

## FAT SOLUBLE VITAMINS

### 10. RETINOL (VITAMIN A)

The retinoids, a family of molecules that are related to retinol (vitamin A), are essential for vision, reproduction, growth, and maintenance of epithelial tissues. Retinoic acid, derived from oxidation of dietary retinol, mediates most of the actions of the retinoids, except for vision, which depends on retinal, the aldehyde derivative of retinol.

#### A. Structure of vitamin A

Vitamin A is often used as a collective term for several related biologically active molecules (Figure 28.18). The term retinoids includes both natural and synthetic forms of vitamin A that may or may not show vitamin A activity.

**1. Retinol:** A primary alcohol containing a  $\beta$ -ionone ring with an unsaturated side chain, retinol is found in animal tissues as a retinyl ester with long-chain fatty acids.

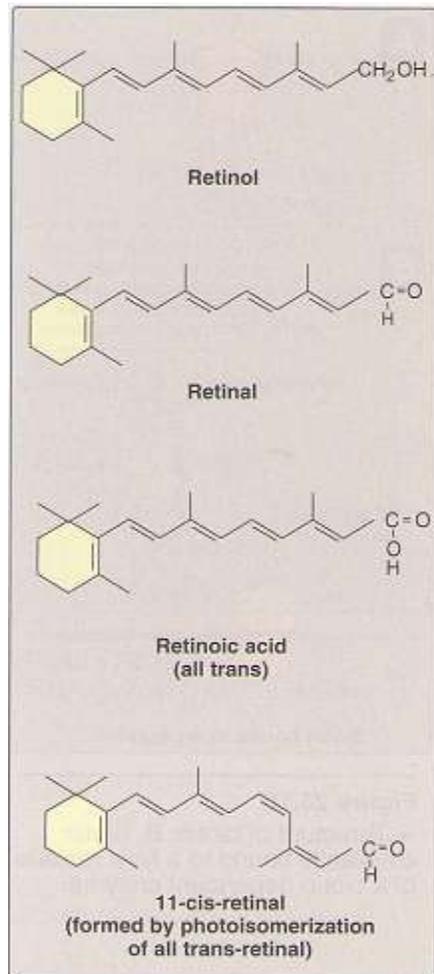
**2. Retinal:** This is the aldehyde derived from the oxidation of retinol. Retinal and retinol can readily be interconverted.

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

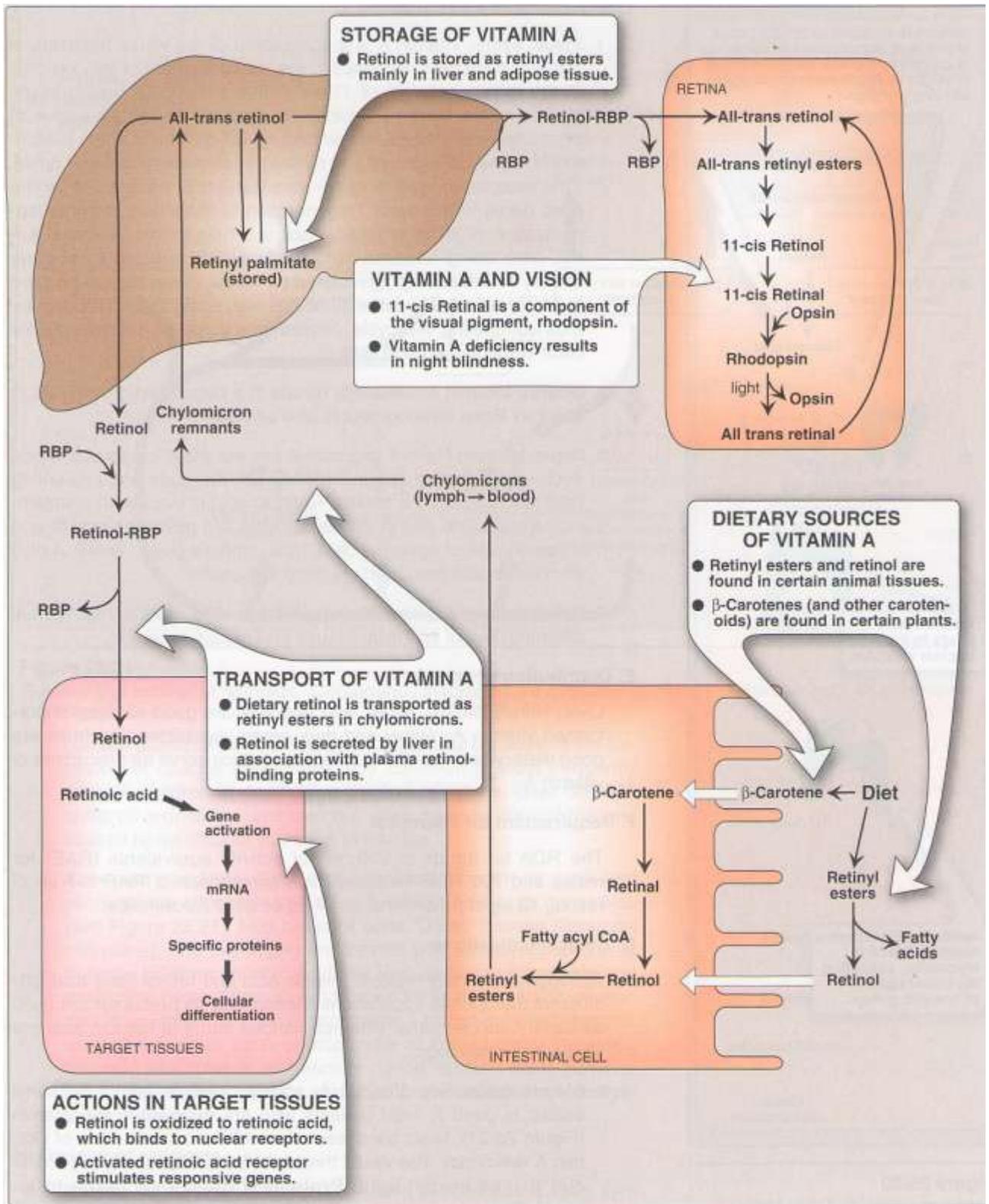
**4.  $\beta$ -Carotene:** Plant foods contain  $\beta$ -carotene, which can be oxidatively cleaved in the intestine to yield two molecules of retinal. In humans, the conversion is inefficient, and the vitamin A activity of  $\beta$ -carotene is only about one twelfth that of retinol.

#### B. Absorption and transport of vitamin A

**1. Transport to the liver:** Retinyl esters present in the diet are hydrolyzed in the intestinal mucosa, releasing retinol and free fatty acids (Figure 28.19). Retinol derived from esters and from the cleavage and reduction of carotenes is re-esterified to long-chain fatty acids in the intestinal mucosa 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.



**Figure 28.18**  
Structure of the retinoids.



**Figure 28.19** Absorption, transport, and storage of vitamin A and its derivatives. RBP = retinol-binding protein.

## 2. Release from the liver:

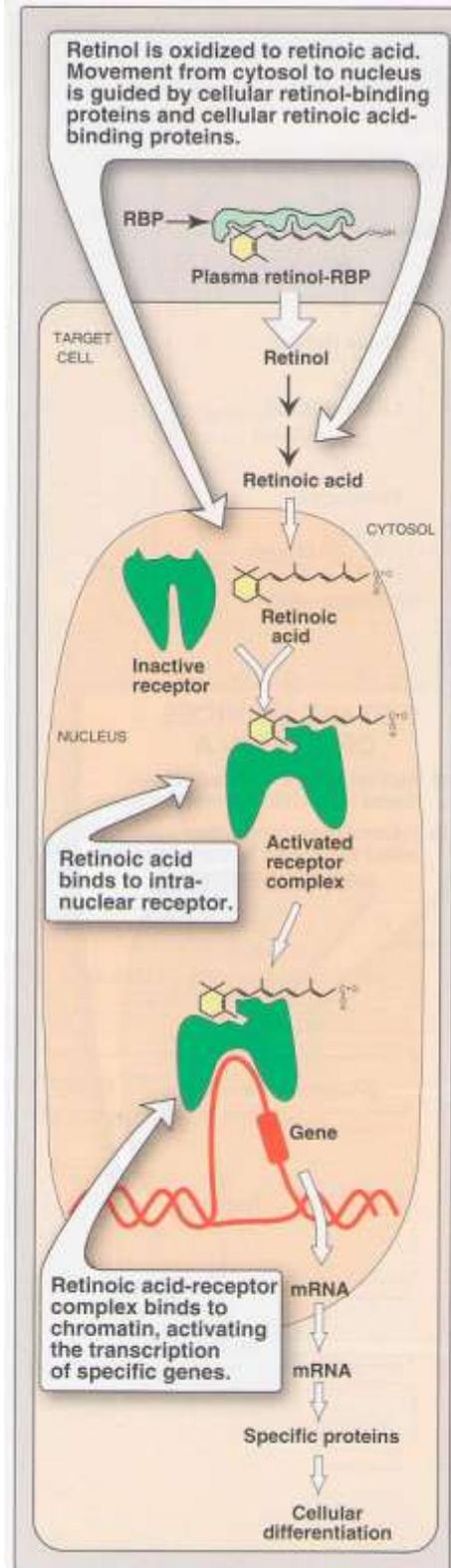
When needed, retinol is released from the liver and transported to extrahepatic tissues by the plasma retinol-binding protein (RBP). The retinol-RBP complex attaches to specific receptors on the surface of the cells of peripheral tissues, permitting retinol to enter. Many tissues contain a cellular retinol-binding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

### C. Mechanism of action of vitamin A

Retinol is oxidized to retinoic acid. Retinoic acid binds with high affinity to specific receptor proteins present in the nucleus of target tissues, such as epithelial cells (Figure 28.20). The activated retinoic acid-receptor complex interacts with nuclear chromatin 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. The specific retinoic acid-receptor proteins are part of the superfamily of transcriptional regulators that includes the steroid and thyroid hormones and 1,25-dihydroxycholecalciferol, all of which function in a similar way.

### D. Functions of vitamin A

**1. 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 specifically bound to the protein opsin. When rhodopsin is exposed to light, a series of photochemical isomerizations occurs, which results in the bleaching of the visual pigment and release of all-trans retinal and opsin. This process triggers a nerve impulse that is transmitted by the optic nerve to the brain.



**Figure 28.20**

Action of retinoids Note: Retinoic acid-receptor complex is a dimer, but is shown as monomer for simplicity [RBP = retinol-binding protein.]

Regeneration of rhodopsin requires isomerization of all-trans retinal back to 11-cis retinal. All-trans retinal, after being released from rhodopsin, 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.

**2. Growth:** Vitamin A deficiency results in a decreased growth rate in children. Bone development is also slowed.

**3. 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; thus, animals given vitamin A only as retinoic acid from birth are blind and sterile.

**4. Maintenance of epithelial cells:** Vitamin A is essential for normal differentiation of epithelial tissues and mucus secretion.

#### **E. Distribution of vitamin A**

Liver, kidney, cream, butter, and egg yolk are good sources of preformed vitamin A. Yellow and dark green vegetables and fruits are good dietary sources of the carotenes, which serve as precursors of vitamin A.

#### **F. Requirement for vitamin A**

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.

#### **G. Clinical indications**

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

### 1. Dietary deficiency:

Vitamin A, administered as retinol or retinyl esters, is used to treat patients who are deficient in the vitamin (Figure 28.21). Night blindness 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 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. The condition is most frequently 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.

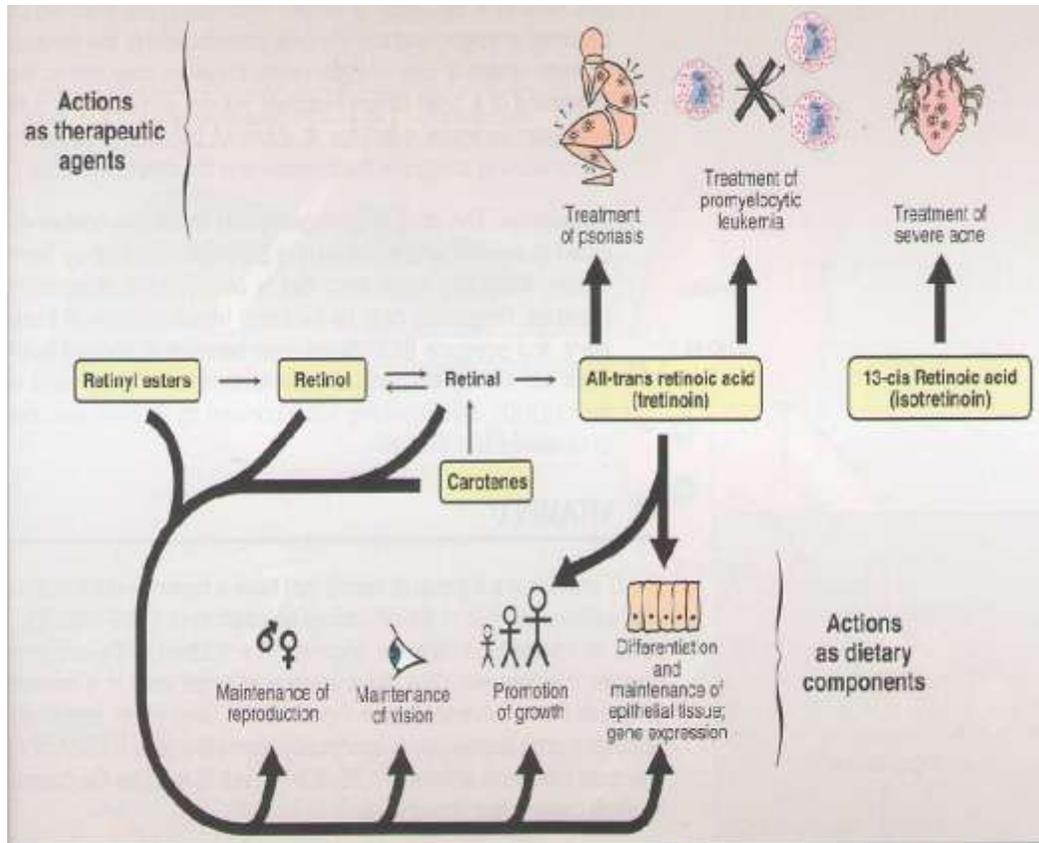


Figure 28.21

Summary of actions of retinoids. Compounds in boxes are available as dietary components or as pharmacologic agents.



Xerophthalmia

**2. Acne and psoriasis:** Dermatologic problems such as acne and psoriasis are effectively treated with retinoic acid or its derivatives (Figure 28.21). Mild cases of acne, Darier disease (keratosis follicularis), and skin aging are treated with topical application of tretinoin (all trans retinoic acid), as well as benzoyl peroxide and antibiotics. [Note: Tretinoin is too toxic for systemic administration and is confined to topical application.] In patients with severe, recalcitrant, cystic acne unresponsive to conventional therapies, the drug of choice is isotretinoin (13-cis retinoic acid) administered orally. Retinoic acid is also used in the treatment of promyelocytic leukemia.



Darier disease

#### **H. Toxicity of retinoids**

**1. Vitamin A:** Excessive intake of vitamin A 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 (due to a decrease in keratin synthesis), the liver, which becomes enlarged and can become cirrhotic, and in the nervous system, where a rise in intracranial pressure may mimic the symptoms of a brain tumor. Pregnant women particularly should not ingest excessive quantities of vitamin A because of its potential for causing congenital malformations in the developing fetus.

**2. Isotretinoin:** The drug 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 initiation of treatment, and adequate birth control must be used. Prolonged treatment with isotretinoin leads to hyperlipidemia and an increase in the LDL/HDL ratio, providing some concern for an increased risk of cardiovascular disease.