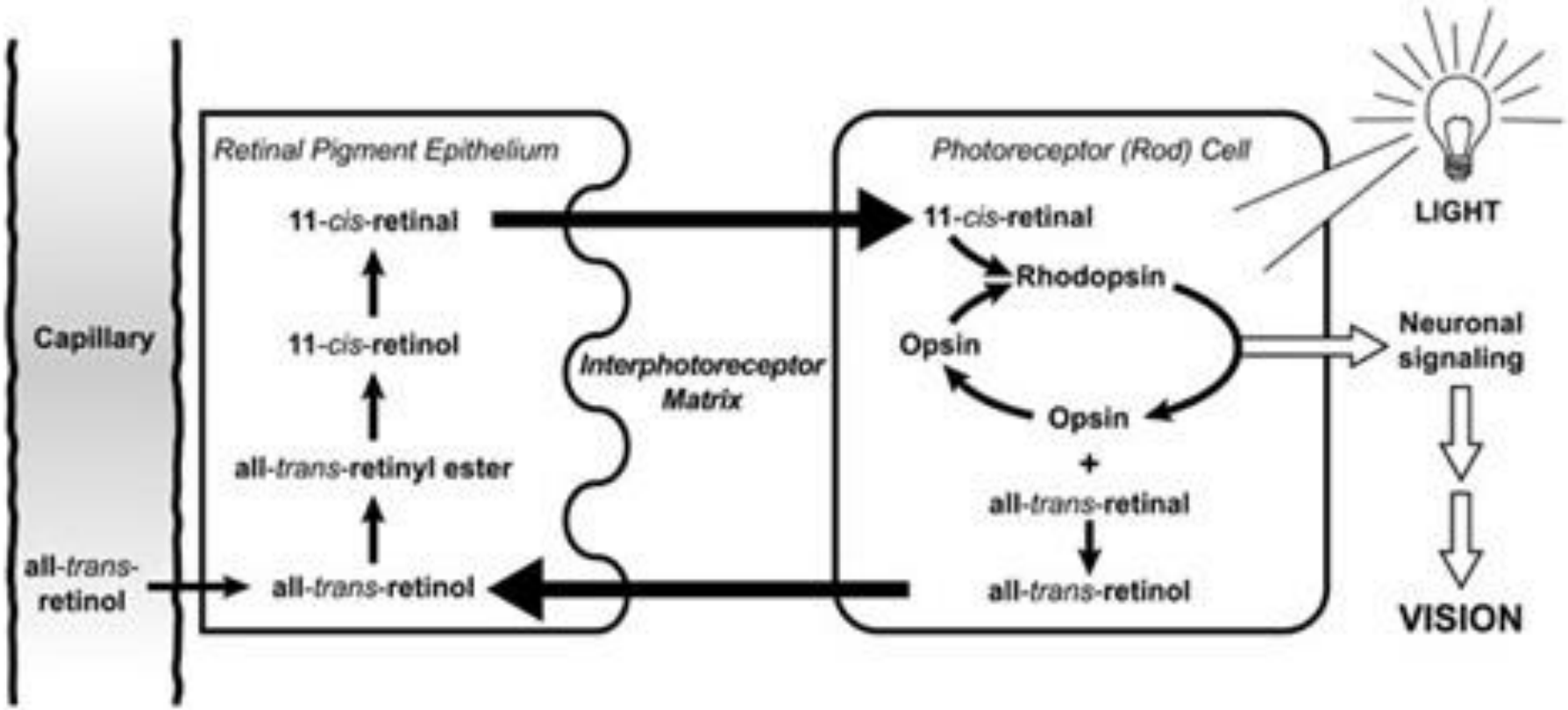
In acute poisoning an increase in the intracranial pressure and vomiting are observed. In chronic poisoning loss of appetite, double vision, headache, excitation, hepatomegaly and splenomegaly, leucopenia, periosteal hypertrophy and osteodynia are observed.

Retinol after translocation to the retina is stored in the rod cells in which under the influence of specific retinol dehydrogenase it is oxidized to *all-trans*-retinal.

All-trans-retinal converts to 11-*cis*-retinal under the influence of retinal isomerase.



The incorporation of retinal into light-sensitive rhodopsin protein


Capillary
all-trans-retinol
Retinal Pigment Epithelium
11-cis-retinal
11-cis-retinol
all-trans-retinyl ester
all-trans-retinol
Interphotoreceptor Matrix
Photoreceptor (Rod) Cell
11-cis-retinal
Rhodopsin
Opsin
Opsin
+
all-trans-retinal
all-trans-retinol
LIGHT
Neuronal signaling
VISION

The aldehyde group of 11-cis-retinal creates Schiff base with the lysine of opsin and next rhodopsin, which is light-sensitive.

When rhodopsin is exposed to light it undergoes degradation to trans-retinal and protein opsin. This reaction is accompanied by a conformation change, which induces the opening of the calcium channel in the rods. An excessive inflow of calcium ions to the rod cells triggers a nerve impulse that is transmitted by the optic nerve to the brain.

Retinoic acid does not influence the vision cycle. It influences the growth and differentiation of epithelium cells and the synthesis of glycoproteins, which are responsible for the transport of oligosaccharides through the membrane cell.

Those skin diseases whose treatment is difficult, especially psoriasis, are indications for the use of synthetic retinoids.

Retinoids:

- normalize differentiation of the keratinocytes of the epidermis
- act antiproliferatively and antiinflammatorily
- modulate immunologic response
- stimulate synthesis of glycoproteins and glycolipids, which normalizes the level of keratinocytes and facilitates creation of healthy epidermis cells.

Retinoids increase the concentration and activity of cAMP-dependent proteokinase in psoroid fibroblasts.

The influence of retinoids on normal fibroblasts has not been established.

Two types of proteokinases have been identified with different subunits (RI, RII). They participate in the proliferation of cells (RI) or in the differentiation and inhibition of growth (RII).

Also the inhibition of the activity of ornithine decarboxylase is significant for the action of retinoids. This enzyme regulates, among others, the biosynthesis of polyamines.

The antiinflammatory action of retinoids is explained as the inhibiton of chemotaxis.

Vitamin A plays an important role in the reproduction process. Retinol and retinal are essential for normal reproduction, supporting spermatogenesis in the male and preventing fetal resorption in the female.

Retinoic acid is inactive in maintaining reproduction.

Synthetic retinoids such as *Etretinate*, *Acitretin and Tazaroten* are used in therapy. Etretinate has a very long half-time (84-168 days). Acitretin is an active metabolite of etretinate which is produced after hydrolysis of the ester group under the influence of esterases. The half-time of acitretin is 50-60 h.

Tazaroten is the first receptor-selective retinoid which has a different chemical structure from vitamin A. It is a pro-drug which is rapidly metabolized to tazarotenoic acid under the influence of esterases. Its elimination half-time is approx. 18 h. When it is administered locally in the treatment of psoriasis, it partly transits into the systemic system. Its resorption from a psoroid skin is greater then from a healthy skin.

Tazaroten demonstrates fewer unwanted effects than some retonoids used previously.

Side effects of synthetic retinoids are significant and depend on dosage.

Side effects may affect:

- skin and mucous membranes by inducing itching, irritation, erythema, exfoliation, cutaneous rash, contact skin inflammation, aggravation of psoriasis, hair loss
- liver function and blood by increasing the levels of triacylglyceride, alanine aminotransferase, aspartate aminotransferase, keratinophosphokinase, alkaline phosphatase, bilirubin, lactic dehydrogenase, uric acid, and by decreasing the level of the HDL fraction of cholesterol
- the osseous system by causing osteoporosis
- produce teratogenic and embryotoxic action.

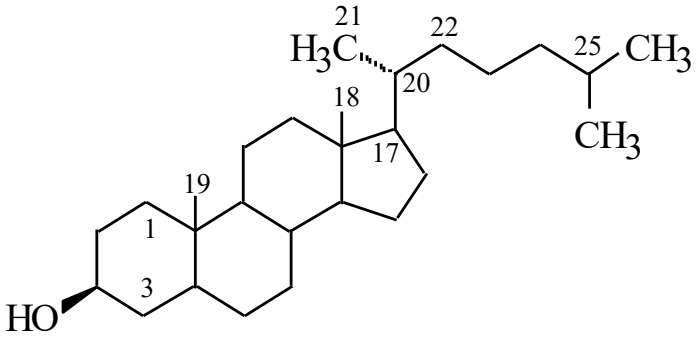
58.1.2. Vitamin D and its derivatives

Ergocalciferol (vitamin D_2), cholecalciferol (vitamin D_3), dihydrotachysterol, their metabolites and alfacalcidiol (1-α-hydroxycalciferol) and calcitriol (1,25-dihydroxycalciferol) are recognized as vitamins D.

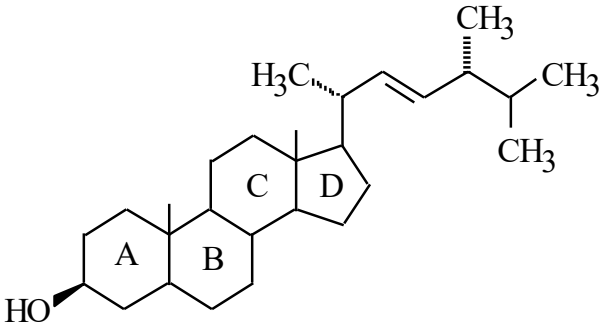
Vitamins D are supplied with food as cholecalciferol and ergocalciferol or their precursors – 7-dehydrocholesterol and ergosterol.

In the human body vitamins D are produced from provitamins, which are present in animals and plants.

Ergosterol is a provitamin found in plants while 7-dehydrocholesterol in animals.
Both compounds differ in the side chain at position C17 (a double bond and a methyl group in the case of ergosterol)



Cholesterol, 3-Hydroxycholest-5-en



Ergosterol, *Provitamin* D_2

(3β, 22*E*)-Ergosta-5,7,22-trien-3-ol

Precursors of vitamin D accumulate in the skin. Several tissues participate in their transformation.

Derivatives of vitamin D with hormonal action are active metabolites of vitamin D. They are classified as β-secosteroids, derivatives with an open β-gonane ring. Each derivative has a different number of hydroxyl groups.

In the skin, in Malpighian cells most of vitamin D is used for the synthesis of vitamin D_2 (*Ergocalciferol*) or D_3 (*Cholecalciferol*).

Absorbed light energy induces photoisomerization by inducing the singlet state, which results in a bond cleavage in positions 9,10 and the creation of pro-vitamin D_3, which undergoes spontaneous isomerization to vitamin D_3. The rate of biosynthesis of vitamins D_2 and D_3 is directly proportional to the radiation rate. As people become older the amount of 7-dehydrocholesterol in the epithelium decreases, which may cause a negative calcium balance in older patients.

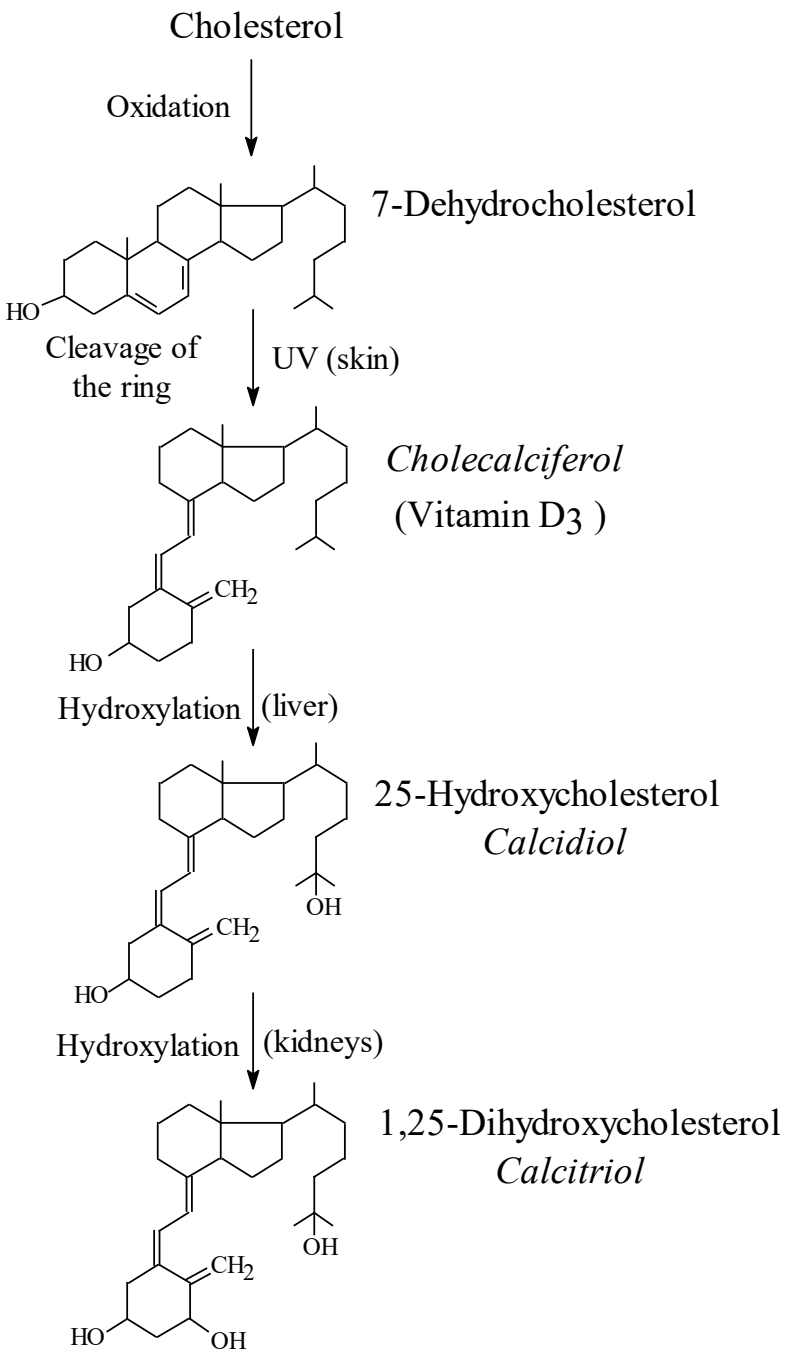
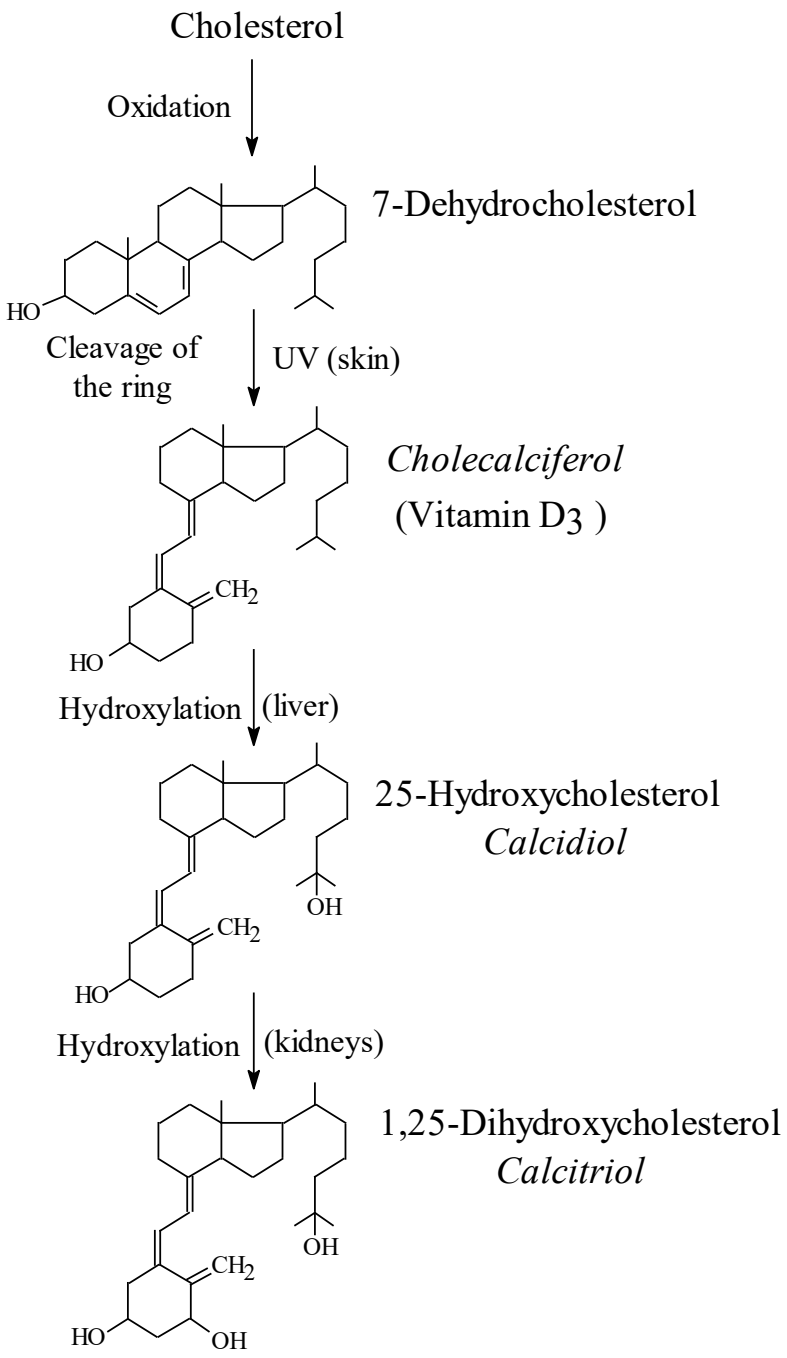


Figure 58.3.

Biosynthesis of 1,25-dihydroxycholecalciferol.

Vitamins D2 and D3 demonstrate the same biological activity. Cholecalciferol, photosynthetized in the skin or absorbed in the instestine, is transported to the liver with the blood as a compound bound with a specific carrier that binds Vitamin D (DBP, D-binding protein), called transcaliferin.



In the liver, in the endoplasmic reticulum, cholecalciferol undergoes 25-hydroxylation to 25-hydroxycalciferol (25-OH-D_3; *Calcidiol*) under the influence of mixed-function oxidases.

Calcidiol is the main form of vitamin D in the body but it demonstrates much less biological activity than the final product.

Calcidiol reappears in the circulation and after binding with the vitamin D-binding protein it is transported to the kidneys, where it is hydroxylated in position 1 by mixed-function oxidases to 1,25-dihydroxyvitamin D_3, i.e. 1,25-dihydroxycholecaciferol. (1,25-$(OH)_2$-D_3; *Calcitriol*).

This reaction is observed in the mitochondria of the cells of the tortuous proximal canaliculus. $1,25(OH)_2$-D_3 is the most active natural metabolite of vitamin D.

The synthesis of calcitriol occurs according to the feedback principle.

Hormonal derivatives of vitamin D_3 are the only hormones that influence calcium homeostase which act on the gastrointestinal level.

They stimulate the transport of calcium from the gastrointestinal lumen through the intestinal epithelium against the calcium concentration gradient.

On the cell level calcitriol acts similarly to other steroid hormones, including vitamin D, by binding with intracellural receptors.

The binding of a hormone with a receptor leads to the expression of a gene.

Vitamin D receptors are located in the intestine, kidneys, bone tissue and in the cells of the immunologic system, such as macrophages, monocytes, activated B and T lymphocytes.

Calcitriol binds with the protein of the nuclear receptor.

The complex created in this way catalyses the nuclear cofactor (nuclear accessory factor, NAF) causing phosphorylation of the receptor and increasing its affinity for DNA.

The complex of receptor-hormone-DNA induces or inhibits the transcription of genes in the acceptor cell.

Calcitriol demonstrates a wide range of action including the kidneys, gastrointestinal tract and bones. In the intestinal mucosa calcitriol increases the intercellular transport of calcium and phosphates.

Together with parathormone it increases the calcium level in plasma by promoting restoration of hydroxyapatite in the bones.

Calcitriol also increases reverse resorption in the kidneys, participates in the regulation of prolactin release and causes differentiation of keratinocytes.

It is also suggested that calcitriol participates in the intercellular homeostase of the cells of the myocardium.

Some animal products such as meat, liver, milk, egg yolk, fish products and codliver oil contain a large amount of vitamin D.

In a deficiency of vitamin D the following diseases may occur: hypocalcemia, hypophosphatemia, skeletal demineralization, osteodynia, susceptibility to fracture and bone deformation in children.

Vitamin D deficiency is observed in the case of:

- insufficient exposure to sunlight
- insufficient supply of vitamin D in food
- malabsorption syndrome
- disorder of conversion of vitamin D to 1,25-$(OH)_2D_3$ in the liver and kidneys.

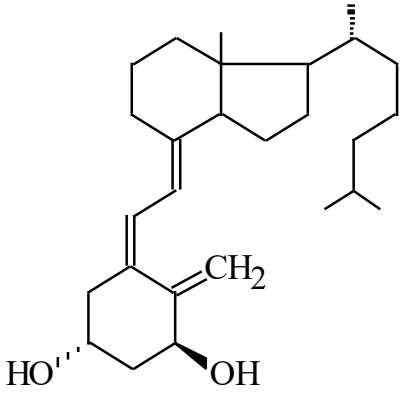
Vitamins D are used in the prevention and treatment of rickets, vitamin D deficency-related osteomalacia and in hypocalcemia caused by hypoparathyroidism.

Vitamins D accumulate mainly in the fatty tissue. Their over-supply leads to:

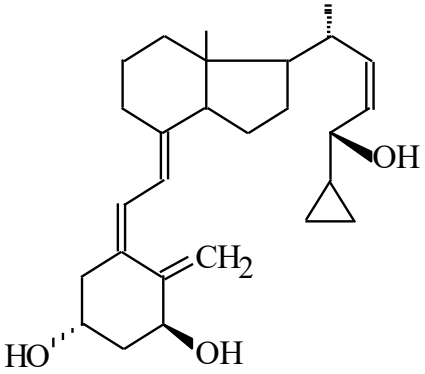
- increased concentration of calcium in the blood and its deposition in blood vessels
- increased elimination of calcium in urine, which can cause renal calculosis and such symptoms as sitophobia, nausea, vomiting, headache, dizziness, polyuria, heart work disorder, psychosis and osteopenia.

Vitamin D overdose in pregnant women may cause skeletal deformation in the fetus.

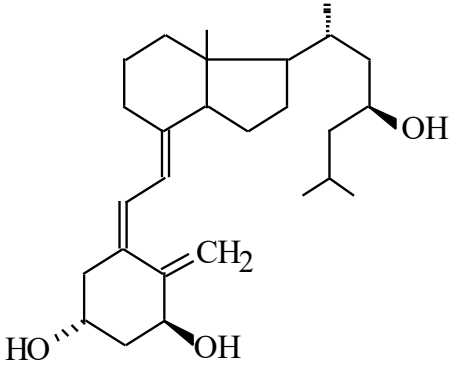
Some derivatives of vitamin D, such as *alfacalcidol*, *calcitriol* and *calcipotriol* have been introduced into therapy.



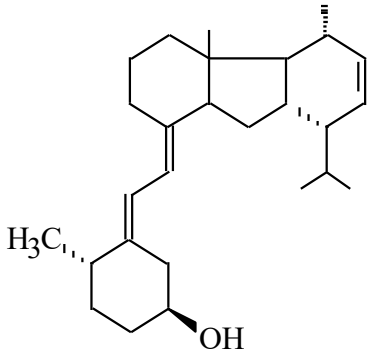
Alfacalcidol, EinsAlfa, ALFA D_3



Calcipotriol, PSOCURTAN



Tacalcitol, CURATODERM



Dihydrotachysterol, TACHYSTIN

9,10-Secoergosta-5,7,22-trien-3β-ol

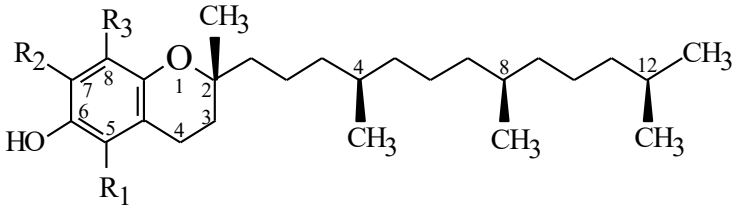
Therapeutic indications for their use are: hypocalcemia caused by vitamin D deficiency or chronic renal failure, osteoporosis caused by bone atrophy, osteopathy (systemic, non-inflammatory bone disesase) and vitamin D-resistant rachitism.

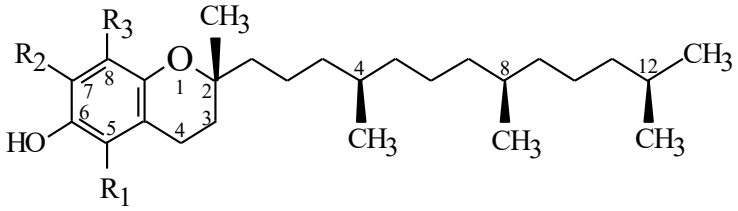
These drugs are also used in the treatment of psoriasis.

58.1.3. Tocopherols (Vitamin E)

Natural vitamins E comprise tocopherols and tocotrienols. The basic configuration in their chemical structure is tocol (chromen-6-ol derivative), which does not appear in nature. In the position 2 of chromen-6-ol is a 16-carbon atom phytyl chain with methyl groups in positions 4, 8 and 12. In the tocotrienols in the chain in positions 3,7 and 11 are double bonds. Natural vitamin E exists in eight different forms or isomers, four tocopherols and four tocotrienols. All isomers have a chromanol ring with a hydroxyl group which can donate a hydrogen atom to reduce free radicals and a hydrophobic side chain which allows for penetration into biological membranes. There are α,β,γ, and δ forms of both tocopherols and tocotrienols, determined by the number of methyl groups on the chromanol ring. All tocopherols and tocotrienols have methyl groups in positions 2 and 8.

They are different in positions 5 and 7.





$R_1 = R_2 = R_3 = CH_3$ =α-Tocopherol = 5,7,8-trimethyltocol = 2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-ol = 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopiran-6-ol; VITAMINUM E

Tocopherols	R_1	R_2	R_3	Biological activity, %
α	CH_3	CH_3	CH_3	100
β	CH_3	H	CH_3	50
γ	H	CH_3	CH_3	10
δ	H	H	CH_3	1
Tocotrienols α, β, γ and δ	As tocoferol			≤ 30
Tocol	H	H	H	-

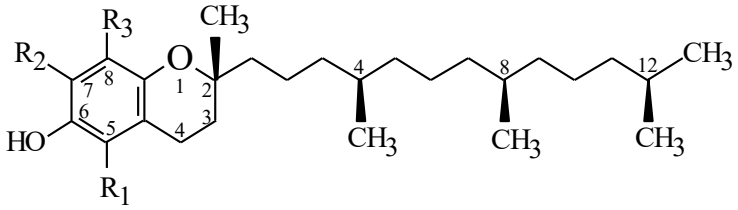
The most active is α-tocopherol, which has methyl groups in all positions.

The lack of one methyl group in position 7 (β-tocopherol) decreases activity by about 50% and the lack of one methyl group in position 5 (γ-tocopherol) decreases activity by approx. 90%.

δ-Tocopherol, which does not have methyl groups in positions 5 and 7 is only 1% as active as α-tocopherol.

Tocol which does not have any methyl groups in positions 5, 7 and 8 is biologically inactive.

Tocotrienols demonstrate less biological activity then tocopherols.



In position 2 of the chroman structure and in positions 4’ and 8’ of the alkyl substituent are asymetric carbon atoms, so 8 stereoisomers are possible.

Natural vitamin E has the configuration 2R,4'R,8'R and is also described as *R,R,R-alfa*-tocopherol or previously as *D-alfa*-tocopherol.

Synthetic vitamin E is an equimolecular mixture of 8 isomers and is called *all-rac-alfa*-tocopherol or formerly *D,L-alfa*-tocopherol.

Each stereoisomer has different biological activity. The most active is the 2R,4'R,8'R-*alfa*-tocopherol isomer (Tab. 58.1).

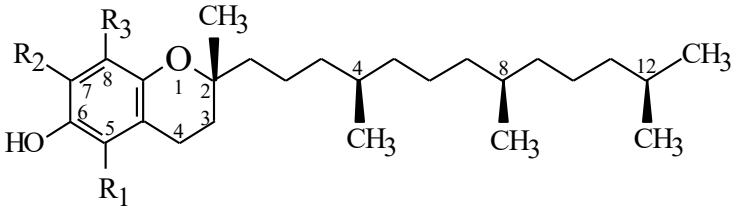


Table 58.1. The biological activity of α-tocopherol stereoisomers

Isomer	Biological activity, %	Isomer	Biological activity, %
2R,4'R,8'R	100	2R,4'S,8'R	57
2R,4'R,8'S	90	2S,4'R,8'S	37
2R,4'S,8'S	73	2S,4'R,8'R	31
2S,4'S,8'S	60	2S,4'S,8'R	21

Table 58.2. Standards for expressing the biological activity of vitamin E

Tocopherols	USP unit/mg	Coefficient mg -TE
R,R,R- α	1,49	1,00
all-rac- α	1,10	0,74
octan all-rac-α	1,00	0,67

The activity of tocopherol is measured in international units.

According to the USP, *all-rac-alfa*-tocopherol is accepted as standard for pharmaceutical preparations.

For standardization of dietary preparations units of α-tocopherol are used.

Biological activity is demonstrated by vitamin E with a free phenol group in position 6, but this form of vitamin is sensitive to oxidation.

By esterification of the phenol group with acetic, succinic, phosphoric or nicotinic acid, resistant derivatives have been obtained, which after resorption recover full activity as a result of the hydrolysis of the ester group.

The amount of vitamin E required by the body is supplied in food.

Meat, eggs, liver, fish, poultry and palm oil are especially rich in vitamin E. Similarly, a high concentration of vitamin E is found in soybean oil (mainly δ-tocopherol), sunflower oil, wheat germ oil, olive oil (mainly α -tocopherol) and palm oil (equal amounts of α-tocopherol and α-tocotrienol).

Resorption of tocopherols, regardless of their chemical structure and configuration, takes place in the duodenum as micelles, together with cholesterol, fatty acids and monoglycerols.

This process requires the presence of bile acids and pancreas enzymes. Enzymes are responsible for the degradation of tocopherol esters to active tocopherol. Only free tocopherol undergoes resorption.

From 60% to 70% of an α-tocopherol dose reaches the enterocytes of the mucous membrane of the small intestine. From the enterocytes tocopherols are transferred to chylomicrons together with cholesterol, triacylglycerols (TG), phospholipids and apolipoproteins.

The chylomicrons, containing tocopherols, enter the circulatory system in the lymph. Under the influence of lipoproteinase located in the vascular wall, the chylomicrons are restored to remnants of chylomicrons which arrive at the specific receptors of remnants in liver cells.

In the liver tocopherols bind stereoselectively with transport protein TBP (tocopherol binding protein). The transport protein binds first with *R,R,R-alfa*-tocopherol, which is a natural stereoisomer appearing in plants.

There is a relationship between the affinity of different tocopherols for TBP and their biological activity.

Tocotrienols are transported in very low-density lipoproteins (VLDL) rich in TG and they are deposited in the fatty tissue.

α-Tocopherol is transported by low-density lipoprotein (LDL), created from VLDL.

By binding lipoprotein with LDL receptors, α-tocopherol arrives at target cells as a result of passive diffusion. Stereoselective selection is also observed.

The elimination of tocopherols in bile increases when the degree of substitution decreases and when an atypical configuration exists.

Vitamin E is used in the treatment of vitamin E deficiency. Its antioxidative action is utilized in the treatment of other diseases too (Section 7.2).

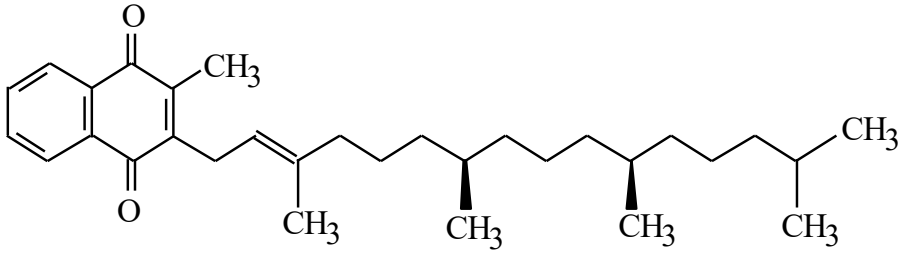
Vitamin E deficency may occur in:

- malabsorption syndrome
- hepatic cirrhosis
- cholestetic jaundice
- abetalipoproteinemia
- chronic enteritis
- untreated celiac disease.

An excess supply of vitamin E (over 240-480 mg of alfa-TE/24 h) may cause diarrhea, anxiety, headache, nausea, stomachache and weakness.

58.1.4. Vitamins K

The term vitamin K refers to natural (K_1 and K_2) and synthetic (K_3, K_4) derivatives of naphthoquinone, which show similar biological activity – blood coagulation.

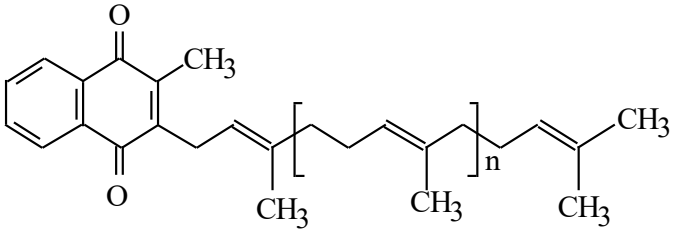


Phytomenadione, Vitamin K_1

VITACON

2-Methyl-3-fityl-1,4- naphthoquinone =

2-methyl-3-(3,7,11,15-tetramethyl-2-hexadecenyl)-1,4-naphtalendion



n = 4; Vitamin $K_{2(30)}$

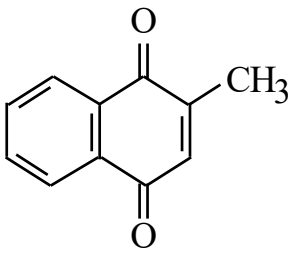
n = 5; Vitamin $K_{2(35)}$

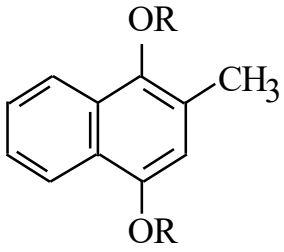
Vitamin K_1 is found in plants, especially lucerne, spinach, cabbage, and in plant oil. Vitamin K_2 is synthesized by saprophytic bacteria.

Both vitamins K contain a methyl group in the position 2 of the naphthoquinone ring but they have different substituents in position 3.

In the position 3 of vitamin K_1 is a 20-carbon phytyl substituent while in vitamin K_2 this substituent consists of a varied number of isoprenyl rests.

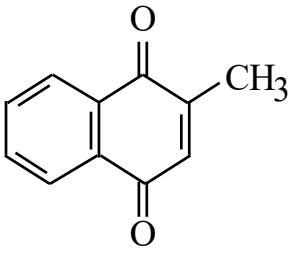
Synthetic vitamins K are derivatives of 2-methylnaphthoquinone (K_3) or 2-methylnaphthohydroquinone (K_4).



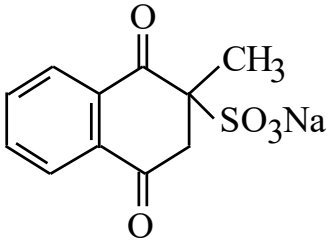


By studying the relationship between the chemical structure and action of vitamin K it was shown that:

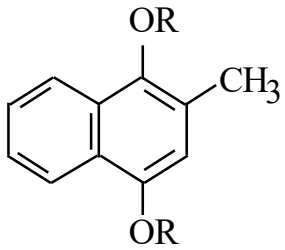
- The 2-methylnaphthoquinone group is necessary for antihemorrhagic activity.
- The methyl substituent in position C2 is vital for the activity of vitamin K. The substituent in position C3 is less important. It is suspected that natural and synthetic vitamins K are converted in the body to 2-methyl-3-digeranyl-1,4-naphthoquinone, i.e. vitamin $K_{2(20)}$, to which antihemorrhagic action should be attributed.
- The replacement of the hydroxyl groups in the naphthoquinone by amine groups does not change activity. Some derivatives, such as 4-amine-2-methyl-1-naphthol (vitamin K_5), 2-methyl-1,4-naphtalendiamine (vitamin K_6) and 1-amine-2-methyl-1-naphthol (vitamin K_7) also demonstrate antihemorrhagic action.



Menadione, Vitamin K_3; 2-Methyl-1,4-naftoquinone



Menadione sodium bisulfite, VITAMINUM K



Menadiol, Witamina K_4, R = H

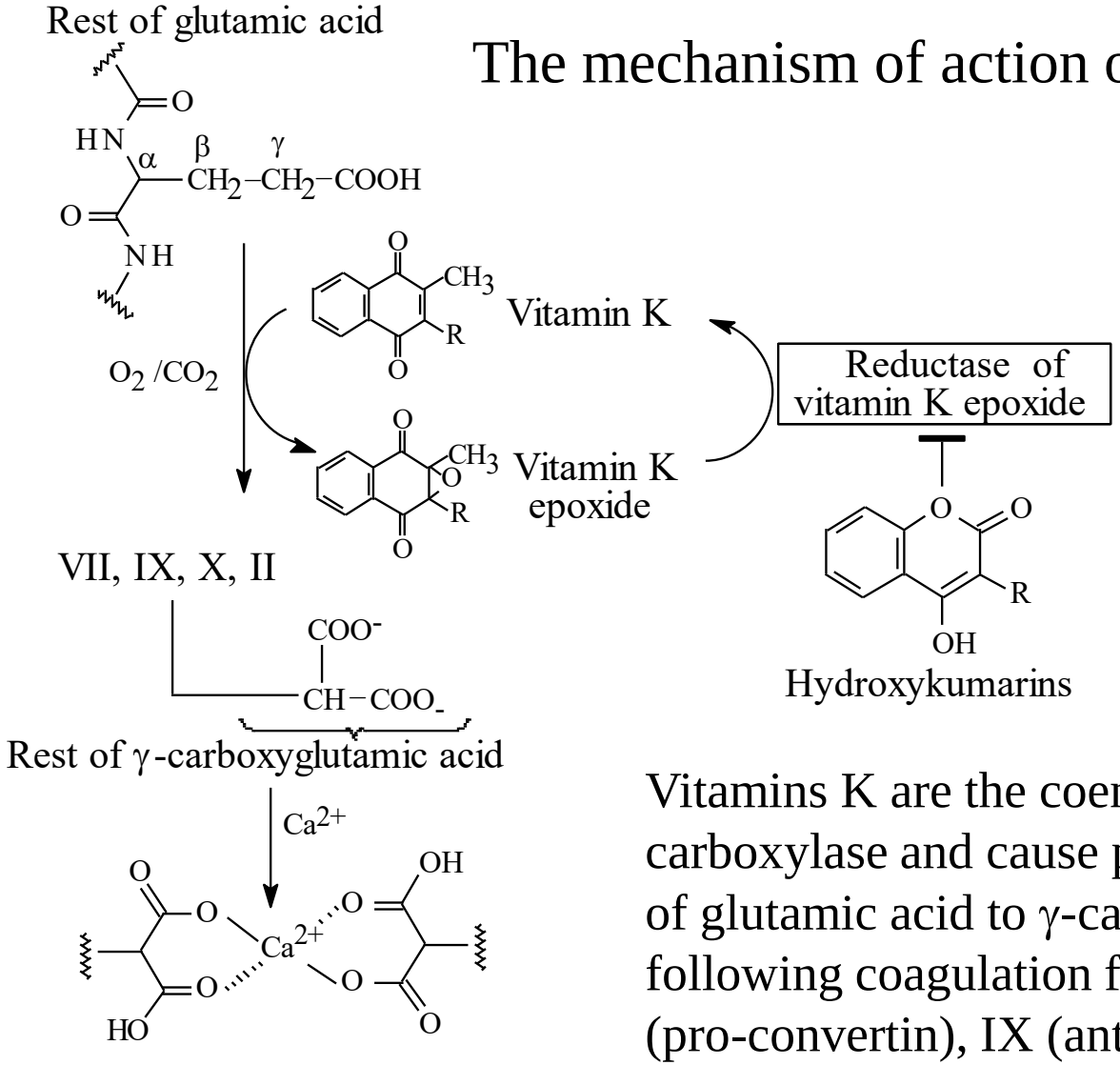
Menadiol sodium sulfate, R = $-SO_3Na$

SOLUCHINON, VITAMINUM K

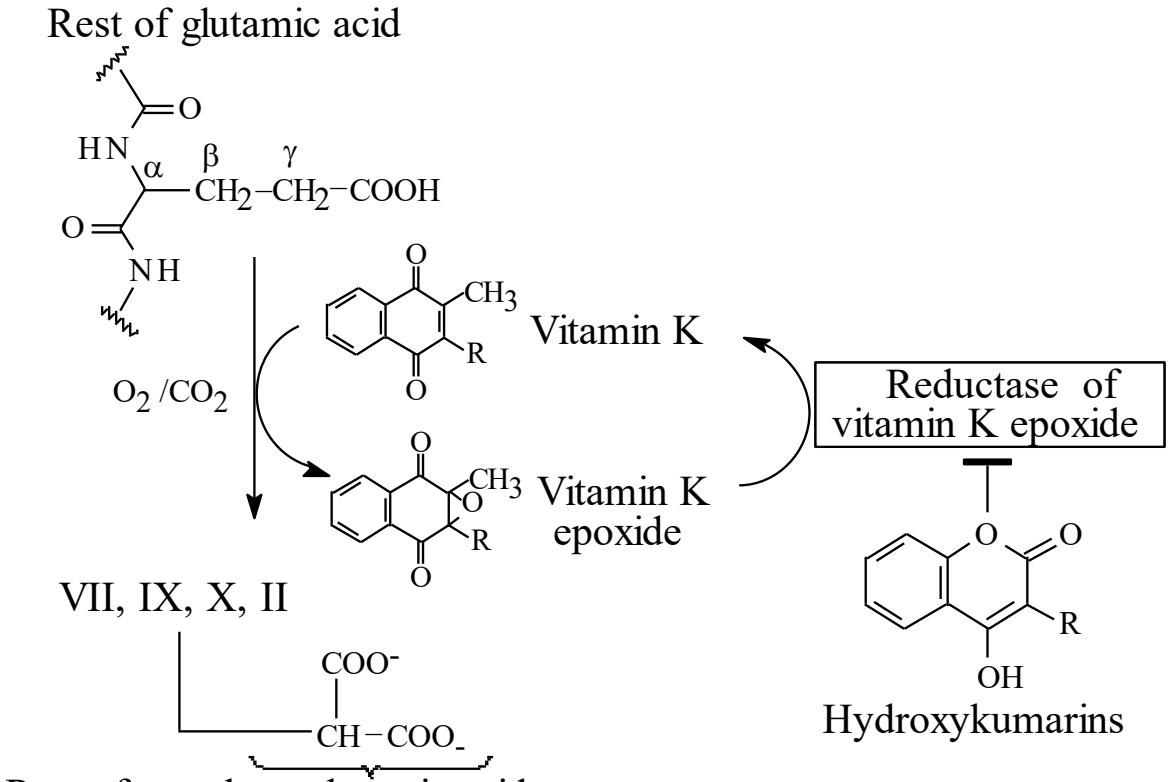
Acetomenaftone, *Menadiol diacetate*,R = $-CO-CH_3$

Menadiol sodium diphosphate, R = $-PO_3Na_2$; SYNKAVIT

The mechanism of action of vitamin K.



Vitamins K are the coenzyme of glutamyl carboxylase and cause posttranslational carboxylation of glutamic acid to γ-carboxyglutamic acid in the following coagulation factors: II (prothrombin), VII (pro-convertin), IX (antihemophilic factor, Christmas factor) and X (Stuart factor).



γ-Carboxyglutamic acid is necessary in those coagulation factors for their biological activity and makes it possible for these factors to bind calcium ions, which are essential in the coagulation process.

When a lack or deficiency of vitamin K appears, factors II, VII, IX and X are created as inactive proteins, called PIVKA (*Protein Induced by Vitamin K Absence*), which are not able to bind calcium ions.

A daily requirement of vitamin K is approx. 1 g/kg of body mass and it is supplied in food and as a result of absorption of vitamin K from the intestine, produced there by the bacterial flora.

Natural vitamins K are absorbed from the gastrointestinal tract in the presence of bile acids but synthetic derivatives soluble in water are absorbed because of diffusion in the distal part of the small intestine and the colon and do not require bile.

A deficiency of vitamin K may result from

- Malabsorption syndrome
- Impaired elimination of bile acids, e.g.. in cholestatic jaundic
- Destruction of saprophytic bacteria, which produce vitamin K, when antibiotics, sulphonamides or other chemotherapeutics are used
- Use of drugs acting antagonistically on vitamin K (cumarin and indandione derivatives, salicylates, methylthiouracil, quinine, quinidine) or inhibiting absorption of vitamin K.

A deficiency of vitamin K causes a tendency to bleeding.

In therapy, vitamin K_1 obtained synthetically, and K_3 and K_4 are used.

Vitamin K_4 is administered as esters of organic or inorganic acids.