Chapter 44

Vitamin A

Overview

- Vitamin A exists as a provitamin in vegetables (i.e., β-carotene).
- Vitamin A exists in three oxidation states; retinal, retinol, and retinoic acid (retin A).
- Retinal plays an important role in vision.
- Retinoic acid plays an important role in reproductive biology, bone remodeling, and epithelial tissue homeostasis.
- Although retinol and retinal are stored in the body, retinoic acid is not.
- Vitamin A is best associated with thyroid hormone action.
- Vitamin A and D excess can be toxic, whereas E and K excess is generally nontoxic.
- Several aspects of vitamin A metabolism are Zn^{++}-dependent.

Fat-Soluble Vitamins

The **fat-soluble vitamins A**, **D**, **E**, and **K** are lipophilic, hydrophobic molecules, that are assembled from isoprenoid units, the same building blocks that are used to synthesize cholesterol (see Chapter 61). Because of their hydrophobic nature, they are transported in blood bound either to lipoproteins (e.g., **chylomicrons**; see Chapter 64), or to more specific carrier proteins. They are absorbed from the intestine along with other dietary lipids (see Chapter 60), therefore, abnormalities in lipid absorption resulting in **steatorrhea** can also result in a **fat-soluble vitamin deficiency**.

As a group, the fat-soluble vitamins have diverse biologic actions (e.g., **vitamin A**, **vision**; **vitamin D**, **Ca^{++}** and **$PO_4^{=}$ homeostasis**; **vitamin E**, **antioxidant activity**; and **vitamin K**, **blood clotting**). Although at one time **vitamin D** was considered to be only a vitamin, now it is considered to be a **prohormone** as well (a precursor to the 1,25-dihydroxy forms of vitamin D ($1,25(OH)_2$-D_2 and $1,25(OH)_2$-D_3; see Chapter 45). Large quantities of the fat-soluble vitamins can be stored in the **liver** and in adipose tissue, and toxicity can result following excessive intake of **vitamins A** and **D**. Vitamins E and K are generally considered nontoxic.

Vitamin A

This vitamin plays a central role in both **photopic** (**day**) and **scotopic** (**night**) **vision**, in **reproductive biology**, in **bone remodeling**, and in the **maintenance and differentiation of epithelial tissues** (**Table 44-1**). It exists in three oxidation states (i.e., **retinol**, the alcohol; **retinal**, the aldehyde; and **retinoic acid**, which is not stored in the body; **Fig. 44-1**). These various oxidation states of the natural vitamin, as well as synthetic analogs and metabolites, are called **retinoids**, stemming from their importance to the physiology of the retina. In mammalian organisms, interconversion of retinol with cis- and trans-retinal occurs, but oxidation of trans-retinal to retinoic acid (retin A) is an irreversible process. Thus, retinoic

Table 44-1
Actions of Vitamin A

Retinol and Retinal
Vision
Rhodopsin synthesis (rods)
Porphyropsin synthesis (cones)
Retinoic Acid
Growth and differentiation of epithelial cells
Glycoprotein synthesis
Expression/production of growth hormone
Mucus production
Bone remodeling
Reproduction
Spermatogenesis
Placental development
Maintain corpus luteum function
Lung surfactant (phospholipid) production
Stimulate myeloid cell differentiation to granular leukocytes
Induce transglutaminases
Crosslinking of proteins (which is necessary for macrophage function, blood clotting, and cell adhesion)

acid can support growth and differentiation of various tissues, but it cannot replace retinol or retinal in their support of the visual system.

Vitamin A exists as a provitamin in vegetables, in the form of the yellow pigment, **β-carotene**. This provitamin consists of two molecules of retinal, joined at the aldehyde ends of their carbon chains. It is only about one-sixth as effective a source of vitamin A as retinol on a weight for weight basis. Carotene-like compounds are known as **carotenoids**, which are important sources of vitamin A to herbivores and omnivores. Ingested β-carotenes may be oxidatively cleaved to all-trans retinal (vitamin A_1) by **β-carotene dioxygenase** in the intestine and liver of herbivores and omnivores, but much less so (if at all) in carnivores. Therefore, carnivores are dependent upon preformed vitamin A (i.e., retinal or retinol) in their diets. **β-Carotene dioxygenase** is induced by thyroxine, therefore hypothyroid herbivores or omnivores may develop **β-carotenemia**.

In the intestinal mucosa of all mammals, **retinal** is **reversibly** reduced to **retinol** by a specific **zinc-dependent retinal reductase** (or dehydrogenase), which uses either NADH or NADPH as a coenzyme. This enzyme is also present in rod and cone photoreceptors. The **intestine** also converts some **retinal** to **retinoic acid** (**retin A**). Most retinol formed in intestinal mucosal cells is esterified to fatty acids, and packaged into **chylomicrons**. These lipoproteins are then exocytosed by mucosal cells, where they are incorporated into lymph, and then enter the systemic circulation (see Chapter 64). Once acted upon by lipoprotein lipase on the capillary endothelium servicing adipocytes, they become **chylomicron remnants**, and are subsequently removed from the circulation by the liver (with their content of retinol esters). For transport to tissues, stored retinol esters in the liver are hydrolyzed, and the retinol is bound to **retinol-binding protein** (**RBP**). In contrast to retinol, retinoic acid is transported in plasma bound to **albumin**.

Following hepatic secretion of the retinol-RBP complex into blood, retinal is taken up into target tissues via cell surface receptors. Once inside extrahepatic target cells (e.g., photoreceptors in the retina), retinol is bound by a **cellular retinol-binding protein** (**CRBP**). Retinol, retinal, and retinoic acid bind to nuclear proteins, where they are most likely involved in the control of gene expression. Thus, vitamin A appears to behave in a manner similar to **steroid** and **thyroid hormones**, and certain proteins may be under dual control (by both triiodothyronine, T_3, and vitamin A). It controls protein (enzyme) biosynthesis.

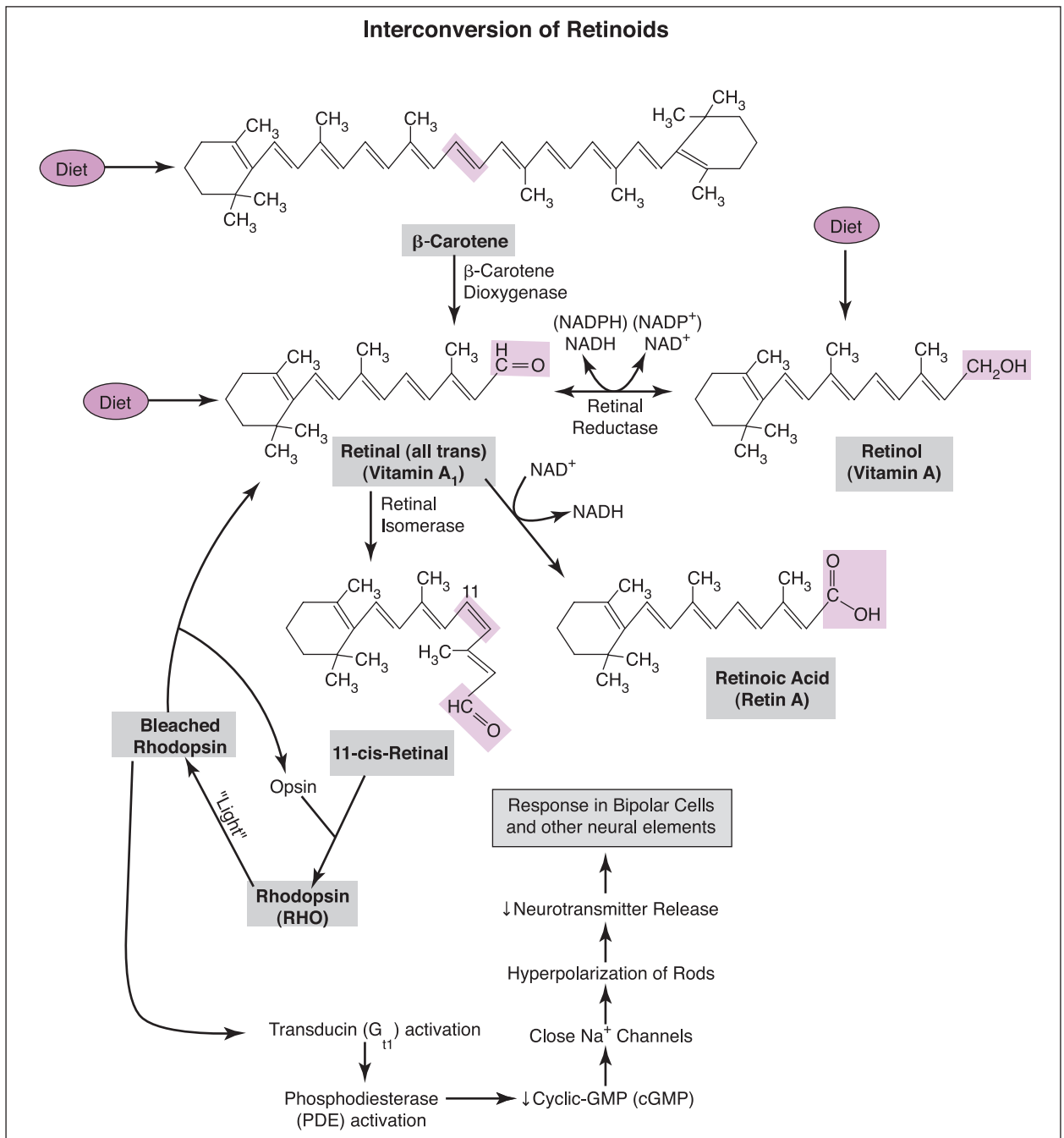

Figure 44-1

Vitamin A Toxicity

Hypervitaminosis A will occur after the capacities of these binding proteins have been exceeded. Symptoms generally include skin erythema and desquamation, increased liver size, abdominal pain, nausea, and appetite loss. Excessive quantities of free retinol will damage plasma membranes of the liver and other tissues, as well as hepatic lysosomal membranes. Although retinoic acid is not stored, excessive consumption over time has been reported to cause bone demineralization through increasing the ratio of osteoclasts to osteoblasts. Vitamin A is normally detoxified by the liver, with metabolites being found in both bile and urine. During pregnancy, excessive retinoic acid interferes with segmentation

genes, thus causing abnormal fetal development.

Vitamin A and Vision

Photoreceptors of the retina contain discs consisting of lipid embedded with the protein, **opsin**. When this protein combines with 11-cis-retinal in **rod photoreceptors**, it forms **rhodopsin** (**RHO**, visual purple), the direct recipient of light energy in dim light (non-colored, gray-black vision). As **light bleaches rhodopsin**, opsin and trans-retinal are reformed, and **transducin** (**G_{t1}**, a membrane-bound GTP-binding protein) is activated. This, in turn, activates a **cyclic-GMP** (**cGMP**)**-specific phosphodiesterase** that cleaves cytoplasmic **cGMP** to inactive **5'-GMP** (**Fig. 44-2**). Cyclic-GMP keeps rod Na^+ channels open, and when **cGMP levels decline**, **Na^+ channels close**, and the rod becomes **hyperpolarized**. Hyperpolarization of rods leads to a **decrease in transmitter release** from synaptic terminals, which in turn leads to a **response in bipolar cells and other neural elements of the retina that is perceived as light**.

This cascade of reactions generally amplifies light signals, and helps explain the remarkable sensitivity of rod photoreceptors to dim light (which are capable of producing a detectable response to as little as one photon of light). **Cones**, which are used in normal (colored) vision, also contain some retinal, combined with cone iodopsin to form **porphyropsins**, which absorb light of lower energy. Similar steps are thought to be involved in cone activation, however, vitamin A deficiency has a much more marked effect on scotopic than on photopic vision.

In contrast to the semi-structural roles of retinol and retinal in visual excitation, the role of **retinoic acid** is more humoral, particularly in epithelial, osteoid (bone), and gonadal tissues. Indeed, the expression/production of growth hormone itself may be turned-on by a specific retinoic acid hormone receptor complex.

Vitamin A Deficiency

Although the primary signs and symptoms of vitamin A deficiency are usually noted in the visual system, **hypovitaminosis A** also leads to a reduction in mucus-secreting cells and replacement of columnar epithelial cells by thick layers of horny, stratified epithelium in several parts of the organism. This includes

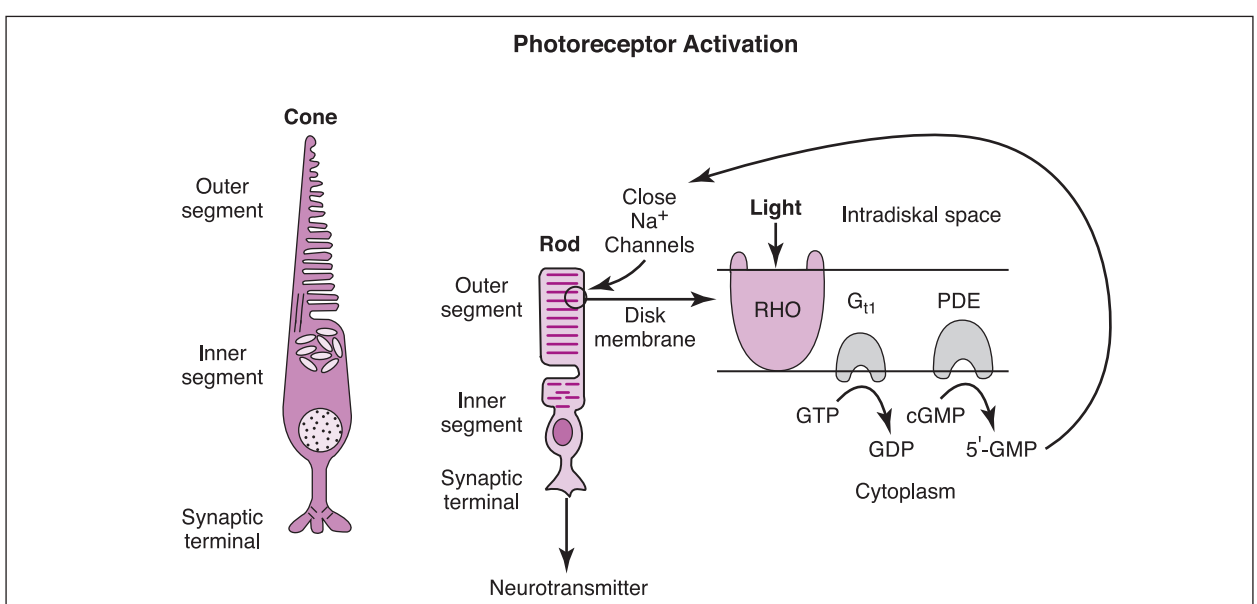

Figure 44-2

keratinization of the corneal epithelium, lung, skin, and intestinal mucosa, as well as a drastic reduction in goblet cells within intestinal crypts and villus areas. Although the rates of columnar cell proliferation and migration along the villus are apparently not altered, the synthesis of specific glycoproteins in the intestinal mucosa and liver can be markedly depressed. **Retinoic acid** is needed for gene expression of glycosyltransferases and fibronectin, as well as transglutaminases. Transglutaminases catalyze the crosslinking of proteins by amidating the γ-carboxyl group of a glutamate residue with an amino group of lysine (which is necessary for macrophage function, blood clotting, and cell adhesion).

Retinoic acid is also essential for the activity of cells in the epiphyseal cartilage, which must undergo a normal cycle of growth, maturation, and degeneration to permit normal bone growth, which is controlled at the epiphyses. **Bone resorption** is retarded in deficiency, although there is apparently no defect in the normal calcification process. Although the mechanism is unclear, it may involve the influence of vitamin A on the osteoclast:osteoblast ratio, since vitamin A up-regulates vitamin D receptors.

Finally, retinoic acid plays a role in **fertility**. In vitamin A deficiency, spermatogenesis is arrested at the spermatid stage in rats, chickens, and cattle, and is reversed with vitamin treatment. Retinoic acid acts on gene transcription in the nucleus of germinal cells of the testes, and CRBP is present in high concentration in the epididymis. Deficiency also interferes with the estrus cycle, placental development, and other aspects of female reproduction in the rat and chicken, causing fetal resorption. Since several aspects of vitamin A metabolism are **zinc-dependent** (i.e., retinal reductase is a zinc-dependent enzyme), deficiency symptoms of this element are similar to those of vitamin A (see Chapter 49).

In summary, the fat-soluble vitamin A is found in several different forms, including **all-trans-retinal** (vitamin A_1), **11-cis-retinal, rhodopsin** (RHO), **retinol** (the alcohol), and **retin A** (the acid). In animal tissues, and especially the liver, vitamin A is stored as **retinol esters** (with long-chain fatty acids), so that these also become a major dietary source to carnivores. The other major sources of this vitamin are the carotenoid pigments present in green plants. The carotenoids are known as provitamins A, and their conversion to vitamin A involves oxidative fission by **β-carotene dioxygenase** in the intestine of herbivores and omnivores, but not in carnivores. This oxidation forms retinal, the corresponding aldehyde which is the active form of the vitamin in the visual cycles, but which is reduced to the alcohol by a specific zinc-dependent retinal reductase (or dehydrogenase) for transport and storage in other tissues.

Vitamin A is absorbed from the small intestine with the aid of **bile acids,** and it is incorporated into **chylomicrons** along with several other large lipophilic compounds (see Chapters 62-64). The most readily apparent role of vitamin A is its participation in the detection of **light** by retinal cells. The retina contains two distinct types of photoreceptor cells, cones and rods. In both, the photoreceptor pigments consist of proteins, opsin in rods and iodopsin in cones, linked covalently to retinal. Although similar steps are thought to be involved in both cone and rod activation, vitamin A deficiency has a much more marked effect of scotopic (night) than on photopic (day) vision.

Retinoic acid, which is not stored in the body, plays a central role in bone remodeling, reproductive biology, and the maintenance and differentiation of epithelial tissues. In the absence of this form of the vitamin, there is a reduction in mucus-secreting cells, seen most often in the corneal epithelium, lung, skin, and intestinal mucosa. Retinoic acid is also

essential to cells of the epiphyseal cartilage as they undergo normal cycles of growth, maturation, and degeneration. Bone resorption is retarded in vitamin A deficiency, and exacerbated in vitamin A toxicity. Retinoic acid also plays an important role in spermatogenesis, ovarian function, fetal and placental development. Since several aspects of vitamin A metabolism are zinc-dependent, several of the signs and symptoms of zinc-deficiency are also seen with vitamin A deficiency.

OBJECTIVES

- Discuss the cause-effect relationship between steatorrhea and a fat-soluble vitamin deficiency.
- Show why retinoic acid can support growth and differentiation of epithelial tissues, and why it cannot replace retinol or retinal in their support of the visual system.
- Identify multiple actions of the different vitamin A oxidation states, and discuss relationships between zinc and vitamin A deficiency.
- Explain why dietary carotenoids are an unsatisfactory source of vitamin A to carnivores, and why hypothyroidism might induce a state of β-carotenemia in herbivores and omnivores.
- Indicate how vitamin A is absorbed from the intestine, carried in plasma, taken-up by target cells and bound intracellularly. Also discuss the cellular mechanisms of vitamin A action.
- Provide reasoning for each of the signs and symptoms of vitamin A toxicity, as well as those for vitamin A deficiency.
- Explain the participation of vitamin A in the cascade of reactions leading to amplification of light signals in retinal photoreceptors.
- Indicate how vitamin A is thought to be involved in bone resorption (see Chapter 45).
- Understand how retinoic acid toxicity affects the pregnant animal.
- Explain common features of vitamin A, steroid and thyroid hormone action.

QUESTIONS

1. β-Carotene consists of two molecules of:
a. Rhodopsin.
b. Retinol.
c. Retin A.
d. Trans-retinal.
e. Transducin.

2. Which one of the following is not stored in the body?
a. Retinoic acid
b. Retinol
c. Retinaldehyde (retinal)
d. Vitamin D
e. Vitamin E

3. Vitamin A is best associated with the transport and action of which hormone?
a. Insulin
b. Thyroxin
c. Aldosterone
d. Calcitonin
e. Follicle Stimulating Hormone

4. When rhodopsin is bleached by light in rod photoreceptors, all of the following occur, EXCEPT:
a. Transducin becomes activated.
b. cGMP-dependent phosphodiesterase activity increases.
c. Na^+ channels close.
d. Rods depolarize.
e. Neurotransmitter release from rods declines.

5. Vitamin A deficiency is associated with all of the following, EXCEPT:
a. Keratinization of the corneal epithelium.
b. Decreased hepatic glycoprotein formation.
c. Enhanced bone resorption.
d. Decreased spermatogenesis.
e. Night blindness.

6. Vitamin A toxicity has the greatest affect on which organ?
a. Brain
b. Kidney
c. Liver
d. Lung
e. Heart

ANSWERS
1. d
2. a
3. b
4. d
5. c
6. c