28: Micronutrients: Vitamins

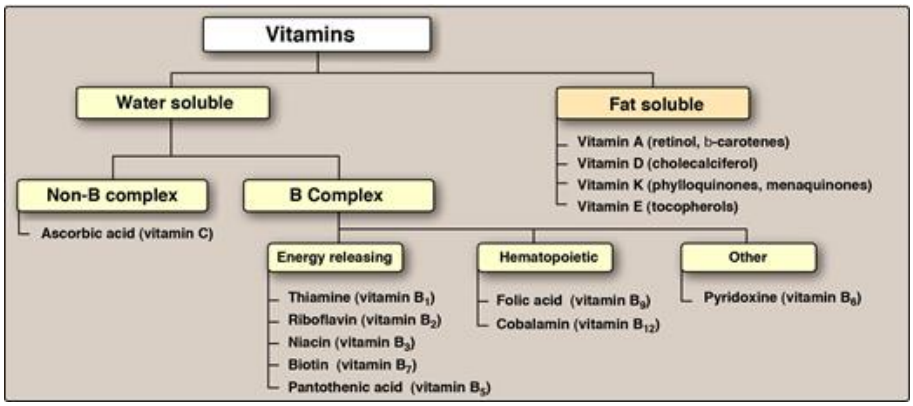
Overview

Vitamins are organic molecules that cannot be synthesized in adequate quantities by humans and, therefore, must be supplied by the diet. Nine vitamins (folic acid, cobalamin, ascorbic acid, pyridoxine, thiamine, niacin, riboflavin, biotin, and pantothenic acid) are classified as water soluble. Because they are readily excreted in the urine, toxicity is rare. However, deficiencies can develop quickly. Four vitamins (A, D, K, and E) are termed fat soluble (Fig. 28.1). They are released, absorbed, and transported (in chylomicrons, see Chapter 18 Section VI B) with dietary fat. They are stored in the liver and adipose tissue and are eliminated slower than the water-soluble vitamins. In fact, consumption of vitamins A and D in excess of the Dietary Reference Intakes (see Chapter 27) can lead to accumulation of toxic quantities of these compounds. Vitamins are required to perform specific cellular functions. For example, many of the water-soluble vitamins are precursors of coenzymes for the enzymes of intermediary metabolism. In contrast to the water-soluble vitamins, only one fat-soluble vitamin (vitamin K) has a coenzyme function.

FIGURE 28.1

Classification of the vitamins.

Because they are required in lesser amounts than the macronutrients (carbohydrate, protein, and lipid), vitamins are termed micronutrients.



Folic Acid (Vitamin B_9)

Vitamin B_9 describes many forms of naturally occurring folate. Folic acid is the synthetic form of folate that is used in supplements and in fortification of foods. However, these two terms, folic acid and folate, are often used interchangeably. Folic acid plays a key role in one-carbon metabolism, and it is essential for the biosynthesis of several compounds. Folic acid deficiency is probably the most common vitamin deficiency in the United States, particularly among pregnant women and individuals with alcoholism. (Note: Leafy, dark-green vegetables are a good source of folic acid.)

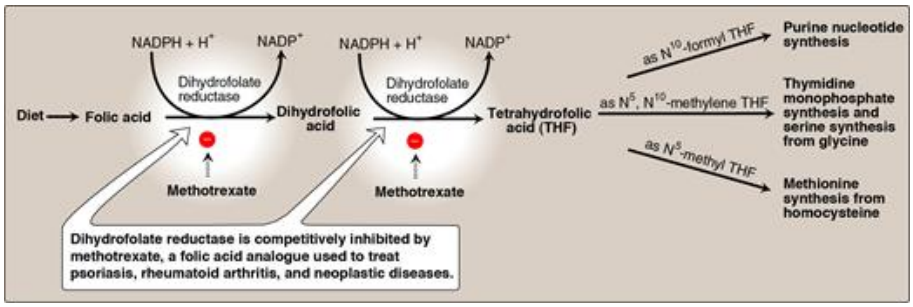
Function

Tetrahydrofolate (THF), the reduced, coenzyme form of folate, receives one-carbon fragments from donors such as serine, glycine, and histidine and transfers them to intermediates in the synthesis of amino acids, purine nucleotides, and thymidine monophosphate (TMP), a pyrimidine nucleotide incorporated into DNA (Fig. 28.2).

FIGURE 28.2

Production and use of tetrahydrofolate.

NADP(H) = nicotinamide adenine dinucleotide phosphate.



Nutritional anemias

Anemia is a condition in which the blood has a lower than normal concentration of hemoglobin, which results in a reduced ability to transport oxygen (O_2). Nutritional anemias (i.e., those caused by inadequate intake of one or more essential nutrients) can be classified according to the size of the red blood cells (RBCs), or mean corpuscular volume (MCV), observed in the blood (Fig. 28.3). Microcytic anemia (MCV below normal), caused by lack of iron, is the most common form of nutritional anemia. The second major category of nutritional anemia, macrocytic (MCV above normal), results from a deficiency in folic acid or vitamin B_{12}. (Note: These macrocytic anemias are commonly called megaloblastic because a deficiency of either vitamin [or both] causes accumulation of large, immature RBC precursors, known as megaloblasts, in the bone marrow and the blood [Fig. 28.4]. Hypersegmented neutrophils are also seen.)

Folate and anemia

Inadequate serum levels of folate can be caused by increased demand (e.g., pregnancy and lactation; see Chapter 27 Section IX), poor absorption caused by pathology of the small intestine, alcoholism, or treatment with drugs (e.g., methotrexate) that are dihydrofolate reductase inhibitors (see Fig. 28.2). A folate-free diet can cause a deficiency within a few weeks. A primary result of folic acid deficiency is megaloblastic anemia (see Fig. 28.4), caused by diminished synthesis of purine nucleotides and TMP, which leads to an inability of cells (including RBC precursors) to make DNA and, therefore, an inability to divide.

FIGURE 28.3

Classification of nutritional anemias by red cell size.

The normal mean corpuscular volume (MCV) for people older than age 18 years is 80 to 100 μm^3. (Note: Microcytic anemia is also seen with heavy metal [e.g., lead] poisoning.)

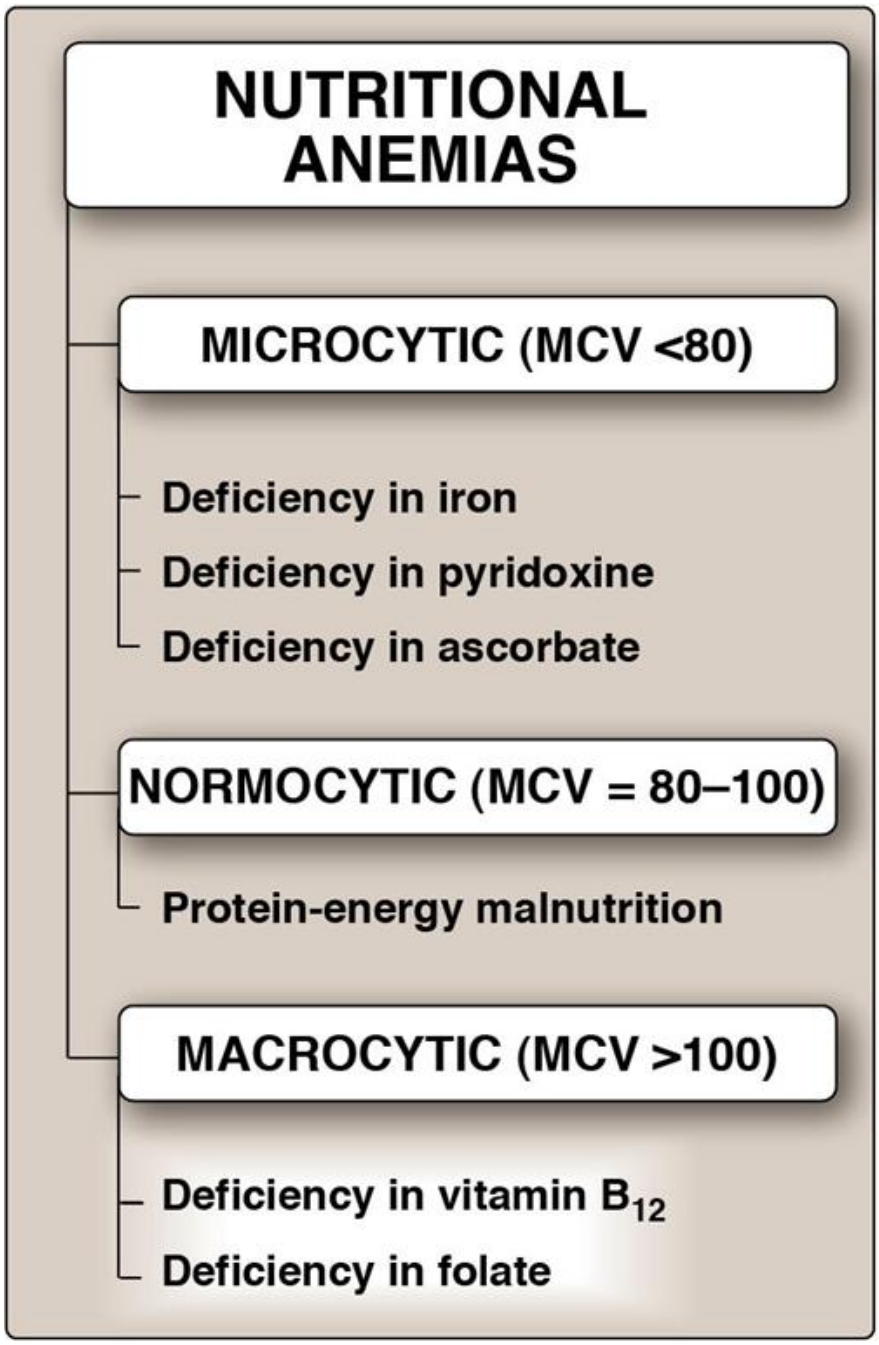


FIGURE 28.4

Bone marrow histology in normal (A) and folate-deficient (B) individuals.

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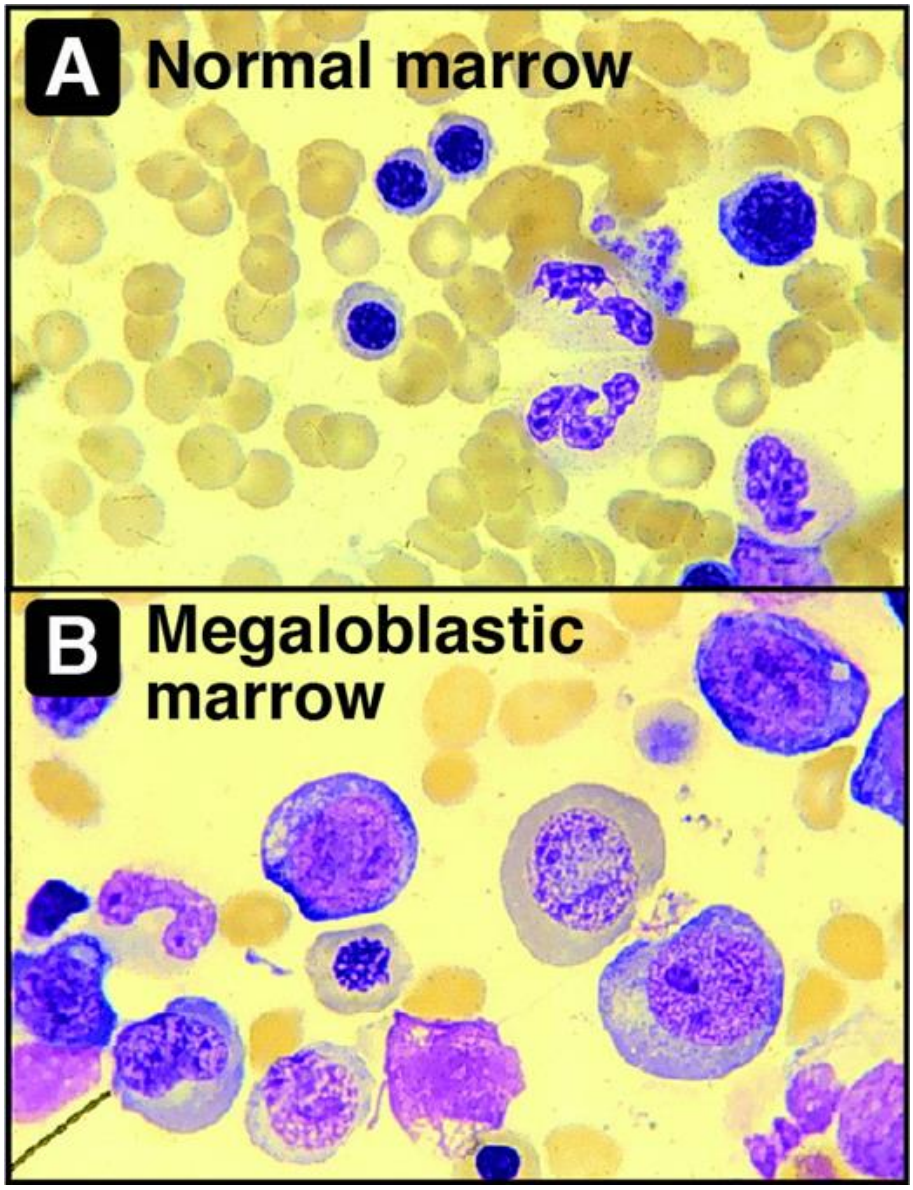


Folate and neural tube defects

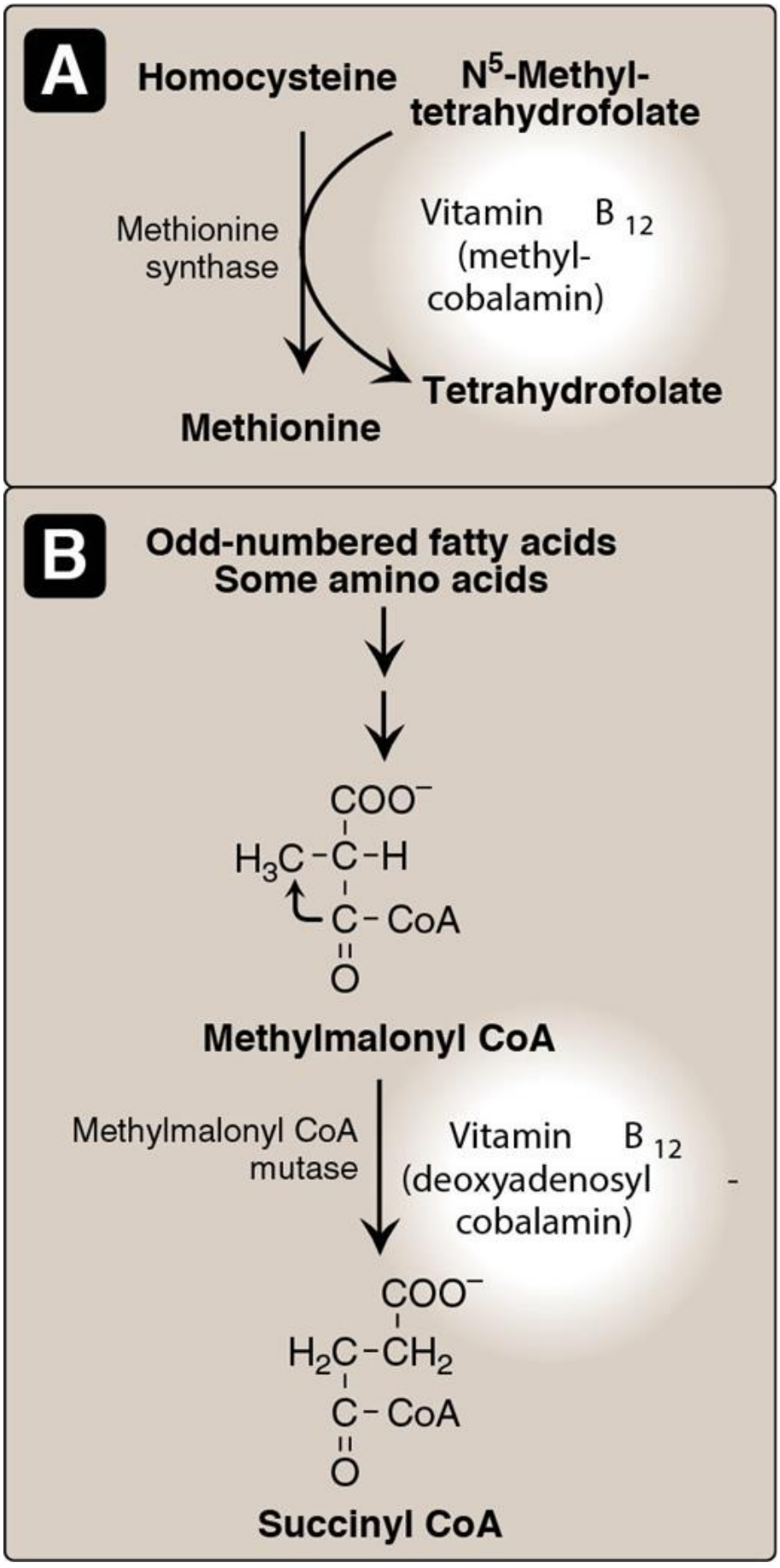
Spina bifida and anencephaly, the most common neural tube defects (NTDs), affect ~3,000 pregnancies in the United States annually. Folic acid supplementation before conception and during the first trimester has been shown to significantly reduce NTD. Therefore, all women of childbearing age are advised to consume 0.4 mg/day (400 µg/day) of folic acid to reduce the risk of having a pregnancy affected by NTD and ten times that amount if a previous pregnancy was affected. Adequate folate nutrition must occur at the time of conception because critical folate-dependent development occurs in the first weeks of fetal life, at a time when many women are not yet aware of their pregnancy. In 1998, the U.S. Food and Drug Administration authorized the fortification of cereal grain products with folic acid and also recommended folate supplementation in the form of pills 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 B_{12})

Vitamin B_{12} is required in humans for two essential enzymatic reactions: the remethylation of homocysteine (Hcy) to methionine and the 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 (Fig. 28.5). 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 B_{12} deficiency. (Note: Folic acid [as N^5-methyl THF] is also required in the remethylation of Hcy. Therefore, deficiency of B_{12} or folate results in elevated Hcy levels.)

FIGURE 28.5

A, B: Reactions requiring coenzyme forms of vitamin B_{12}. CoA = coenzyme A.

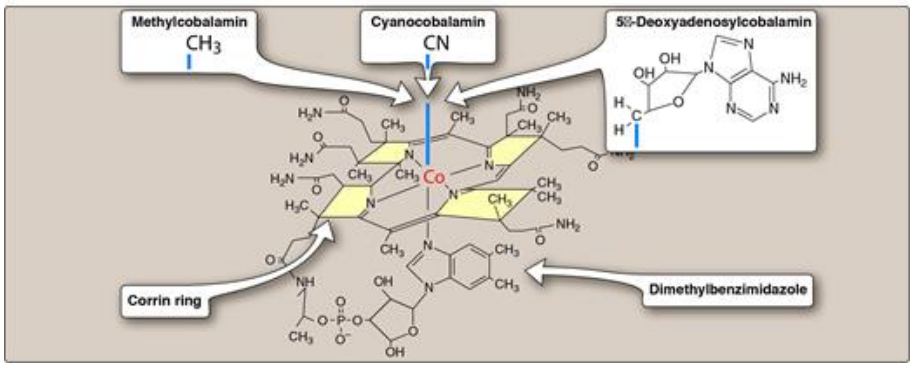


Structure and coenzyme forms

Cobalamin contains a corrin ring system that resembles the porphyrin ring of heme (see Chapter 21), but differs in that two of the pyrrole rings are linked directly rather than through a methene bridge. Cobalt (see Chapter 29 Section IV) is held in the center of the corrin ring by four coordination bonds with the nitrogens of the pyrrole groups. The remaining coordination bonds of the cobalt are with the nitrogen of 5,6-dimethylbenzimidazole and with cyanide in commercial preparations of the vitamin in the form of cyanocobalamin (Fig. 28.6). The physiologic coenzyme forms of cobalamin are 5′-deoxyadenosylcobalamin and methylcobalamin, in which cyanide is replaced with 5′-deoxyadenosine or a methyl group, respectively (see Fig. 28.6).

FIGURE 28.6

Structure of vitamin B_{12} (cyanocobalamin) and its coenzyme forms (methylcobalamin and 5′-deoxyadenosylcobalamin).



Distribution

Vitamin B_{12} is synthesized only by microorganisms, and it is not present in plants. Animals obtain the vitamin preformed from their intestinal microbiota (see Chapter 27 Section IX A) 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

The 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 N^5,N^{10}-methylene and N^{10}-formyl forms of THF for the synthesis of nucleotides required for DNA replication (see pp. 325 and 336). However, in vitamin B_{12} deficiency, the utilization of the N^5-methyl form of THF in the B_{12}-dependent methylation of Hcy to methionine is impaired. Because the methylated form cannot be converted directly to other forms of THF, folate is trapped in the N^5-methyl form, which accumulates. The levels of the other forms decrease. Thus, cobalamin deficiency leads to a deficiency of the THF forms needed in purine and TMP synthesis, resulting in the symptoms of megaloblastic anemia.

Clinical indications for cobalamin

In contrast to other water-soluble vitamins, significant amounts (2 to 5 mg) of vitamin B_{12} are stored in the body. As a result, it may take several years for the clinical symptoms of B_{12} deficiency to develop as a result of decreased intake of the vitamin. (Note: Deficiency happens much more quickly [in months] if absorption is impaired [see below]. The Schilling test evaluates B_{12} absorption.) B_{12} deficiency can be determined by the level of methylmalonic acid in blood, which is elevated in individuals with low intake or decreased absorption of the vitamin.

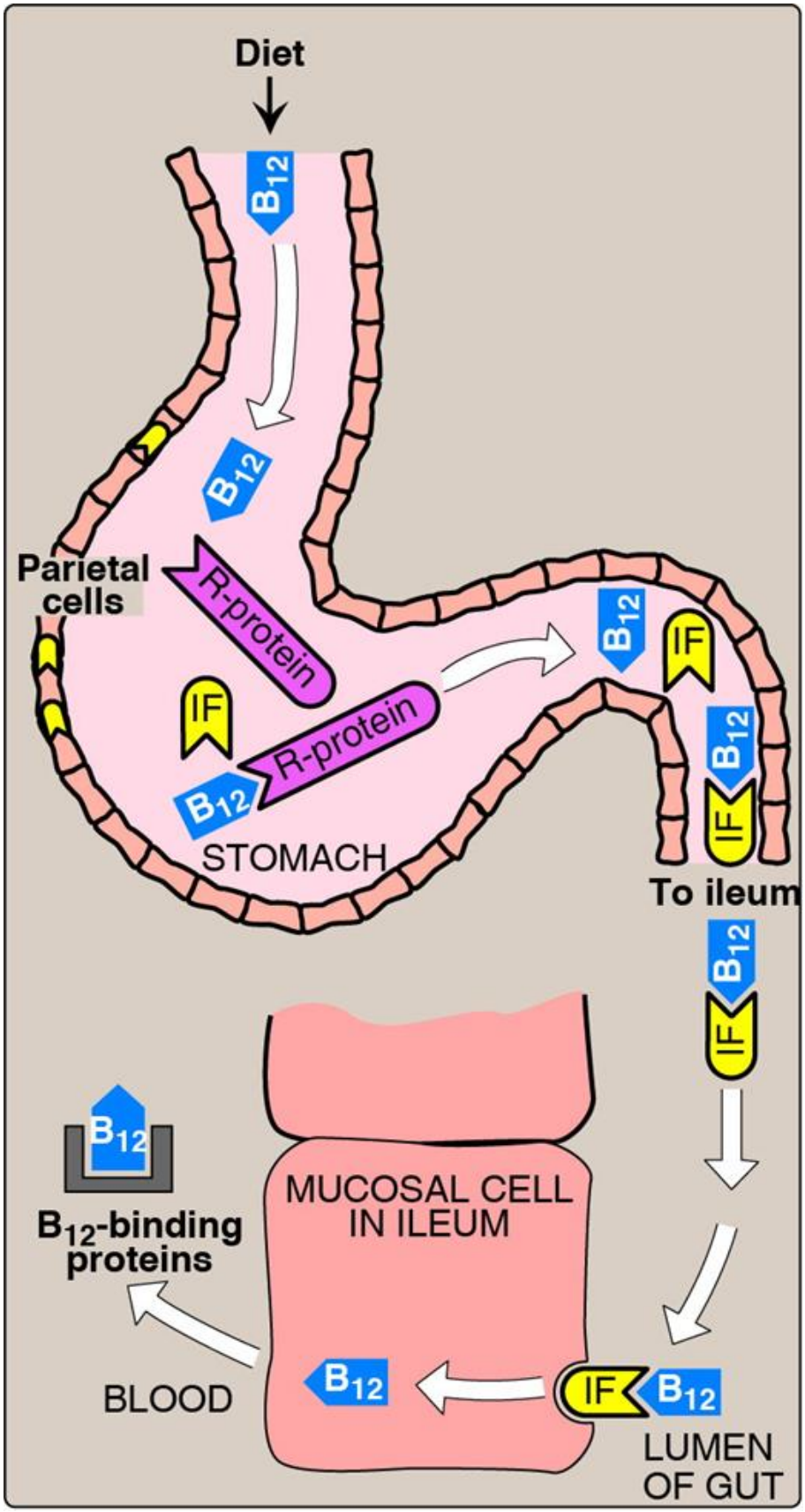
Pernicious anemia

Vitamin B_{12} deficiency is most commonly seen in patients who fail to absorb the vitamin from the intestine (Fig. 28.7). B_{12} is released from food in the acidic environment of the stomach. (Note: Malabsorption of cobalamin in the elderly is most often due to reduced secretion of gastric acid [achlorhydria].) Free B_{12} then binds a glycoprotein (R-protein or haptocorrin), and the complex moves into the intestine. B_{12} is released from the R-protein by pancreatic enzymes and binds another glycoprotein, intrinsic factor (IF). The cobalamin–IF complex travels through the intestine and binds to a receptor (cubilin) on the surface of mucosal cells in the ileum. The cobalamin is transported into the mucosal cell and, subsequently, into the general circulation, where it is carried by its binding protein (transcobalamin). B_{12} is taken up and stored in the liver, primarily. It is released into bile and efficiently reabsorbed in the ileum. Severe malabsorption of vitamin B_{12} leads to pernicious anemia. This disease is most commonly a result of an autoimmune destruction of the gastric parietal cells that are responsible for the synthesis of IF (lack of IF prevents B_{12} absorption). (Note: Patients who have had a partial or total gastrectomy become IF deficient and, therefore, B_{12} deficient.) Individuals with cobalamin deficiency are usually anemic (folate recycling is impaired), and they show neuropsychiatric symptoms as the disease develops. The CNS effects are irreversible. Pernicious anemia requires lifelong treatment with either high-dose oral B_{12} or intramuscular injection of cyanocobalamin. (Note: Supplementation works even in the absence of IF because ~1% of B_{12} uptake is by IF-independent diffusion.)

FIGURE 28.7

Absorption of vitamin B_{12}.

(Note: Acid-dependent release of B_{12} from food is not shown.) IF = intrinsic factor.



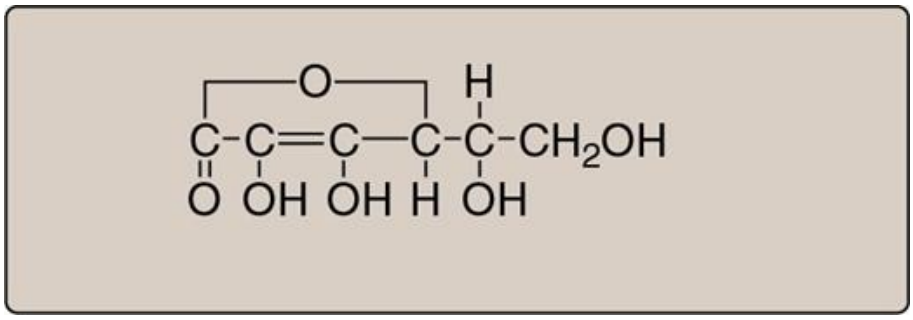
Folic acid supplementation can partially reverse the hematologic abnormalities of B_{12} deficiency and, therefore, can mask a cobalamin deficiency. Thus, to prevent the later CNS effects of B_{12} deficiency, therapy for megaloblastic anemia is initiated with both vitamin B_{12} and folic acid until the cause of the anemia can be determined.

Ascorbic Acid (Vitamin C)

The active form of vitamin C is ascorbic acid (Fig. 28.8). Its main function is as a reducing agent. Vitamin C is a coenzyme in hydroxylation reactions (e.g., hydroxylation of prolyl and lysyl residues in collagen, and hydroxylation of dopamine to norepinephrine in epinephrine synthesis), where its role is to keep the iron (Fe) of **hydroxylases** in the reduced, ferrous (Fe^{+2}) form. Thus, vitamin C is required for the maintenance of normal connective tissue as well as for wound healing. Vitamin C also facilitates the absorption of dietary nonheme iron from the intestine by reduction of the ferric form (Fe^{+3}) to the ferrous form (Fe^{+2}) (see Chapter 29 Section III B).

FIGURE 28.8

Structure of ascorbic acid.

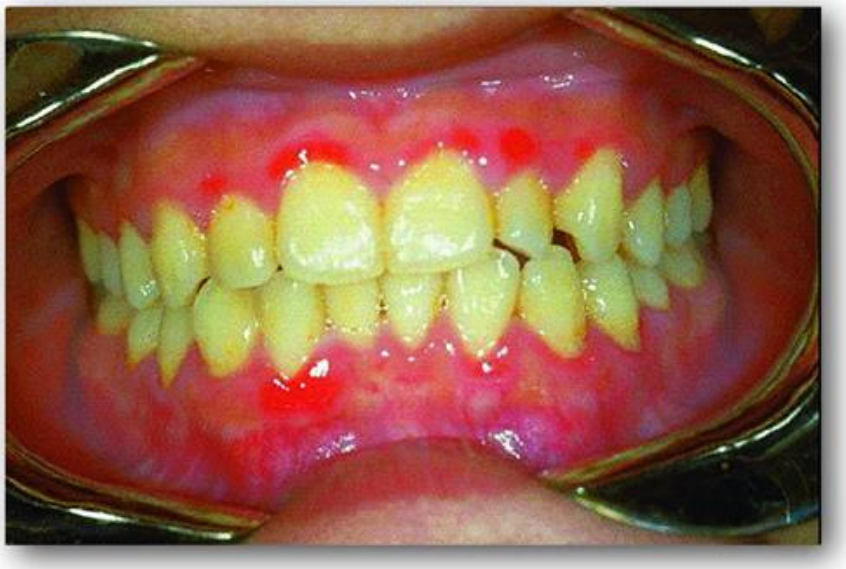


Deficiency

Ascorbic acid deficiency results in scurvy, a disease characterized by sore and spongy gums, loose teeth, fragile blood vessels, hemorrhage, swollen joints, bone changes, and fatigue (Fig. 28.9). Many of the deficiency symptoms can be explained by the decreased hydroxylation of collagen, resulting in defective connective tissue. A microcytic anemia caused by decreased absorption of iron may also be seen.

FIGURE 28.9

Oral manifestations in a patient with scurvy.



Chronic disease prevention

Vitamin C is one of a group of nutrients that includes vitamin E (see p. 442) and β-carotene (see Section XI A), which are known as antioxidants. (Note: Vitamin C regenerates the functional, reduced form of vitamin E.) Even though there is a belief that Vitamin C or Vitamin E supplementation may reduce the incidence of some chronic diseases, there is no evidence to support these claims.

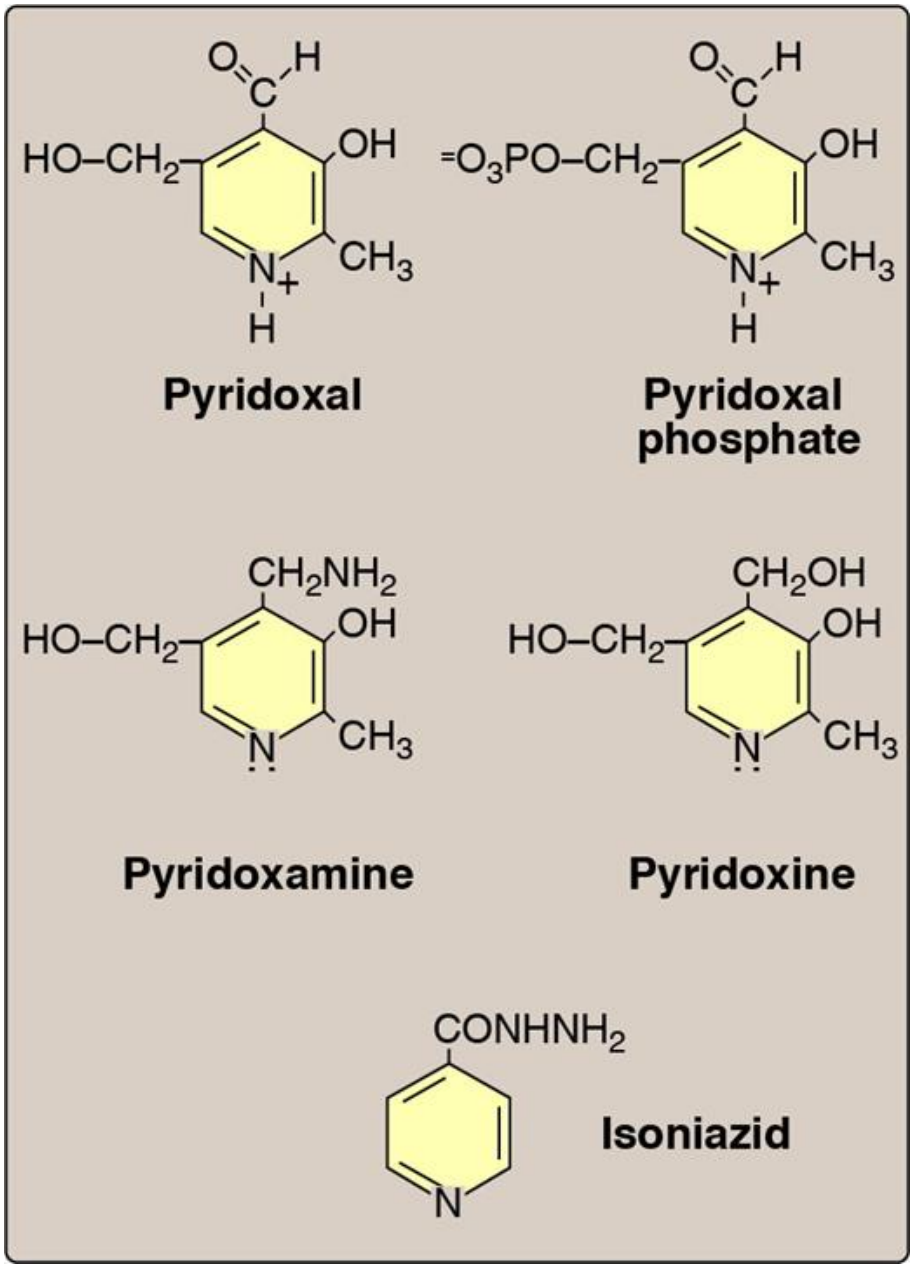
Pyridoxine (Vitamin B_6)

Vitamin B_6 is a collective term for pyridoxine, pyridoxal, and pyridoxamine, all derivatives of pyridine. They differ only in the nature of the functional group attached to the ring (Fig. 28.10). Pyridoxine occurs primarily in plants, whereas pyridoxal and pyridoxamine are found in foods obtained from animals. All three compounds can serve as precursors of the biologically active coenzyme, pyridoxal phosphate (PLP). PLP functions as a coenzyme for a large number of enzymes, particularly those that catalyze reactions involving amino acids, for example, in the transsulfuration of Hcy to cysteine, and in the synthesis of dopamine and serotonin. (Note: PLP is also required by **glycogen phosphorylase** [see Chapter 11].)

Reaction type	Example
Transamination	Oxaloacetate + glutamate ⇄ aspartate + α-ketoglutarate
Deamination	Serine → pyruvate + NH_3
Decarboxylation	Histidine → histamine + CO_2
Condensation	Glycine + succinyl CoA → δ-aminolevulinic acid

FIGURE 28.10

Structures of vitamin B_6 and the antituberculosis drug isoniazid.



Clinical indications for pyridoxine

Isoniazid, a drug commonly used to treat tuberculosis, can induce a vitamin B_6 deficiency by forming an inactive derivative with PLP. Thus, B6 supplementation is essential for some patients to prevent the development of peripheral neuropathy. Otherwise, dietary deficiencies in pyridoxine are rare but have been observed in newborn infants fed formulas low in B_6, in women taking oral contraceptives, and in those with alcoholism.

Toxicity

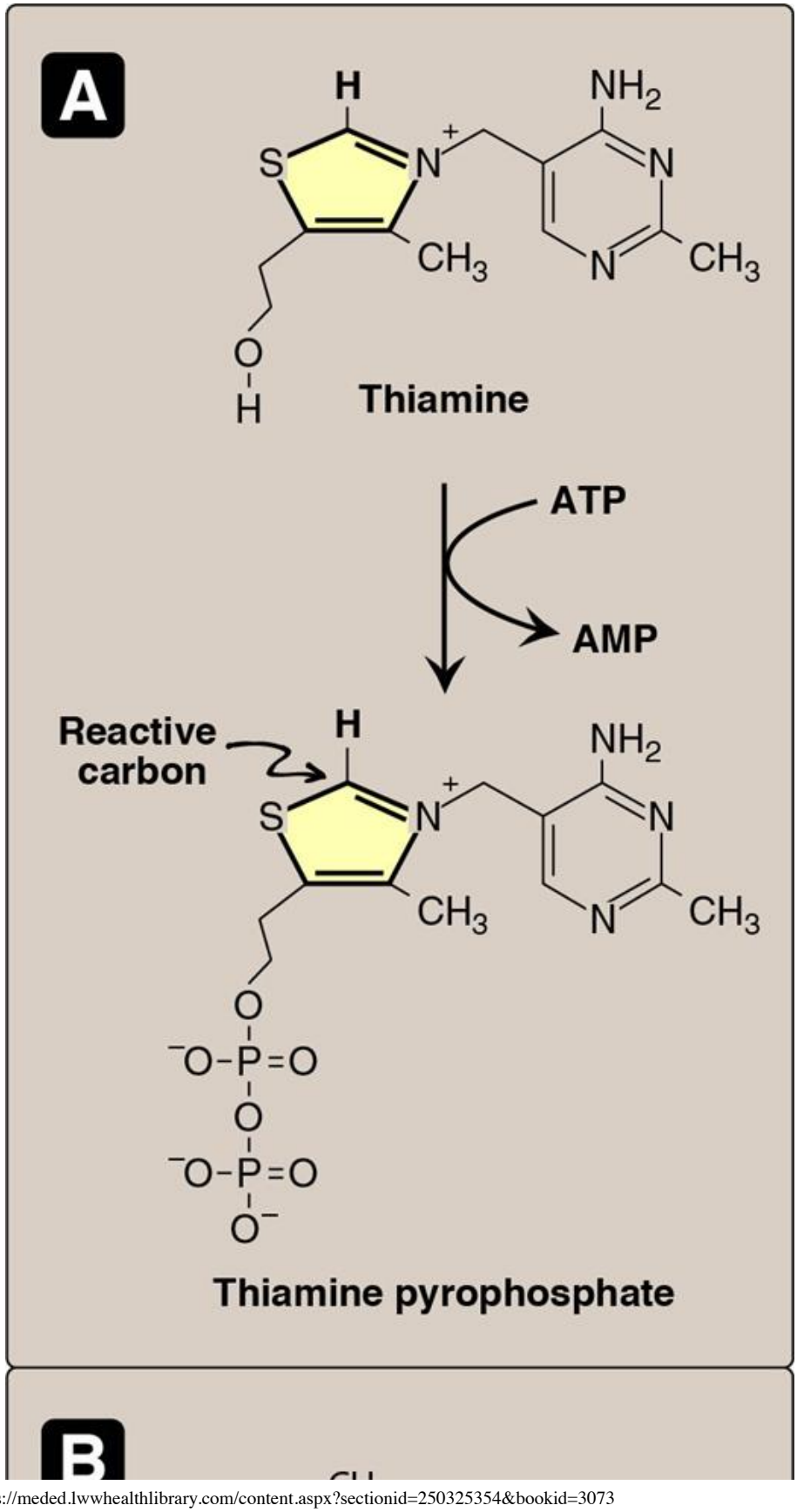
Vitamin B_6 is the only water-soluble vitamin with significant toxicity. Neurologic symptoms (sensory neuropathy) occur at intakes above 500 mg/day, an amount nearly 400 times the recommended dietary allowance (RDA) and over five times the tolerable upper limit (UL). (See Chapter 27 for a discussion of RDA and UL.) Substantial improvement, but not complete recovery, occurs when the vitamin is discontinued.

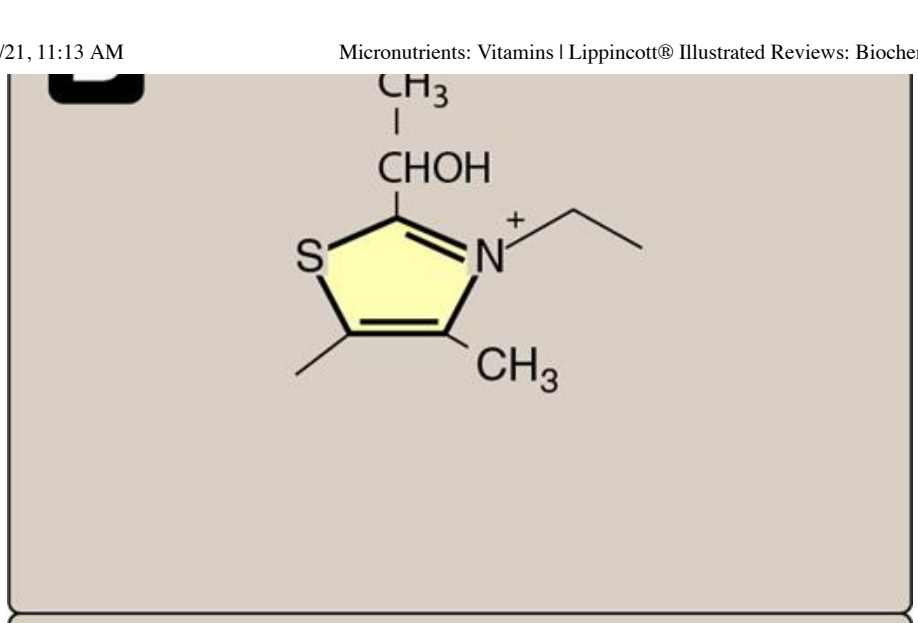
Thiamine (Vitamin B_1)

Thiamine pyrophosphate (TPP) is the biologically active form of the vitamin, formed by the transfer of a pyrophosphate group from ATP to thiamine (Fig. 28.11). TPP serves as a coenzyme in the formation or degradation of α-ketols by **transketolase** (Fig. 28.12A) and in the oxidative decarboxylation of α-keto acids (Fig. 28.12B).

FIGURE 28.11

A: Structure of thiamine and its coenzyme form, thiamine pyrophosphate. **B:** Structure of intermediate formed in the reaction catalyzed by *pyruvate dehydrogenase*. **C:** Structure of intermediate formed in the reaction catalyzed by *α-ketoglutarate dehydrogenase*. AMP = adenosine monophosphate.




CH3
CHOH
S
N
+
CH3

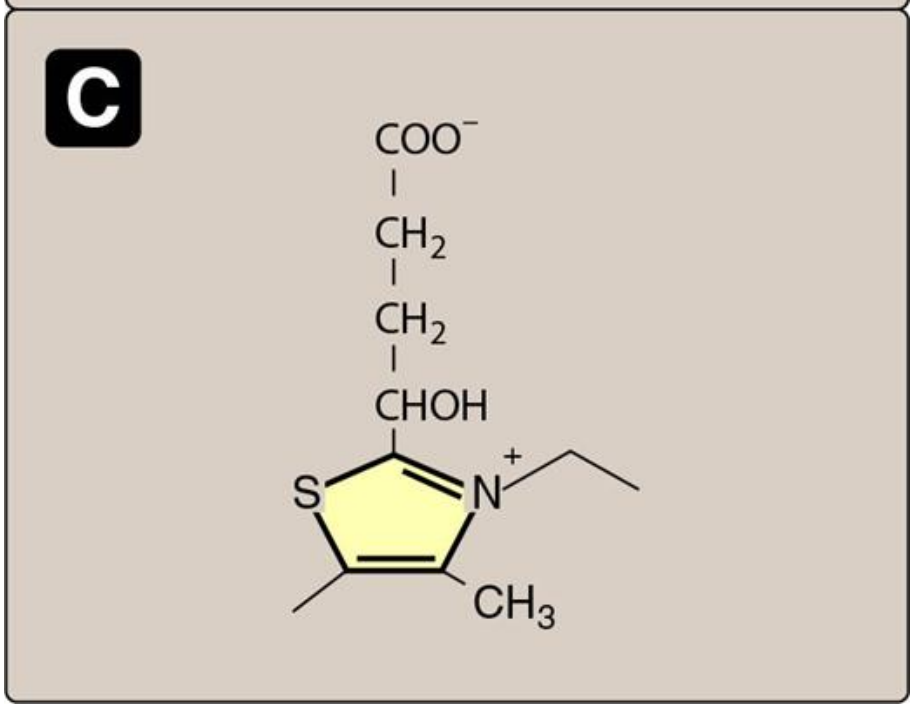
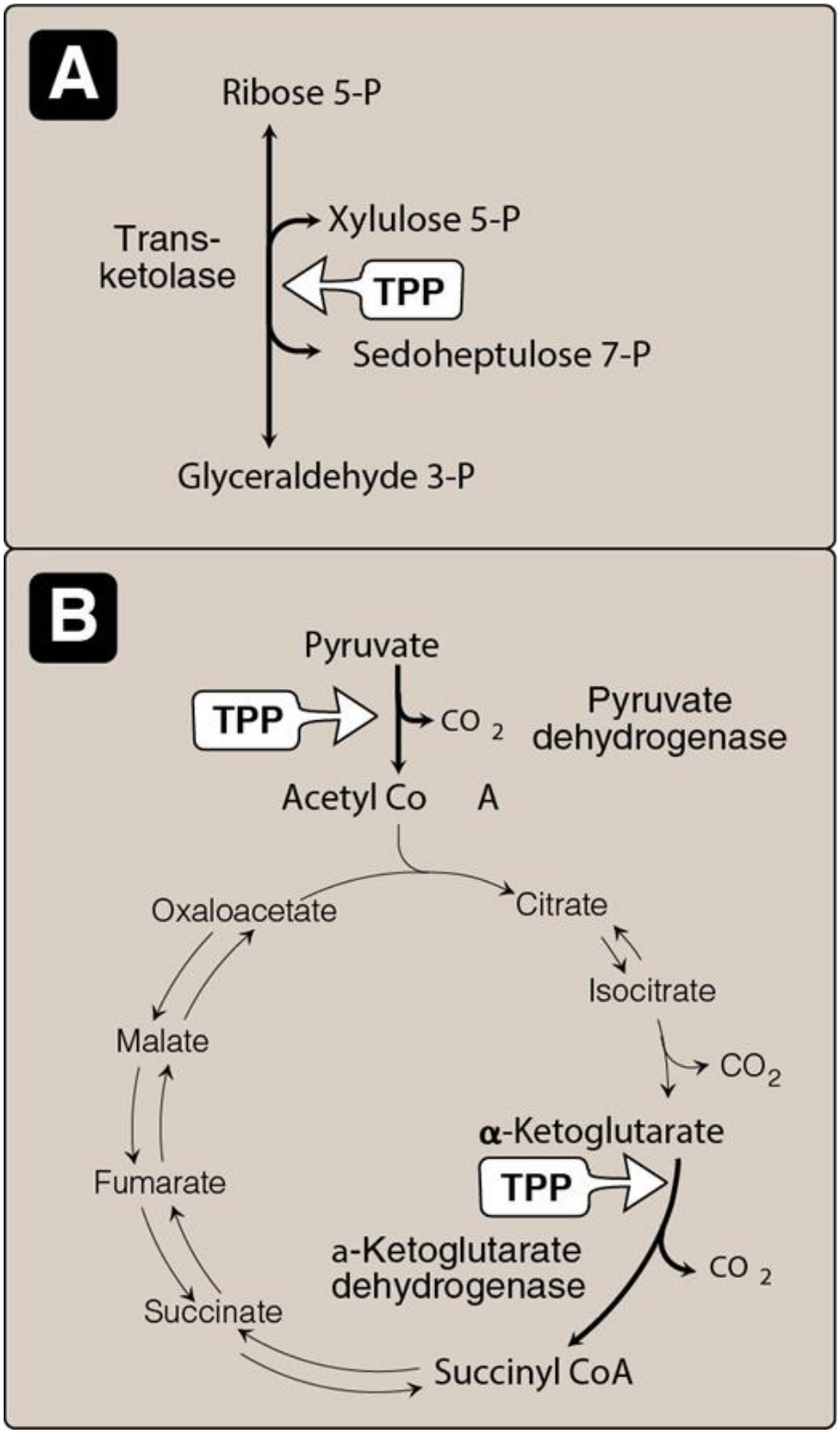

C
COO−
CH2
CH2
CHOH
S
N
+
CH3

FIGURE 28.12

Reactions that use thiamine pyrophosphate (TPP) as coenzyme.

A: *Transketolase*. **B:** *Pyruvate dehydrogenase* and *α-ketoglutarate dehydrogenase*. (Note: TPP is also used by *branched-chain α-keto acid dehydrogenase*.) P = phosphate; CoA = coenzyme A; CO_2 = carbon dioxide.



Clinical indications for thiamine

The oxidative decarboxylation of pyruvate and α-ketoglutarate, which plays a key role in energy metabolism of most cells, is particularly important in tissues of the CNS. In thiamine deficiency, the activity of these two dehydrogenase-catalyzed reactions is decreased, resulting in decreased production of ATP and, therefore, impaired cellular function. TPP is also required by branched-chain α-keto acid dehydrogenase of muscle (see p. 295). (Note: It is the decarboxylase of each of these α-keto acid dehydrogenase multienzyme complexes that requires TPP.) Thiamine deficiency is diagnosed by an increase in erythrocyte transketolase activity observed with addition of TPP.

Beriberi

This severe thiamine-deficiency syndrome is found in areas where there is severe malnutrition or in areas where starchy, low-thiamine food, such as polished rice is the major component of the diet. Adult beriberi is classified as dry (characterized by peripheral neuropathy, especially in the legs) or wet (characterized by edema because of dilated cardiomyopathy).

Wernicke–Korsakoff syndrome

In the United States, thiamine deficiency, which is seen primarily in association with chronic alcoholism, is due to dietary insufficiency or impaired intestinal absorption of the vitamin. Some individuals with alcoholism develop Wernicke–Korsakoff syndrome, a thiamine-deficiency state characterized by mental confusion, gait ataxia, nystagmus (a to-and-fro motion of the eyeballs), and ophthalmoplegia (weakness of eye muscles) with Wernicke encephalopathy as well as memory problems and hallucinations with Korsakoff dementia. The syndrome is treatable with thiamine supplementation, but recovery of memory is typically incomplete.

Niacin (Vitamin B_3)

Niacin, or nicotinic acid, is a substituted pyridine derivative. The biologically active coenzyme forms are nicotinamide adenine dinucleotide (NAD^+) and its phosphorylated derivative, nicotinamide adenine dinucleotide phosphate ($NADP^+$), as shown in Figure 28.13. Nicotinamide, a derivative of nicotinic acid that contains an amide instead of a carboxyl group, also occurs in the diet. Nicotinamide is readily deaminated in the body and, therefore, is nutritionally equivalent to nicotinic acid. NAD^+ and $NADP^+$ serve as coenzymes in oxidation–reduction reactions in which the coenzyme undergoes reduction of the pyridine ring by accepting two electrons from a hydride ion, as shown in Figure 28.14. The reduced forms of NAD^+ and $NADP^+$ are NADH and NADPH, respectively. (Note: A metabolite of tryptophan, quinolinate, can be converted to NAD[P]. In comparison, 60 mg of tryptophan = 1 mg of niacin.)

FIGURE 28.13

Structure and biosynthesis of oxidized nicotinamide adenine dinucleotide (NAD^+) and nicotinamide adenine dinucleotide phosphate ($NADP^+$).

ADP = adenosine diphosphate.

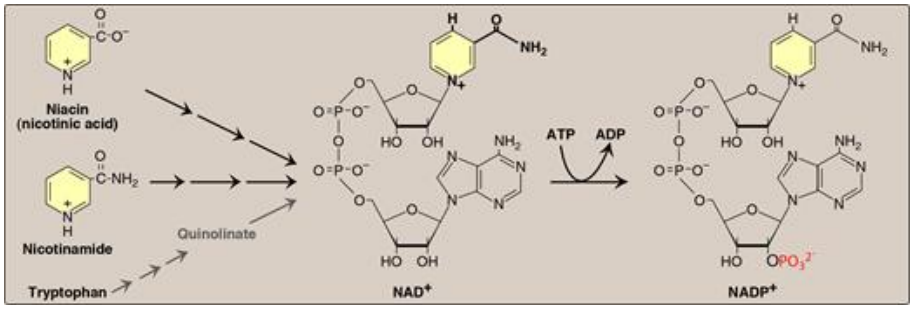
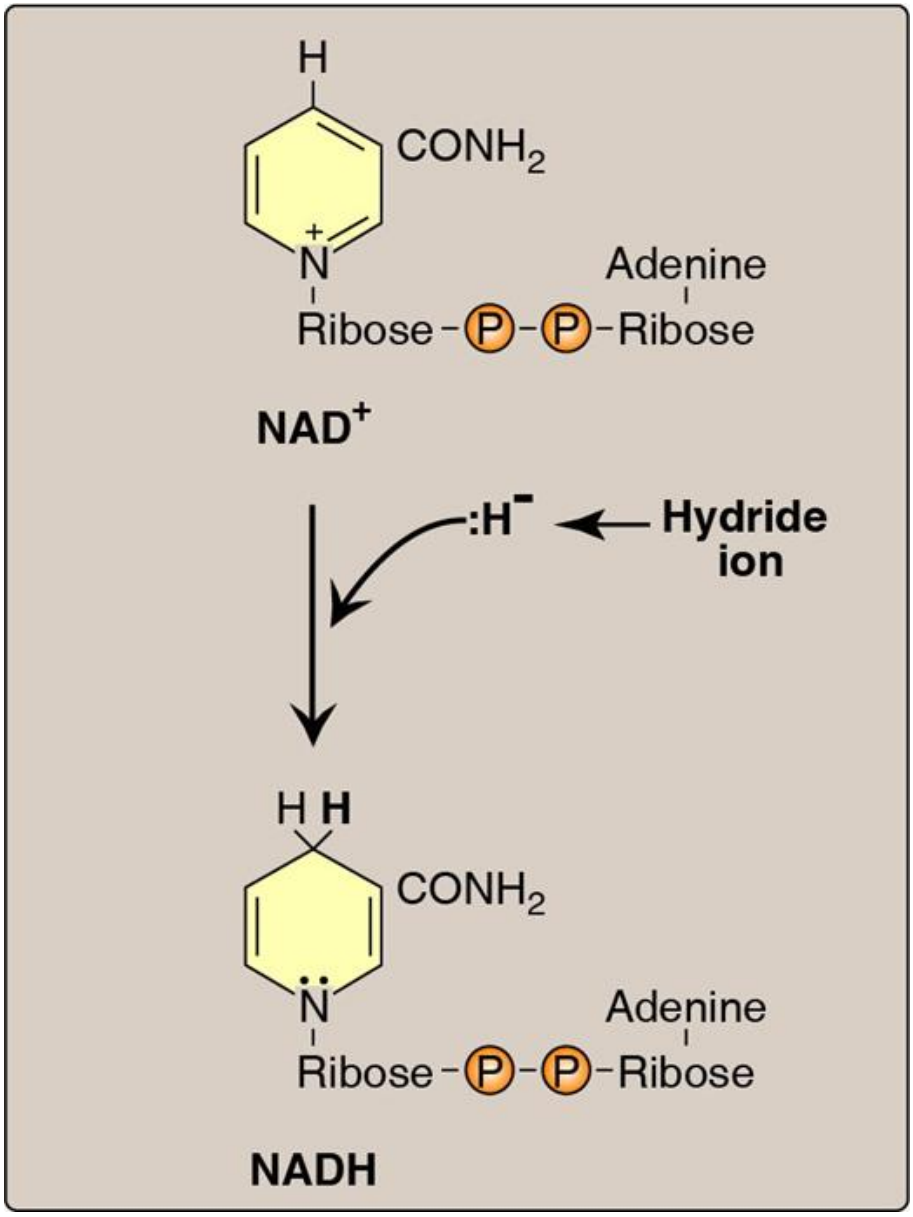


FIGURE 28.14

Reduction of oxidized nicotinamide adenine dinucleotide (NAD^+) to NADH.

(Note: The hydride ion consists of a hydrogen [H] atom plus an electron.) Ⓟ = phosphate.



Distribution

Niacin is found in unrefined and enriched grains and cereal, milk, and lean meats (especially liver).

Clinical indications for niacin

Deficiency

A deficiency of niacin causes pellagra, a disease involving the skin, gastrointestinal tract, and CNS. The symptoms of pellagra progress through the three Ds: dermatitis (photosensitive), diarrhea, and dementia. If untreated, death (a fourth D) occurs. Hartnup disorder, characterized by defective absorption of tryptophan, can result in pellagra-like symptoms. (Note: Corn is low in both niacin and tryptophan. Corn-based diets can cause pellagra.)

Hyperlipidemia treatment

Niacin at doses of 1.5 g/day, or 100 times the RDA, strongly inhibits lipolysis in adipose tissue, the primary producer of circulating free fatty acids (FFAs). The liver normally uses these circulating FFA as a major precursor for triacylglycerol (TAG) synthesis. Thus, niacin causes a decrease in liver TAG synthesis, which is required for very–low-density lipoprotein ([VLDL] see p. 256) production. Low-density lipoprotein (LDL, the cholesterol-rich lipoprotein) is derived from VLDL in the plasma. Thus, both plasma TAG (in VLDL) and cholesterol (in LDL) are lowered. Therefore, niacin is particularly useful in the treatment of type IIb hyperlipoproteinemia, in which both VLDL and LDL are elevated. The high doses of niacin required can cause acute, prostaglandin-mediated flushing. Aspirin can reduce this side effect by inhibiting prostaglandin synthesis (see p. 237). Itching may also occur. (Note: Niacin raises high-density lipoprotein and lowers Lp[a] levels [see p. 262].)

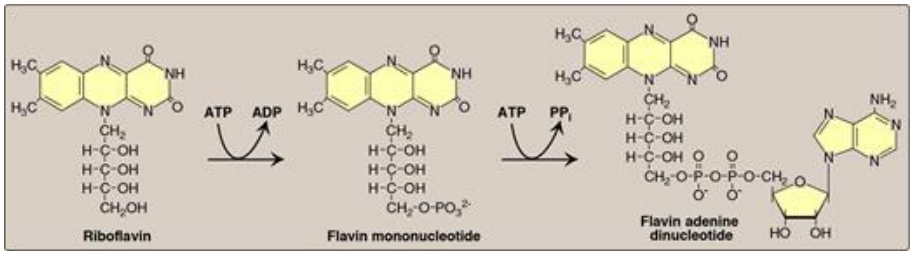
Riboflavin (Vitamin B_2)

The two biologically active forms of B_2 are flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), formed by the transfer of an adenosine monophosphate moiety from ATP to FMN (Fig. 28.15). FMN and FAD are each capable of reversibly accepting two hydrogen atoms, forming $FMNH_2$ or $FADH_2$, respectively. FMN and FAD are bound tightly, sometimes covalently, to flavoenzymes (e.g., NADH dehydrogenase [FMN] and succinate dehydrogenase [FAD]) that catalyze the oxidation or reduction of a substrate. Riboflavin deficiency is not associated with a major human disease, although it frequently accompanies other vitamin deficiencies. Deficiency symptoms include dermatitis, cheilosis (fissuring at the corners of the mouth), and glossitis (the tongue appearing smooth and dark). (Note: Because riboflavin is light sensitive, phototherapy for hyperbilirubinemia [see p. 317] may require supplementation with the vitamin.)

FIGURE 28.15

Structure and biosynthesis of the oxidized forms of flavin mononucleotide and flavin adenine dinucleotide.

ADP = adenosine diphosphate; PP_i = pyrophosphate.

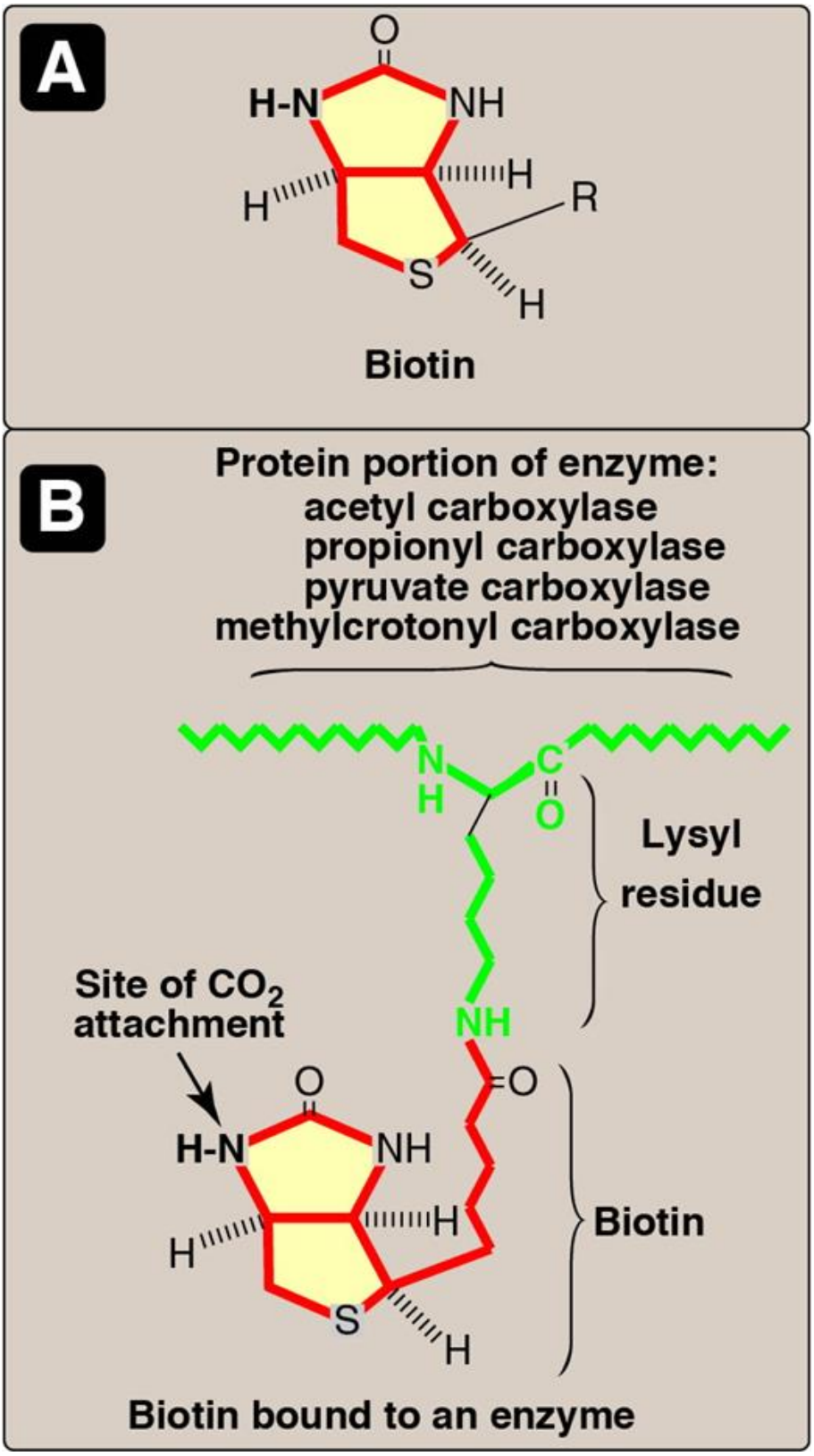


Biotin (Vitamin B_7)

Biotin is a coenzyme in carboxylation reactions, in which it serves as a carrier of activated carbon dioxide (CO_2) for the mechanism of biotin-dependent carboxylations. Biotin is covalently bound to the ε-amino group of lysine residues in biotin-dependent enzymes (Fig. 28.16). Biotin deficiency does not occur naturally because the vitamin is widely distributed in food. Also, a large percentage of the biotin requirement in humans is supplied by intestinal bacteria. However, the addition of raw egg white to the diet as a source of protein can induce symptoms of biotin deficiency, namely, dermatitis, hair loss, loss of appetite, and nausea. Raw egg white contains the glycoprotein avidin, which tightly binds biotin and prevents its absorption from the intestine. With a normal diet, however, it has been estimated that 20 eggs/day would be required to induce a deficiency syndrome. (Note: Inclusion of raw eggs in the diet is not recommended because of the possibility of salmonellosis caused by infection with *Salmonella enterica*.)

FIGURE 28.16

A: Structure of biotin. **B:** Biotin covalently bound to a lysyl residue of a biotin-dependent enzyme. CO_2 = carbon dioxide.



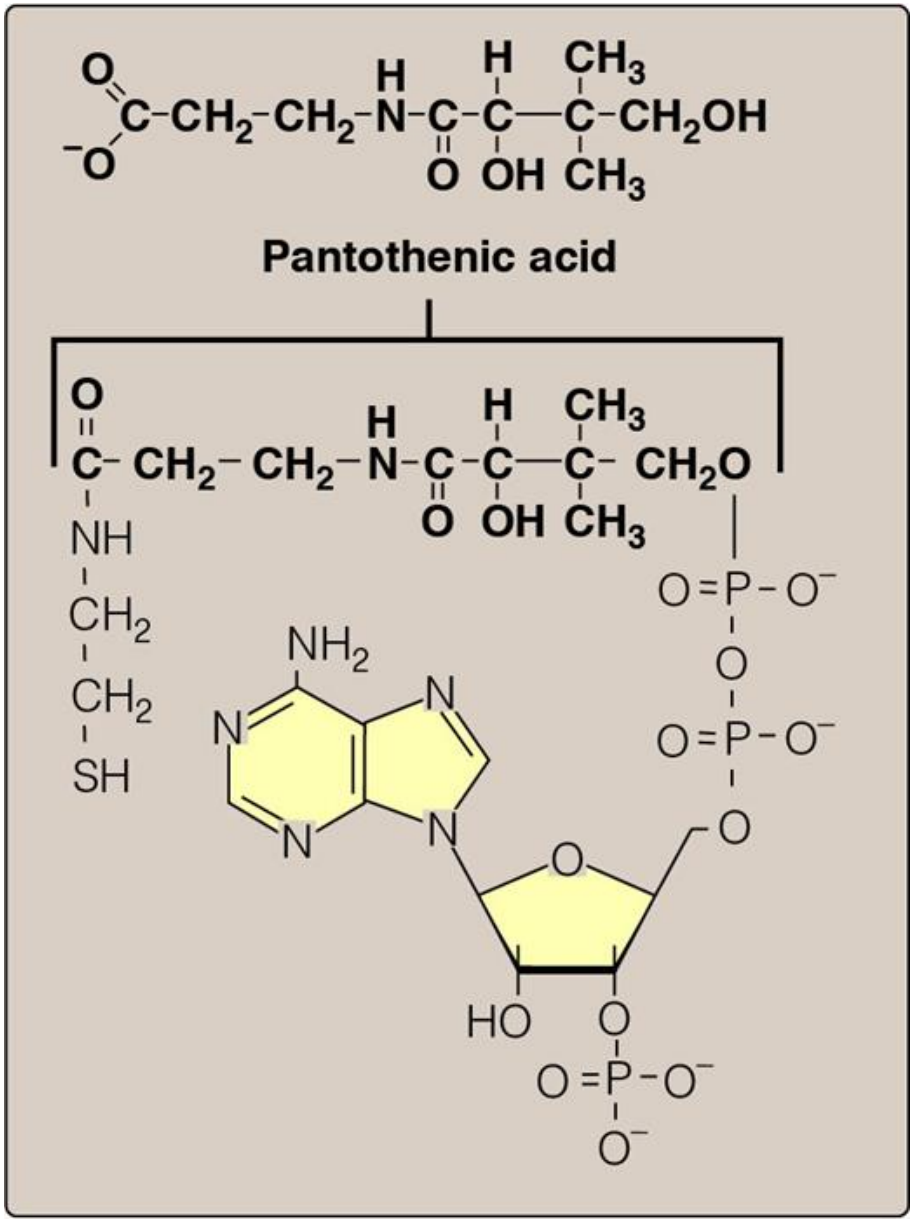
Multiple carboxylase deficiency results from decreased ability to add biotin to carboxylases during their synthesis or to remove it during their degradation. Treatment is biotin supplementation.

Pantothenic Acid (VITAMIN B_5)

Pantothenic acid is a component of CoA, which functions in the transfer of acyl groups (Fig. 28.17). CoA contains a thiol group that carries acyl compounds as activated thiol esters. Examples of such structures are succinyl CoA, fatty acyl CoA, and acetyl CoA. Pantothenic acid is also a component of the acyl carrier protein domain of **fatty acid synthase**. Eggs, liver, and yeast are the most important sources of pantothenic acid, although the vitamin is widely distributed. Pantothenic acid deficiency is not well characterized in humans, and no RDA has been established.

FIGURE 28.17

Structure of coenzyme A.



Vitamin A

Vitamin A is a fat-soluble vitamin that comes primarily from animal sources as retinol (preformed vitamin A), a retinoid. The retinoids, a family of structurally related molecules, are essential for vision, reproduction, growth, and maintenance of epithelial tissues. They also play a role in immune function. Retinoic acid, derived from oxidation of retinol, mediates most of the actions of the retinoids, except for vision, which depends on retinal, the aldehyde derivative of retinol.

Structure

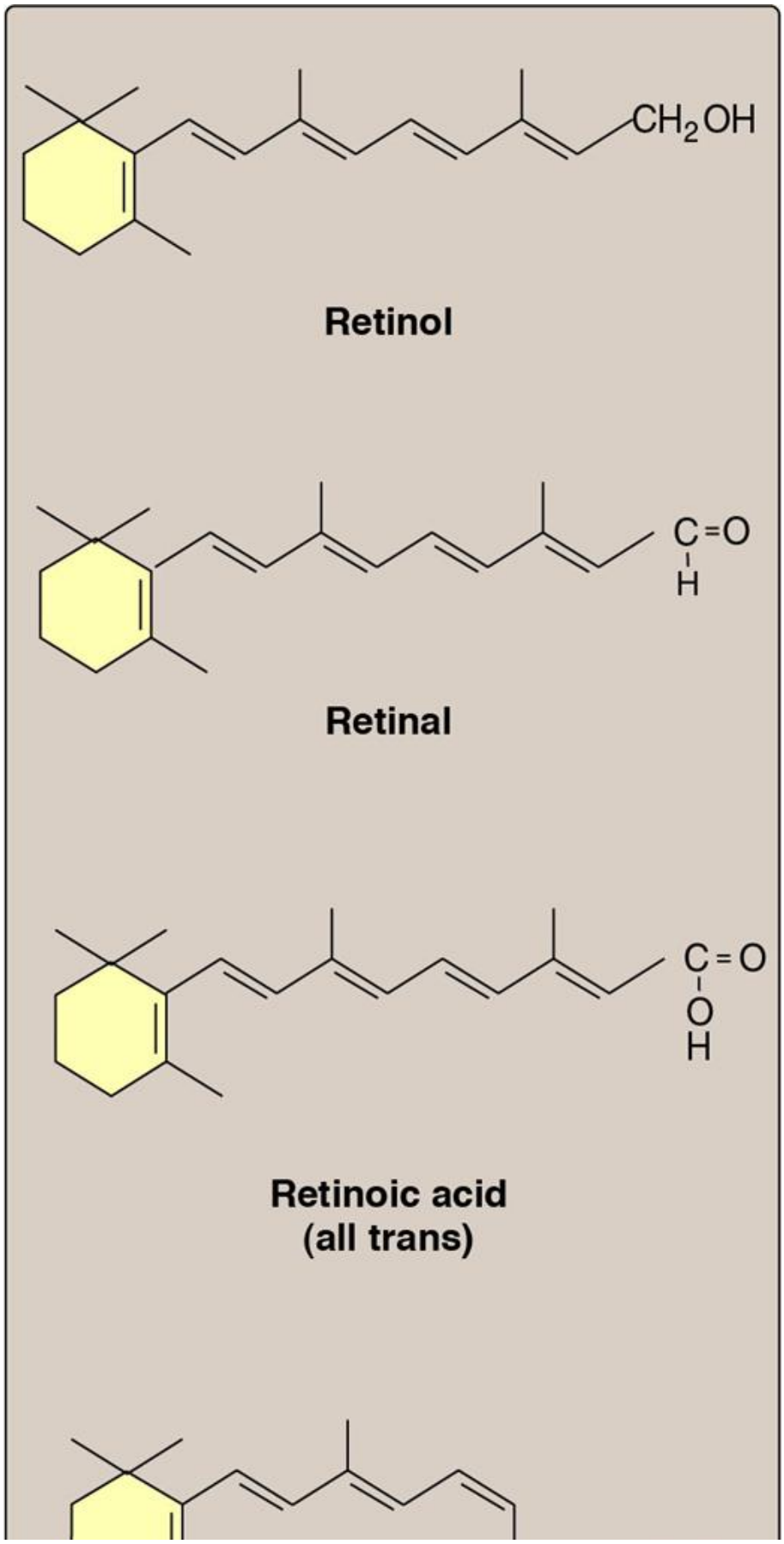
The retinoids include the natural forms of vitamin A, retinol and its metabolites (Fig. 28.18), and synthetic forms (drugs).

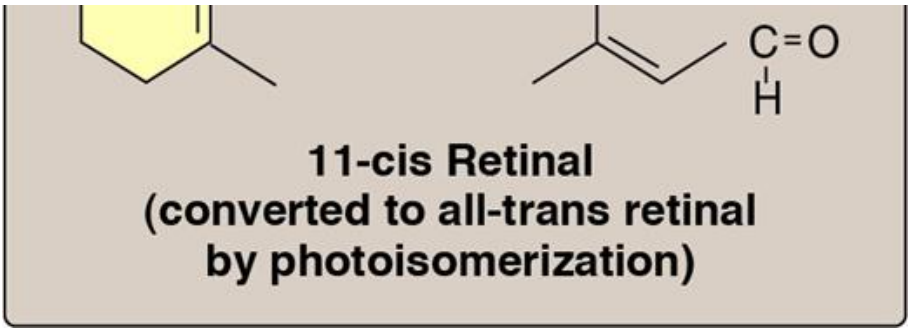
Retinol

A primary alcohol containing a β-ionone ring with an unsaturated side chain, retinol is found in animal tissues as a retinyl ester with long-chain FA. It is the storage form of vitamin A.

FIGURE 28.18

Structure of the retinoids.





Retinal

This is the aldehyde derived from the oxidation of retinol. Retinal and retinol can readily be interconverted.

Retinoic acid

This is the acid derived from the oxidation of retinal. Retinoic acid cannot be reduced in the body and, therefore, cannot give rise to either retinal or retinol.

β-Carotene

Plant foods contain β-carotene (provitamin A), which can be oxidatively and symmetrically cleaved in the intestine to yield two molecules of retinal. In humans, the conversion is inefficient, and the vitamin A activity of β-carotene is only about 1/12 that of retinol.

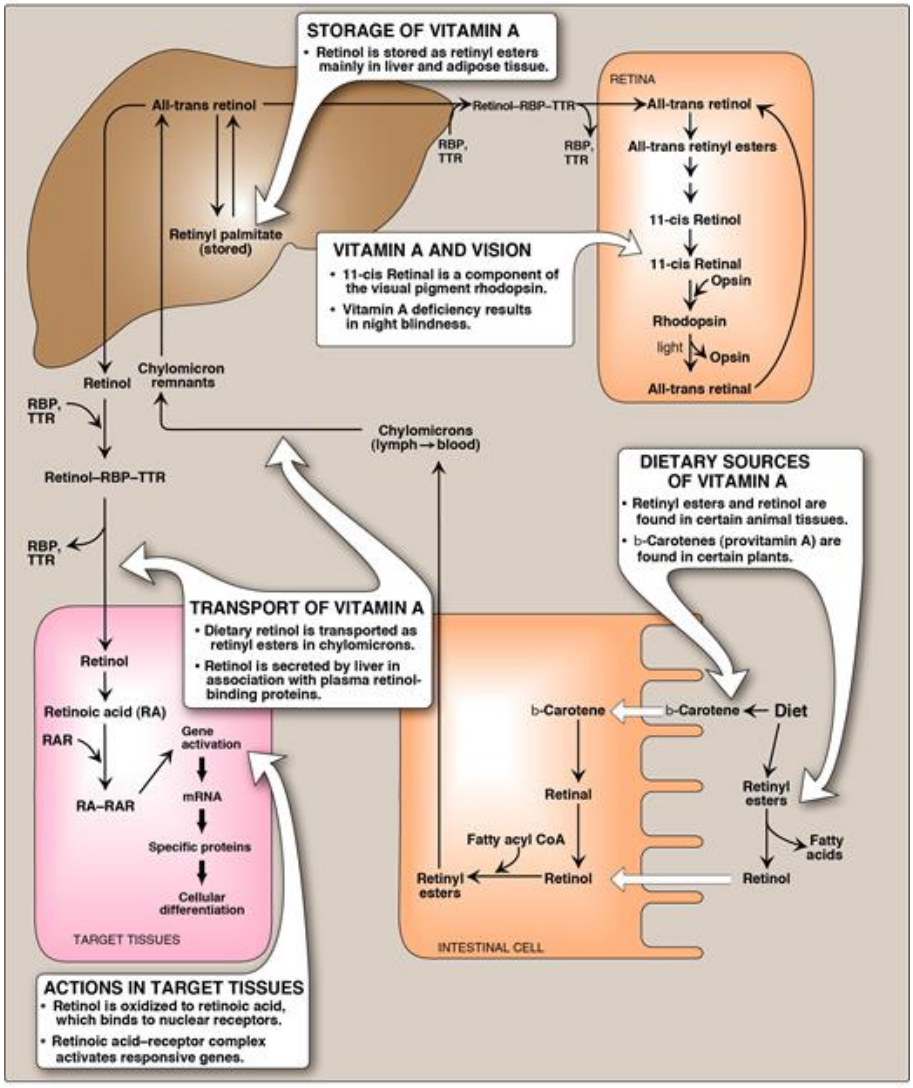
Absorption and transport to the liver

Retinyl esters from the diet are hydrolyzed in the intestinal mucosa, releasing retinol and FFA (Fig. 28.19). Retinol derived from esters and from the reduction of retinal from β-carotene cleavage is reesterified to long-chain FA within the enterocytes and secreted as a component of chylomicrons into the lymphatic system. Retinyl esters contained in chylomicron remnants are taken up by, and stored in, the liver. (Note: All fat-soluble vitamins are carried in chylomicrons.)

FIGURE 28.19

Absorption, transport, and storage of vitamin A and its derivatives.

(Note: β-Carotene is a carotenoid, a plant pigment with antioxidant activity.) RBP = retinol-binding protein; TTR = transthyretin; RAR = retinoic acid receptor; CoA = coenzyme A; mRNA = messenger RNA.



Release from the liver

When needed, retinol is released from the liver and transported through the blood to extrahepatic tissues by retinol-binding protein complexed with transthyretin (see Fig. 28.19). The ternary complex binds to a transport protein on the surface of the cells of peripheral tissues, permitting retinol to enter. An intracellular retinol-binding protein carries retinol to sites in the nucleus where the vitamin regulates transcription in a manner analogous to that of steroid hormones.

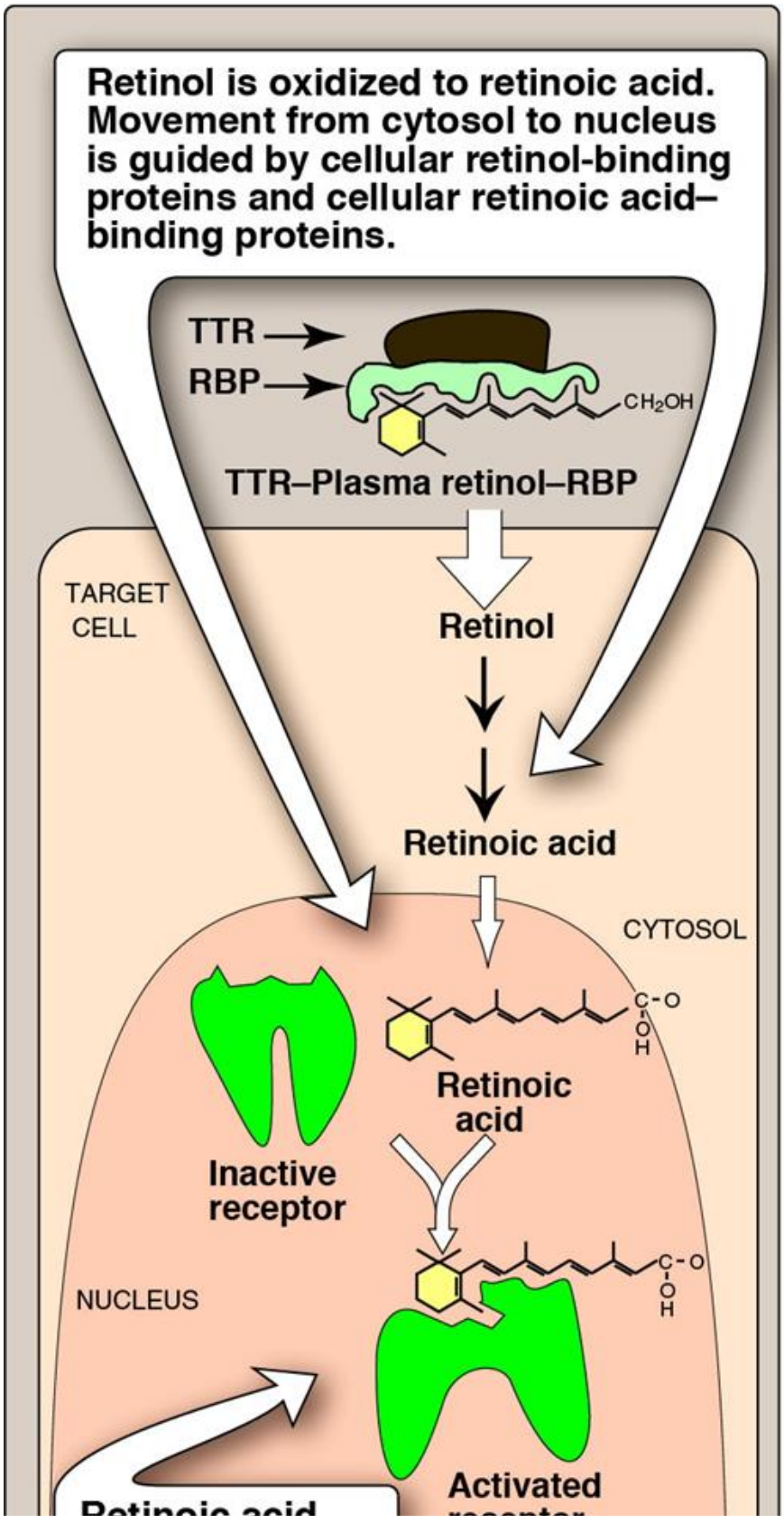
Retinoic acid mechanism of action

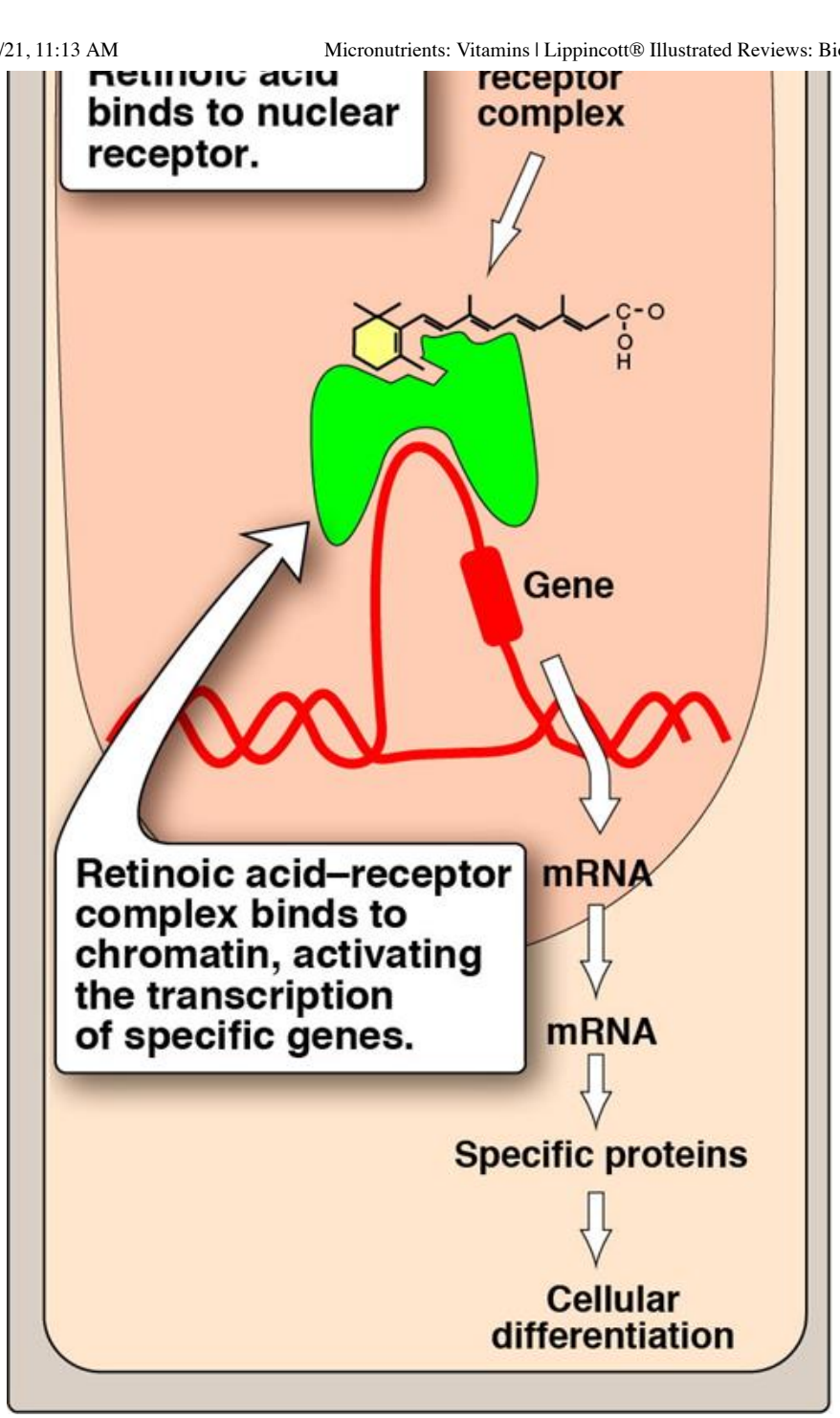
Retinol is oxidized to retinoic acid. Retinoic acid binds with high affinity to specific receptor proteins (retinoic acid receptors [RARs]) present in the nucleus of target tissues such as epithelial cells (Fig. 28.20). The activated retinoic acid–RAR complex binds to response elements on DNA and recruits activators or repressors to regulate retinoid-specific RNA synthesis, resulting in control of the production of specific proteins that mediate several physiologic functions. For example, retinoids control the expression of the gene for keratin in most epithelial tissues of the body. (Note: The RAR proteins are part of the superfamily of transcriptional regulators that includes the nuclear receptors for steroid and thyroid hormones and vitamin D, all of which function in a similar way [see p. 265].)

FIGURE 28.20

Action of the retinoids.

(Note: Retinoic acid–receptor complex forms a dimer, but is shown as monomer for simplicity.) TTR = transthyretin; RBP = retinol-binding protein; mRNA = messenger RNA.





Functions

Visual cycle

Vitamin A is a component of the visual pigments of rod and cone cells. Rhodopsin, the visual pigment of the rod cells in the retina, consists of 11-cis retinal bound to the protein opsin (see Fig. 28.19). 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 to the brain. Regeneration of rhodopsin requires isomerization of all-trans retinal back to 11-cis retinal. All-trans retinal is reduced to all-trans retinol, esterified, and isomerized to 11-cis retinol that is oxidized to 11-cis retinal. The latter combines with opsin to form rhodopsin, thus completing the cycle. Similar reactions are responsible for color vision in the cone cells.

Epithelial cell maintenance

Vitamin A is essential for normal differentiation of epithelial tissues and mucus secretion and, thus, supports the body's barrier-based defense against pathogens.

Reproduction

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 and in the visual cycle but promotes growth and differentiation of epithelial cells.

Distribution

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).

Requirement

The RDA for adults is 900 retinol activity equivalents (RAE) for males and 700 RAE for females. In comparison, 1 RAE = 1 μg of retinol, 12 μg of β-carotene, or 24 μg of other carotenoids.

Clinical indications for vitamin A

Although chemically related, retinoic acid and retinol have distinctly different therapeutic applications. Retinol and its carotenoid precursor are used as dietary supplements, whereas various forms of retinoic acid are useful in dermatology (Fig. 28.21).

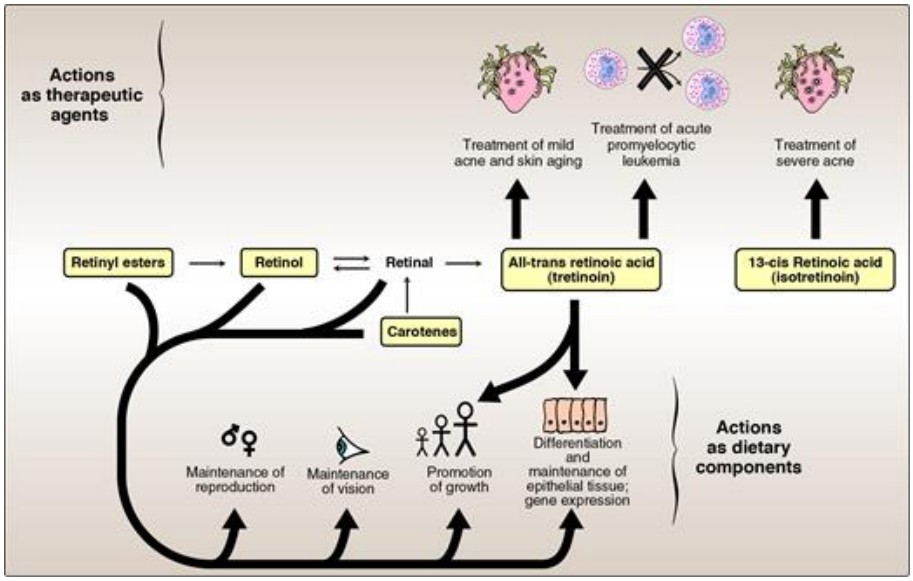
Deficiency

Vitamin A, administered as retinol or retinyl esters, is used to treat patients who are deficient in the vitamin. Night blindness (nyctalopia) is one of the earliest signs of vitamin A deficiency. The visual threshold is increased, making it difficult to see in dim light. Prolonged deficiency leads to an irreversible loss in the number of visual cells. Severe deficiency leads to xerophthalmia, a pathologic dryness of the conjunctiva and cornea, caused, in part, by increased keratin synthesis. If untreated, xerophthalmia results in corneal ulceration and, ultimately, in blindness because of the formation of opaque scar tissue. The condition is most commonly seen in children in developing tropical countries. Over 500,000 children worldwide are blinded each year by xerophthalmia caused by insufficient vitamin A in the diet.

FIGURE 28.21

Summary of actions of retinoids.

Compounds in boxes are available as dietary components or as pharmacologic agents.



Skin conditions

Dermatologic problems such as acne are effectively treated with retinoic acid or its derivatives (see Fig. 28.21). Mild cases of acne and skin aging are treated with tretinoin (all-trans retinoic acid). Tretinoin is too toxic for systemic (oral) administration in treating skin conditions and is confined to topical application. (Note: Oral tretinoin is used in treating acute promyelocytic leukemia.) In patients with severe cystic acne unresponsive to conventional therapies, isotretinoin (13-cis retinoic acid) is administered orally. An oral synthetic retinoid is used to treat psoriasis.

Retinoid toxicity

Vitamin A

Excessive intake of vitamin A (but not carotene) produces a toxic syndrome called hypervitaminosis A. Amounts exceeding 7.5 mg/day of retinol should be avoided. Early signs of chronic hypervitaminosis A are reflected in the skin, which becomes dry and pruritic (because of decreased keratin synthesis); in the liver, which becomes enlarged and can become cirrhotic; and in the CNS, where a rise in intracranial pressure may mimic the symptoms of a brain tumor. Pregnant women, in particular, should not ingest excessive quantities of vitamin A because of its potential for teratogenesis (causing congenital malformations in the developing fetus). UL is 3,000 µg preformed vitamin A/day. (Note: Vitamin A promotes bone growth. In excess, however, it is associated with decreased bone mineral density and increased risk of fractures.)

Isotretinoin

The drug, an isomer of retinoic acid, is teratogenic and absolutely contraindicated in women with childbearing potential unless they have severe, disfiguring cystic acne that is unresponsive to standard therapies. Pregnancy must be excluded before treatment begins, and birth control must be used. Prolonged treatment with isotretinoin can result in an increase in TAG and cholesterol, providing some concern for an increased risk of CVD.

Vitamin D

The D vitamins are a group of sterols that have a hormone-like function. The active molecule, 1,25-dihydroxycholecalciferol ([1,25-diOH-D_3], or calcitriol), binds to intracellular receptor proteins. The 1,25-diOH-D_3–receptor complex interacts with response elements in the nuclear DNA of target cells in a manner similar to that of vitamin A (see Fig. 28.20) and either selectively stimulates or represses gene transcription. The most prominent actions of calcitriol are to regulate the serum levels of calcium and phosphorus.

Distribution

Endogenous vitamin precursor

7-Dehydrocholesterol, an intermediate in cholesterol synthesis, is converted to cholecalciferol in the dermis and epidermis of humans exposed to sunlight and transported to liver bound to vitamin D–binding protein.

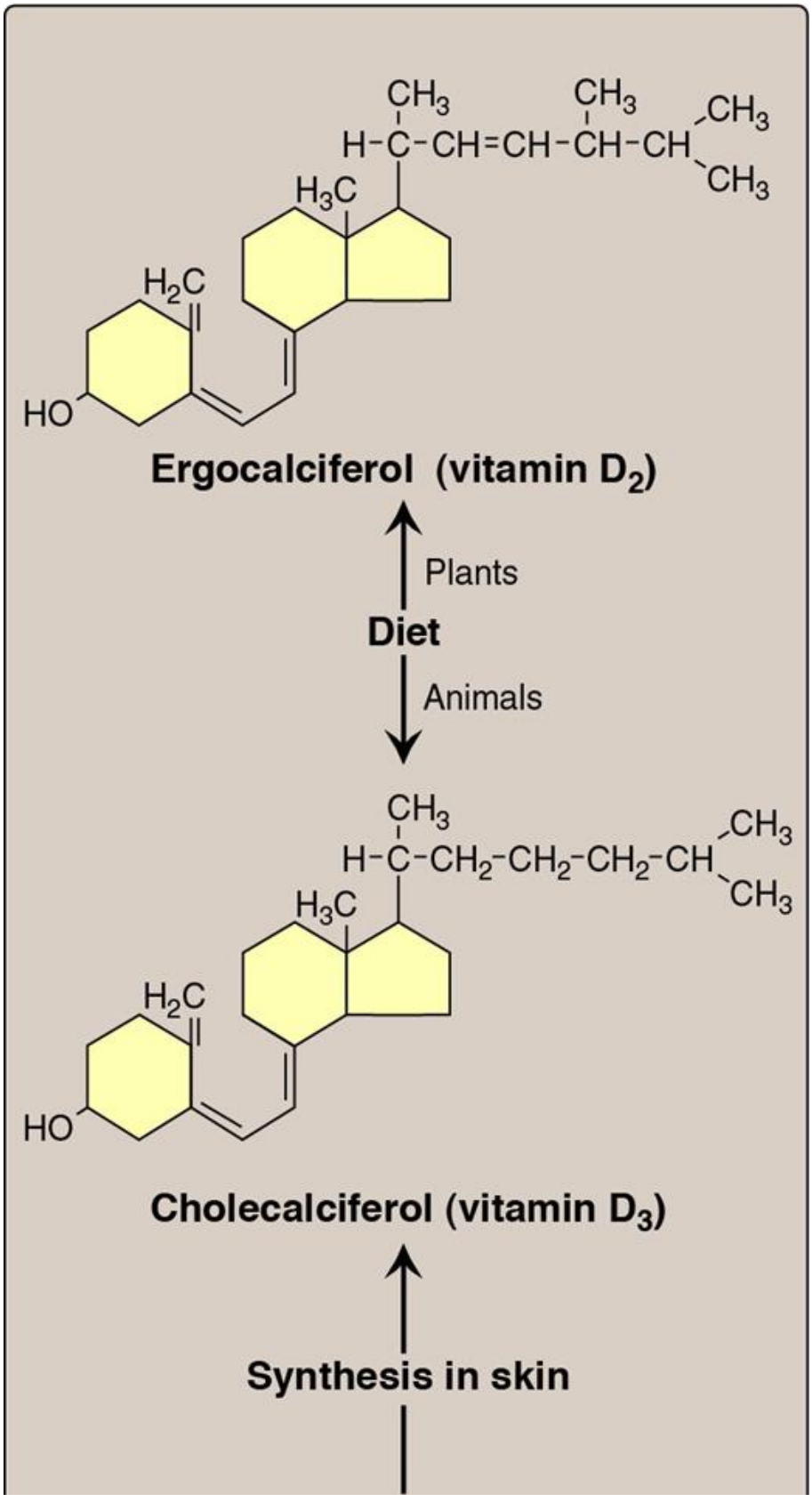
Diet

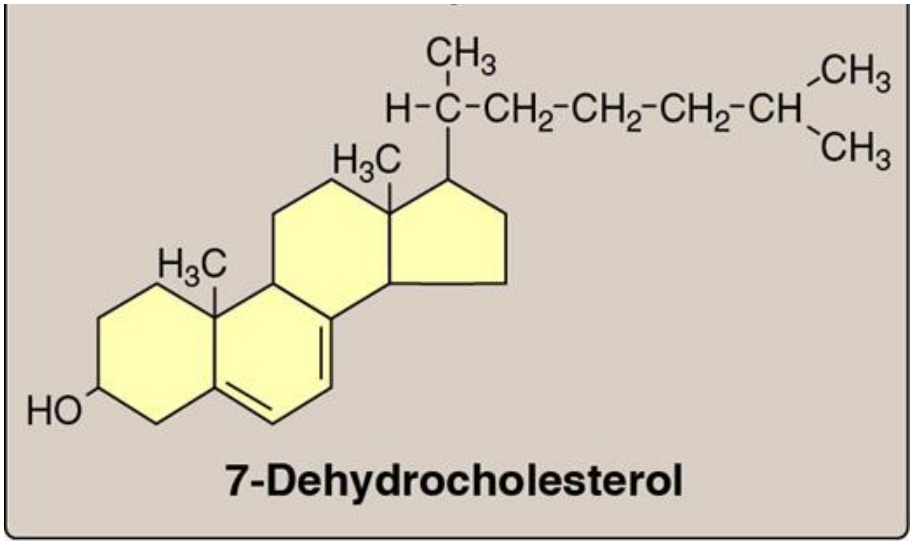
Ergocalciferol (vitamin D_2), found in plants, and cholecalciferol (vitamin D_3), found in animal tissues, are sources of preformed vitamin D activity (Fig. 28.22). Vitamin D_2 and vitamin D_3 differ chemically only in the presence of an additional double-bond and methyl group in the plant sterol. Dietary vitamin D is packaged into chylomicrons. (Note: Preformed vitamin D is a dietary requirement only in individuals with limited exposure to sunlight.)

FIGURE 28.22

Sources of vitamin D.

Vitamins D_2 and D_3 are first converted to calcidiol and then to calcitriol (active vitamin D). (Note: 7-Dehydrocholesterol [provitamin D_3] is decreased in the skin of older adults.)





Metabolism

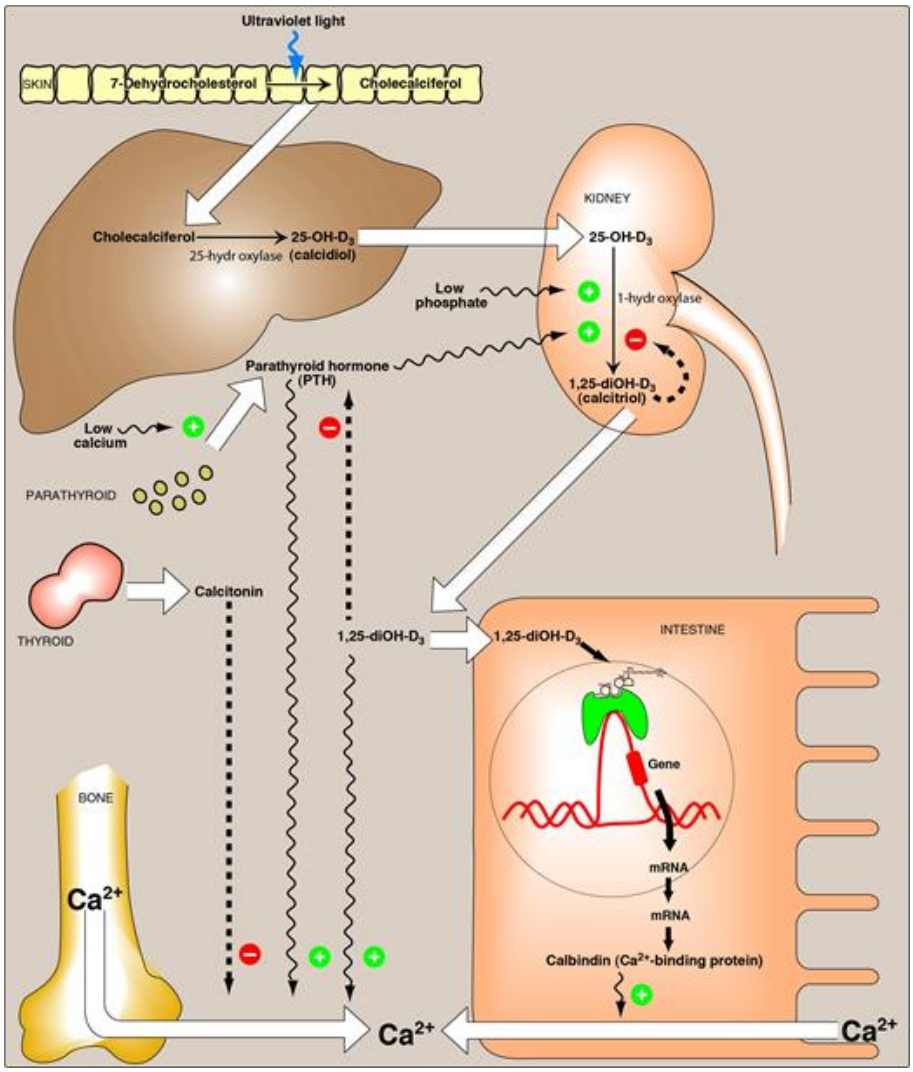
1,25-Dihydroxycholecalciferol formation

Vitamins D_2 and D_3 are not biologically active but are converted *in vivo* to calcitriol, the active form of the D vitamin, by two sequential hydroxylation reactions (Fig. 28.23). The first hydroxylation occurs at the 25 position and is catalyzed by a specific **25-hydroxylase** in the liver. The product of the reaction, 25-hydroxycholecalciferol ([25-OH-D_3], calcidiol), is the predominant form of vitamin D in the serum and the major storage form. 25-OH-D_3 is further hydroxylated at the 1 position by **25-hydroxycholecalciferol 1-hydroxylase** found primarily in the kidney, resulting in the formation of 1,25-diOH-D_3 (calcitriol). (Note: Both hydroxylases are cytochrome P450 proteins [see Chapter 13].)

FIGURE 28.23

Metabolism and actions of vitamin D.

(Note: Calcitonin, a thyroid hormone, decreases blood calcium [Ca^{2+}] by inhibiting mobilization from bone, absorption from the intestine, and reabsorption by the kidney. It opposes the actions of PTH.) mRNA = messenger RNA; 25-OH-D_3 = 25-hydroxycholecalciferol; 1,25-diOH-D_3 = 1,25-dihydroxycholecalciferol.



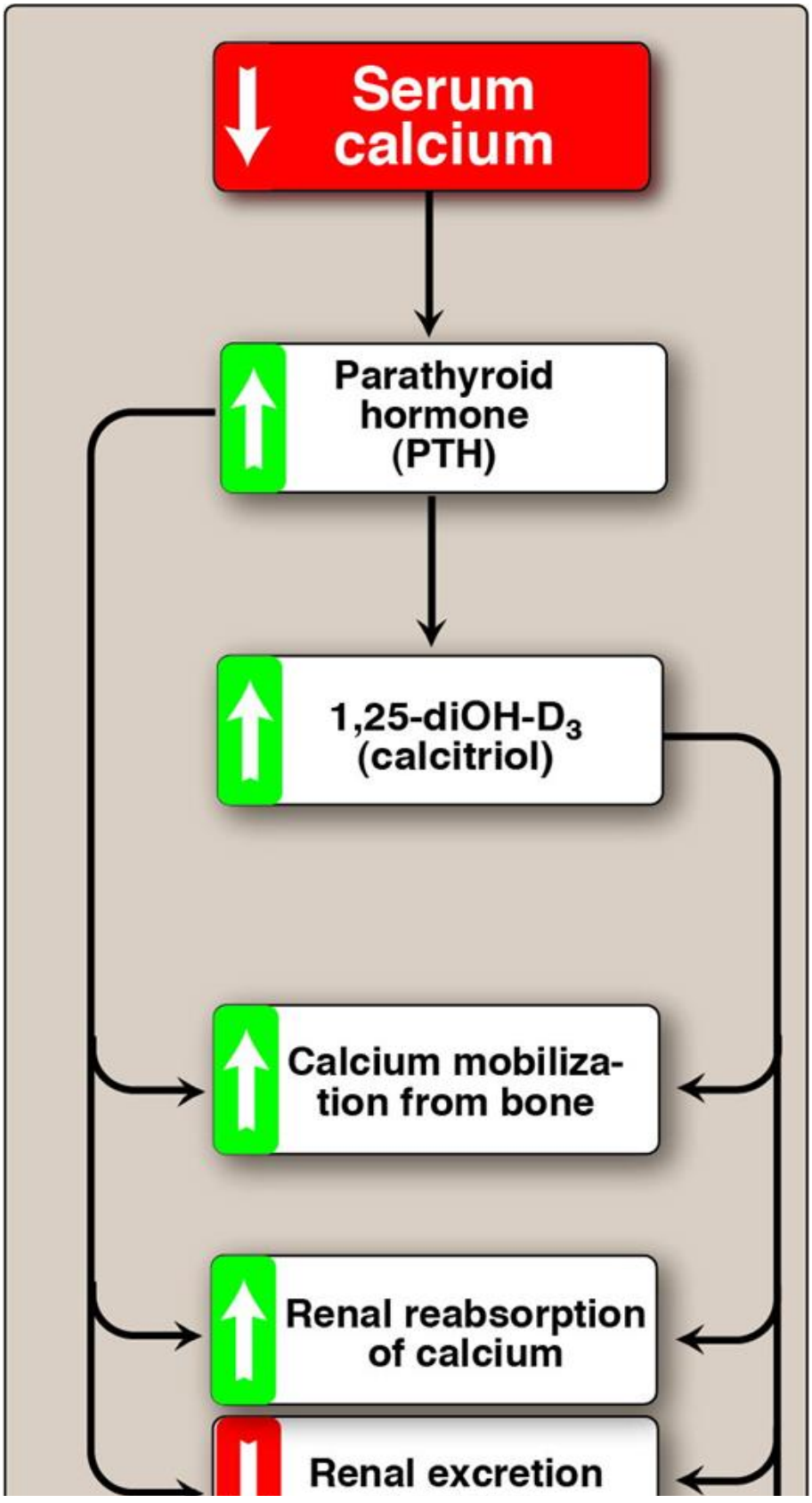
Hydroxylation regulation

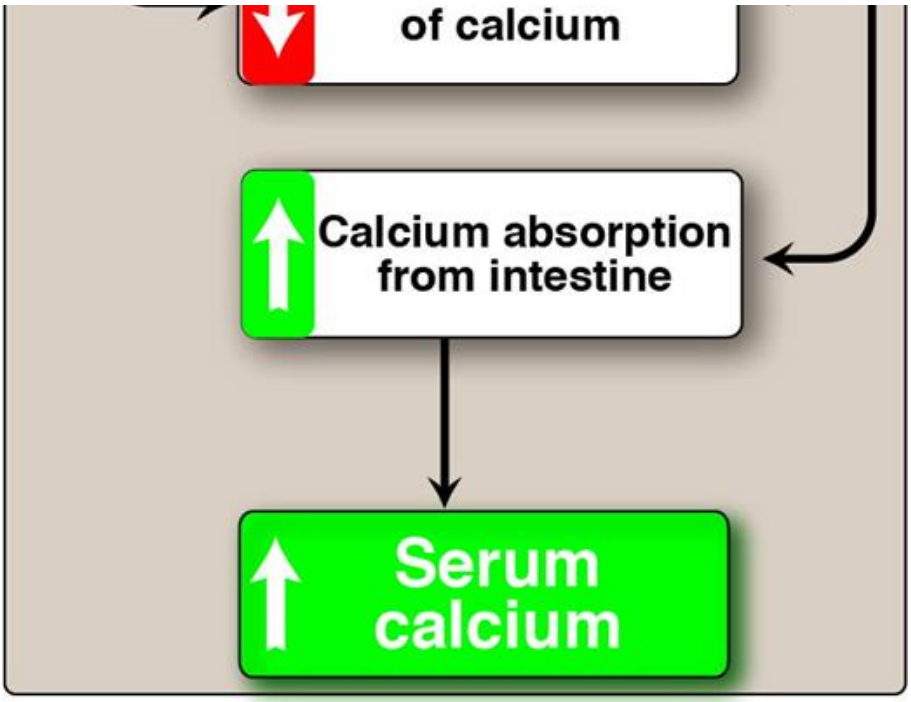
Calcitriol is the most potent vitamin D metabolite. Its formation is tightly regulated by the level of serum phosphate (PO_4^{3-}) and calcium ions (Ca^{2+}) as shown in Figure 28.24. **25-Hydroxycholecalciferol 1-hydroxylase** activity is increased directly by low serum PO_4^{3-} or indirectly by low serum Ca^{2+}, which triggers the secretion of parathyroid hormone (PTH) from the chief cells of the parathyroid gland. PTH upregulates the **1-hydroxylase**. Thus, hypocalcemia caused by insufficient dietary Ca^{2+} results in elevated levels of serum 1,25-diOH-D_3. (Note: 1,25-diOH-D_3 inhibits expression of PTH, forming a negative-feedback loop. It also inhibits activity of the 1-hydroxylase.)

FIGURE 28.24

Response to low serum calcium.

(Note: Calcitriol also increases intestinal absorption and renal reabsorption of phosphate. In contrast, PTH decreases renal reabsorption of phosphate.). 1,25-diOH-D_3 = 1,25-dihydroxycholecalciferol.





Function

The overall function of calcitriol is to maintain adequate serum levels of Ca^{2+}. It performs this function by (1) increasing uptake of Ca^{2+} by the intestine, (2) minimizing loss of Ca^{2+} by the kidney by increasing reabsorption, and (3) stimulating resorption (demineralization) of bone when blood Ca^{2+} is low (see Fig. 28.23).

Effect on the intestine

Calcitriol stimulates intestinal absorption of Ca^{2+} by first entering the intestinal cell and binding to a cytosolic receptor. The 1,25-diOH-D_3–receptor complex then moves to the nucleus where it selectively interacts with response elements on the DNA. As a result, Ca^{2+} uptake is enhanced by increased expression of the calcium-binding protein calbindin. Thus, the mechanism of action of 1,25-diOH-D_3 is typical of steroid hormones (see p. 265).

Effect on bone

Bone is composed of collagen and crystals of $Ca_5(PO_4)_3OH$ (hydroxylapatite). When blood Ca^{2+} is low, 1,25-diOH-D_3 stimulates bone resorption by a process that is enhanced by PTH. The result is an increase in serum Ca^{2+}. Therefore, bone is an important reservoir of Ca^{2+} that can be mobilized to maintain serum levels. (Note: PTH and calcitriol also work together to prevent renal loss of Ca^{2+}.)

Distribution and requirement

Vitamin D occurs naturally in fatty fish, liver, and egg yolk. Milk, unless it is artificially fortified, is not a good source. The RDA for individuals of ages 1 to 70 years is 15 µg/day and 20 µg/day if over age 70 years. Experts disagree, however, on the optimal level of vitamin D needed to maintain health. (Note: 1 µg vitamin D = 40 international units [IU].) Because breast milk is a poor source of vitamin D, supplementation is recommended for breastfed babies.

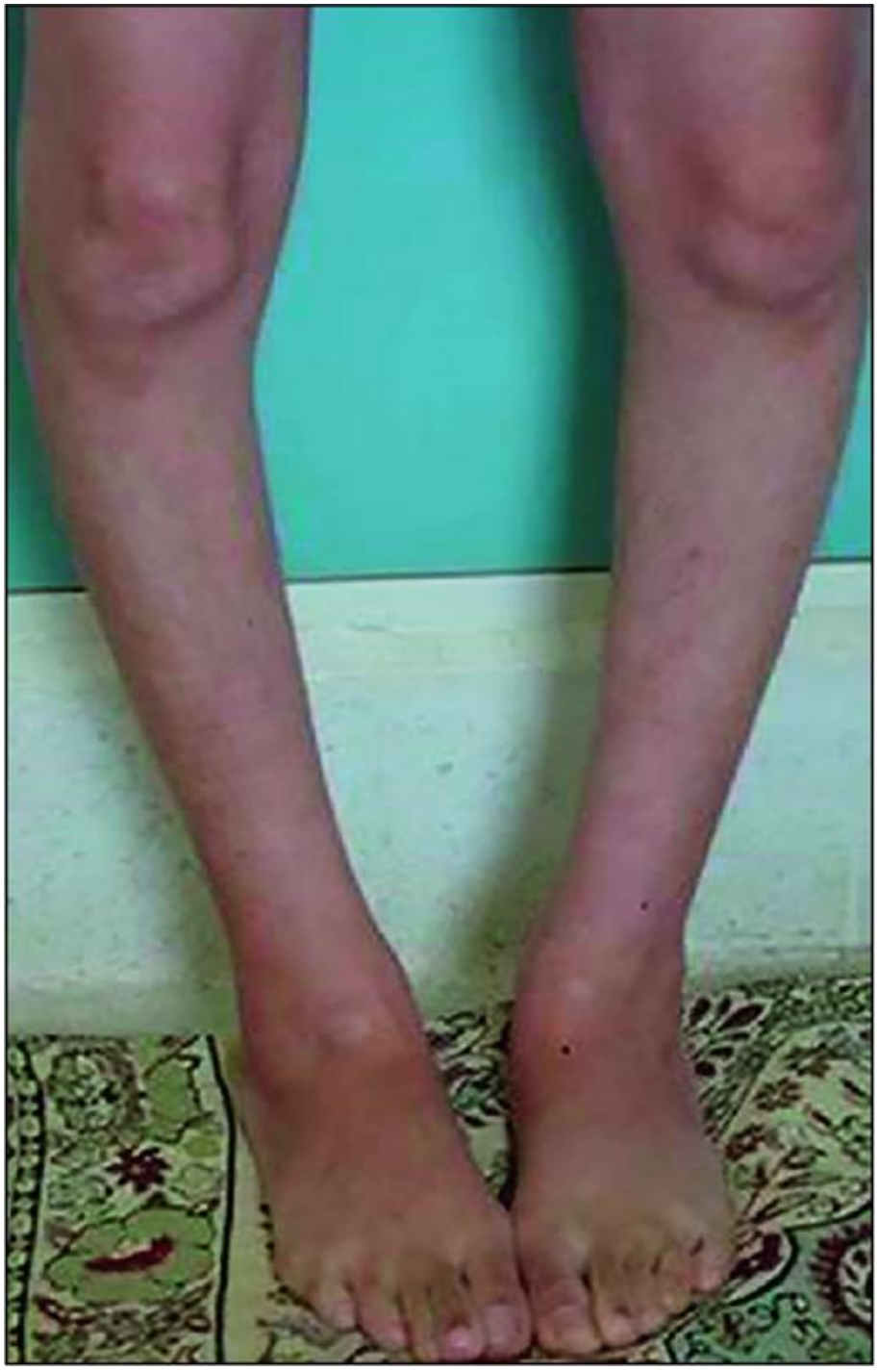
Clinical indications for vitamin D

Nutritional rickets

Vitamin D deficiency causes a net demineralization of bone, resulting in rickets in children and osteomalacia in adults (Fig. 28.25). Rickets is characterized by the continued formation of the collagen matrix of bone, but incomplete mineralization results in soft, pliable bones. In osteomalacia, demineralization of pre-existing bones increases their susceptibility to fracture. Insufficient exposure to daylight and/or deficiencies in vitamin D consumption occurs predominantly in infants and the elderly. Vitamin D deficiency is more common in the northern latitudes, because less vitamin D synthesis occurs in the skin as a result of reduced exposure to ultraviolet light. (Note: Loss-of-function mutations in the vitamin D receptor result in hereditary vitamin D–deficient rickets.)

FIGURE 28.25

Bowed legs of middle-aged man with osteomalacia, a nutritional vitamin D deficiency that results in demineralization of the skeleton.



Renal osteodystrophy

Chronic kidney disease causes decreased ability to form active vitamin D as well as increased retention of PO_4^{3-}, resulting in hyperphosphatemia and hypocalcemia. The low blood Ca^{2+} causes a rise in PTH and associated bone demineralization with release of Ca^{2+} and PO_4^{3-}. Supplementation with vitamin D is an effective therapy. However, supplementation must be accompanied by PO_4^{3-} reduction therapy to prevent further bone loss and precipitation of calcium phosphate crystals.

Hypoparathyroidism

Lack of PTH causes hypocalcemia and hyperphosphatemia. (Note: PTH increases phosphate excretion.) Patients may be treated with vitamin D and calcium supplementation.

Toxicity

Like all fat-soluble vitamins, vitamin D can be stored in the body and is only slowly metabolized. 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 result in hypercalcemia, which can lead to deposition of calcium salts in soft tissue (metastatic calcification). The 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. (Note: 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 of vitamin K 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, for example, in plants as phylloquinone (or vitamin K_1), and in intestinal bacteria as menaquinone (or vitamin K_2). A synthetic form of vitamin K, menadione, is able to be converted to K_2.

Function

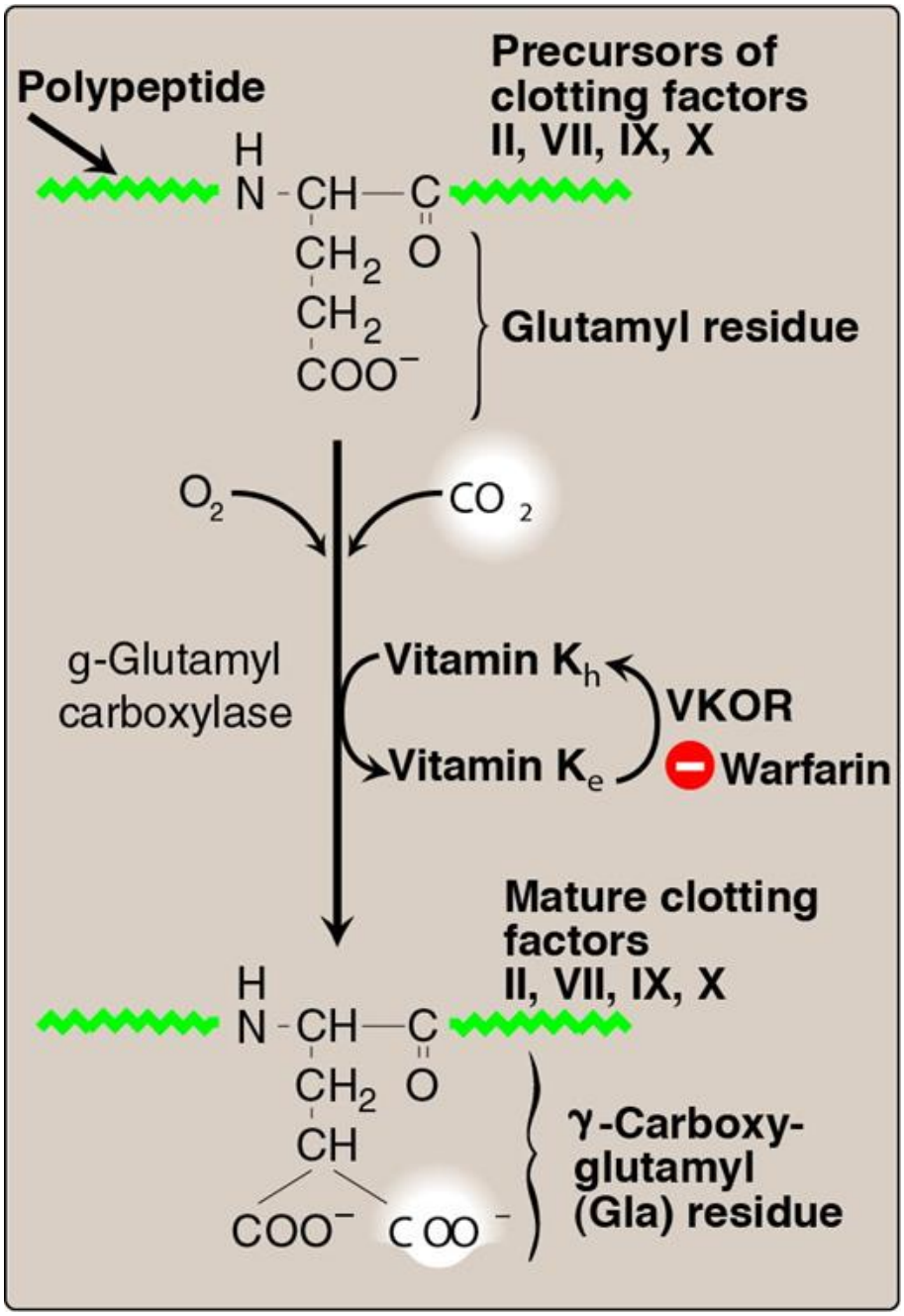
γ-Carboxyglutamate formation

Vitamin K is required for the posttranslational modification of coagulation factors prothrombin, FVII, FIX and FX (See Chapter 35) which are synthesized in the liver. Formation of the functional versions of these enzyme factors requires the vitamin K–dependent carboxylation of several glutamic acid residues to γ-carboxyglutamate (Gla) residues (Fig. 28.26). 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). The 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.

FIGURE 28.26

Carboxylation of glutamate to form γ-carboxyglutamate.

h = hydroquinone; e = epoxide; *VKOR* = *vitamin K epoxide reductase*.



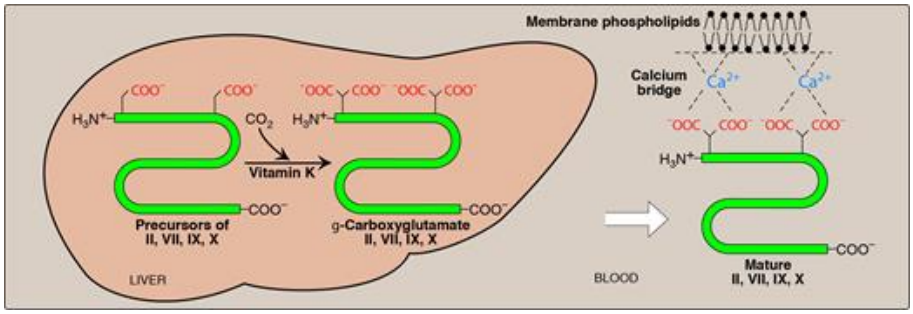
Prothrombin interaction with membranes

The Gla residues are good chelators of positively charged calcium ions, because of their two adjacent, negatively charged carboxylate groups. With prothrombin, for example, the prothrombin–calcium complex is able to bind to 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 (Fig. 28.27).

FIGURE 28.27

Role of vitamin K in blood coagulation.

CO_2 = carbon dioxide.



γ-Carboxyglutamate residues in other proteins

Gla residues are also present in proteins other than those involved in forming a blood clot. For example, osteocalcin and matrix Gla protein of bone and proteins C and S (involved in limiting the formation of blood clots) also undergo γ-carboxylation.

Distribution and requirement

Vitamin K is found in cabbage, kale, spinach, egg yolk, and liver. The 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

Deficiency

A true vitamin K deficiency is unusual because adequate amounts are generally obtained from the diet and produced by intestinal bacteria. If the bacterial population in the gut is decreased (e.g., by antibiotics), the amount of endogenously formed vitamin is decreased, and this can lead to hypoprothrombinemia in the marginally malnourished individual (e.g., a debilitated geriatric patient). This condition may require supplementation with vitamin K to correct the bleeding tendency. In addition, certain cephalosporin antibiotics (e.g., cefamandole) cause hypoprothrombinemia, apparently by a warfarin-like mechanism that inhibits **VKOR**. Consequently, their use in treatment is usually supplemented with vitamin K. Deficiency can also affect bone health.

Deficiency in the newborn

Because newborns have sterile intestines, they initially lack the bacteria that synthesize vitamin K. Because 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

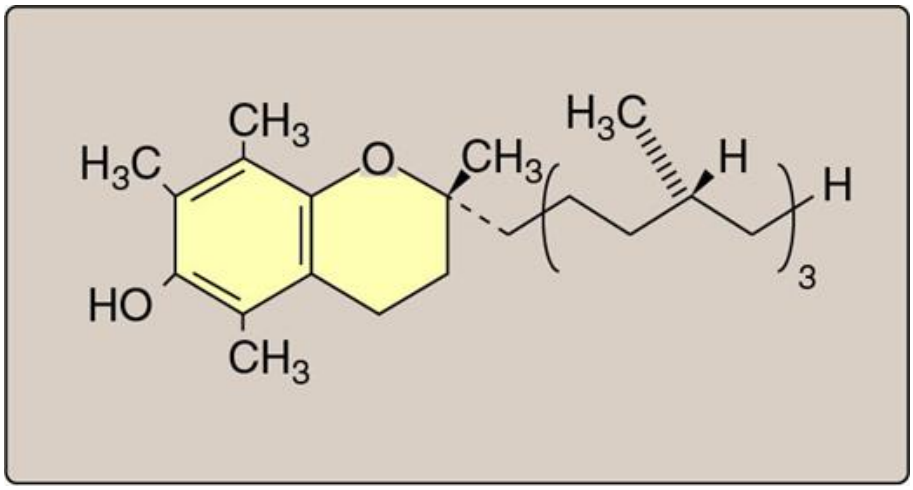
Prolonged administration of large doses of menadione can produce hemolytic anemia and jaundice in the infant, because of toxic effects on the RBC membrane. Therefore, it is no longer used to treat vitamin K deficiency. No UL for the natural form has been set.

Vitamin E

The E vitamins consist of eight naturally occurring tocopherols, of which α-tocopherol is the most active (Fig. 28.28). Vitamin E functions as an antioxidant in prevention of nonenzymic oxidations (e.g., oxidation of LDL and peroxidation of polyunsaturated FA by O_2 and free radicals). (Note: Vitamin C regenerates active vitamin E.)

FIGURE 28.28

Structure of vitamin E (α-tocopherol).



Distribution and requirements

Vegetable oils are rich sources of vitamin E, whereas liver and eggs contain moderate amounts. The RDA for α-tocopherol is 15 mg/day for adults. The vitamin E requirement increases as the intake of polyunsaturated FA increases to limit FA peroxidation.

Deficiency

Newborns have low reserves of vitamin E, but breast milk (and formulas) contains the vitamin. Very–low-birth-weight infants may be given supplements to prevent the hemolysis and retinopathy associated with vitamin E deficiency. When observed in adults, deficiency is usually associated with defective lipid absorption or transport. (Note: Abetalipoproteinemia, caused by a defect in the formation of chylomicrons [and VLDL], results in vitamin E deficiency [see p. 256].)

Clinical indications for vitamin E

Vitamin E is not recommended for the prevention of chronic disease, such as CVD or cancer. Clinical trials using vitamin E supplementation have been uniformly disappointing. For example, subjects in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study trial who received high doses of vitamin E not only lacked cardiovascular benefit but also had an increased incidence of stroke. (Note: Vitamins E and C are used to slow the progression of age-related macular degeneration.)

Toxicity

Vitamin E is the least toxic of the fat-soluble vitamins, and no toxicity has been observed at doses of 300 mg/day (UL = 1,000 mg/day).

Populations consuming diets high in fruits and vegetables show decreased incidence of some chronic diseases. However, clinical trials have failed to show a definitive benefit from supplements of folic acid; vitamins A, C, or E; or antioxidant combinations for the prevention of cancer or CVD.

Chapter Summary

The vitamins are summarized in Figure 28.29.

FIGURE 28.29

Summary of vitamins.

(Note: Choline, like vitamin D, is considered an essential micronutrient in humans even though we are able to synthesize it.) P = phosphate; NAD(P) = nicotinamide adenine dinucleotide (phosphate); FMN = flavin mononucleotide; FAD = flavin adenine dinucleotide; CoA = coenzyme A.

VITAMIN	OTHER NAMES	ACTIVE FORM	FUNCTION	DEFICIENCY	SIGNS AND SYMPTOMS	TOXICITY	NOTES
Vitamin B_9	Folic acid	Tetrahydrofolic acid	Transfer one-carbon units; synthesis of methionine, serine, purine nucleotides, and thymidine monophosphate	Megaloblastic anemia Neural tube defects	Anemia Birth defects	None	Administration of high levels of folate can mask vitamin B_{12} deficiency
Vitamin B_{12}	Cobalamin	Methylcobalamin Deoxyadenosyl cobalamin	Coenzyme for reactions: Homocysteine ⇄ methionine Methylmalonyl CoA ⇄ succinyl CoA	Pernicious anemia Dementia Spinal degeneration	Megaloblastic anemia Neuropsychiatric symptoms	None	Pernicious anemia is treated with intramuscular or high-dose oral vitamin B_{12}
Vitamin C	Ascorbic acid	Ascorbic acid	Antioxidant Coenzyme for hydroxylation reactions, for example: In procollagen: Proline ⇄ hydroxyproline Lysine ⇄ hydroxylysine	Scurvy	Sore, spongy gums Loose teeth Poor wound healing Bleeding	None	Benefits of supplementation not established in controlled trials
Vitamin B_6	Pyridoxine Pyridoxamine Pyridoxal	Pyridoxal phosphate	Coenzyme for enzymes, particularly in amino acid metabolism	Rare	Glossitis Neuropathy	Yes	Deficiency can be induced by isoniazid Sensory neuropathy occurs at high doses
Vitamin B_1	Thiamine	Thiamine pyrophosphate	Coenzyme of enzymes catalyzing: Pyruvate ⇄ acetyl CoA α-Ketoglutarate ⇄ Succinyl CoA Ribose 5-P + xylulose 5-P ⇄ Sedoheptulose 7-P + Glyceraldehyde 3-P Branched-chain α-keto acid oxidation	Beriberi Wernicke-Korsakoff syndrome (most common in alcoholism)	Peripheral neuropathy (dry form), edema and cardiomyopathy (wet form) Confusion, ataxia, memory loss, hallucinations, dysregulated eye movements	None	–
Vitamin B_3	Niacin Nicotinic acid	NAD^+, $NADP^+$	Electron transfer	Pellagra	Dermatitis Diarrhea Dementia	None	High doses of niacin used to treat hyperlipidemia
Vitamin B_2	Riboflavin	FMN, FAD	Electron transfer	Rare	Dermatitis Angular stomatitis	None	–
Vitamin B_7	Biotin	Enzyme-bound biotin	Carboxylation reactions	Rare	Dermatitis	None	Consumption of large amounts of raw egg whites (which contains a protein, avidin, that binds biotin) can induce a biotin deficiency
Vitamin B_5	Pantothenic acid	Coenzyme A	Acyl carrier	Rare	–	None	–
			WATER SOLUBLE				WATER SOLUBLE
Vitamin A	Retinol Retinal Retinoic acid β-Carotene	Retinol Retinal Retinoic acid	Maintenance of reproduction Vision Promotion of growth Differentiation and maintenance of epithelial tissues Gene expression	Night blindness Xerophthalmia Infertility Growth retardation	Increased visual threshold Dryness of cornea	Yes	β-Carotene not acutely toxic, but supplementation is not recommended Excess vitamin A can increase incidence of fractures
Vitamin D	Cholecalciferol Ergocalciferol	1,25-Dihydroxycholecalciferol	Calcium uptake Gene expression	Rickets (in children) Osteomalacia (in adults)	Soft, pliable bones	Yes	Vitamin D is not a true vitamin because it can be synthesized in skin; application of sunscreen lotions or presence of dark skin color decreases this synthesis
Vitamin K	Menadione Menaquinone Phylloquinone	Menadione Menaquinone Phylloquinone	γ-Carboxylation of glutamate residues in clotting and other proteins				
Vitamin E	α-Tocopherol	Any of several tocopherol derivatives	Antioxidant				
			FAT SOLUBLE				FAT SOLUBLE

			Dark skin color decreases this synthesis.
Newborn Rare in adults	Bleeding	Rare	Vitamin K produced by intestinal bacteria. Vitamin K deficiency common in newborns Intramuscular treatment with vitamin K is recommended at birth
Rare	Red blood cell fragility leads to hemolytic anemia	None	Benefits of supplementation for disease prevention not established in controlled trials

Study Questions

Choose the ONE best answer.

For Questions 28.1–28.5, match the vitamin deficiency to the clinical consequence.

A. Folic acid

B. Niacin

C. Vitamin A

D. Vitamin B_{12}

E. Vitamin C

F. Vitamin D

G. Vitamin E

H. Vitamin K

28.1. Bleeding

28.2. Diarrhea and dermatitis

28.3. Neural tube defects

28.4. Night blindness (nyctalopia)

28.5. Sore, spongy gums and loose teeth

Correct answers = H, B, A, C, E. Vitamin K is required for formation of the γ-carboxyglutamate residues in several proteins required for blood clotting. Consequently, a deficiency of vitamin K results in a tendency to bleed. Niacin deficiency is characterized by the three Ds: diarrhea, dermatitis, and dementia (and death, a fourth D, if untreated). Folic acid deficiency can result in neural tube defects in the developing fetus. Night blindness is one of the first signs of vitamin A deficiency. Rod cells in the retina detect white and black images and work best in low light, for example, at night. Rhodopsin, the visual pigment of the rod cells, consists of 11-cis retinal bound to the protein opsin. Vitamin C is required for the hydroxylation of proline and lysine during collagen synthesis. Severe vitamin C deficiency (scurvy) results in defective connective tissue, characterized by sore and spongy gums, loose teeth, capillary fragility, anemia, and fatigue.

28.6. A 52-year-old female presents with fatigue of several months' duration. Blood studies reveal a macrocytic anemia, reduced levels of hemoglobin, elevated levels of homocysteine, and normal levels of methylmalonic acid. Which of the following is most likely deficient in this patient?

A. Folic acid

B. Folic acid and vitamin B_{12}

C. Iron

D. Vitamin C

Correct answer = A. Macrocytic anemia is seen with deficiencies of folic acid, vitamin B_{12}, or both. Vitamin B_{12} is utilized in only two reactions in the body: the remethylation of homocysteine (Hcy) to methionine, which also requires folic acid (as tetrahydrofolate [THF]), and the isomerization of methylmalonyl coenzyme A to succinyl coenzyme A, which does not require THF. The elevated Hcy and normal methylmalonic acid levels in the patient's blood reflect a deficiency of folic acid as the cause of the macrocytic anemia. Iron deficiency causes microcytic anemia, as can vitamin C deficiency.

28.7. A 10-month-old African American female, whose family recently located from Maine to Virginia, is being evaluated for the bowed appearance of her legs. The parents report that the baby is still being breastfed and takes no supplements. Radiologic studies confirm the suspicion of rickets caused by vitamin D deficiency. Which one of the following statements concerning vitamin D is correct?

A. A deficiency results in an increased secretion of calbindin.

B. Chronic kidney disease results in overproduction of 1,25-dihydroxycholecalciferol (calcitriol).

C. 25-Hydroxycholecalciferol (calcidiol) is the active form of the vitamin.

D. It is required in the diet of individuals with limited exposure to sunlight.

E. Its actions are mediated through binding to G protein–coupled receptors.

F. It opposes the effect of parathyroid hormone.

Correct answer = D. Vitamin D is required in the diet of individuals with limited exposure to sunlight, such as those living at northern latitudes like Maine and those with dark skin. Note that breast milk is low in vitamin D, and the lack of supplementation increases the risk of a deficiency. Vitamin D deficiency results in decreased synthesis of calbindin. Chronic kidney disease decreases production of calcitriol (1,25-dihydroxycholecalciferol), the active form of the vitamin. Vitamin D binds to nuclear receptors and alters gene transcription. Its effects are synergistic with parathyroid hormone.

28.8. Why might a deficiency of vitamin B_6 result in a fasting hypoglycemia? Deficiency of what other vitamin could also result in hypoglycemia?

Vitamin B_6 is required for glycogen degradation by glycogen phosphorylase. A deficiency would result in fasting hypoglycemia. Additionally, a deficiency of biotin (required by pyruvate carboxylase of gluconeogenesis) would also result in fasting hypoglycemia.