Vitamin A

The term vitamin A refers to some poly-isoprenoid compounds found only in animals. However, their precursors, carotenoids are found in plant, mainly as β- carotene. The latter consists, effectively, of two molecules of vitamin A joined end to end.

Vitamin A and pro-vitamin A (carotenoid) are poly-isoprenoid compounds comprising two distinct components (Fig. 18.12). :

(a) a cyclohexene ring, and (b) a sidechain made up of several isoprene units, which is attached to the cyclohexene ring (Fig. 18.12).

The pro-vitamin carotenoids are also included in the vitamin A family. They are present in a variety of plants. The most important, quantitatively, is β-carotene (Table 18.3) (responsible for the orange colour of carrots).

Chemistry and Nomenclature of Vitamin A

Vitamin A refers to three biologically active vitamins and Related compounds (collectively known as carotenoids):

A- retinol, retinal and retinoic acid, all of which are found only in animals.

1- retinol (an alcohol): is found only in foods of animal origin and a small number of bacteria, mainly as the ester retinyl palmitate.
2- retinal (an aldehyde).
3- retinoic acid (an acid): is a metabolite of retinol and has important biological activities in its own right. The **oxidation of retinaldehyde** to retinoic acid **is irreversible**, and retinoic acid cannot be converted to retinol in vivo, and does not support either vision or fertility in deficient animals.

Note: Since retinol and retinal are interconvertible and can also be converted to retinoic acid, they can perform all functions of vitamin A. However, retinoic acid cannot perform other functions of vitamin A.

B- Related compounds (collectively known as carotenoids), which can be cleaved oxidative to yield retinaldehyde, and hence retinol and retinoic acid. Those

carotenoids that can be cleaved to yield retinaldehyde are known as are known as **pro-vitamin A carotenoid**.

The term retinoid has been used to define these three compounds (and other associated synthetic compounds with vitamin A-like activity).

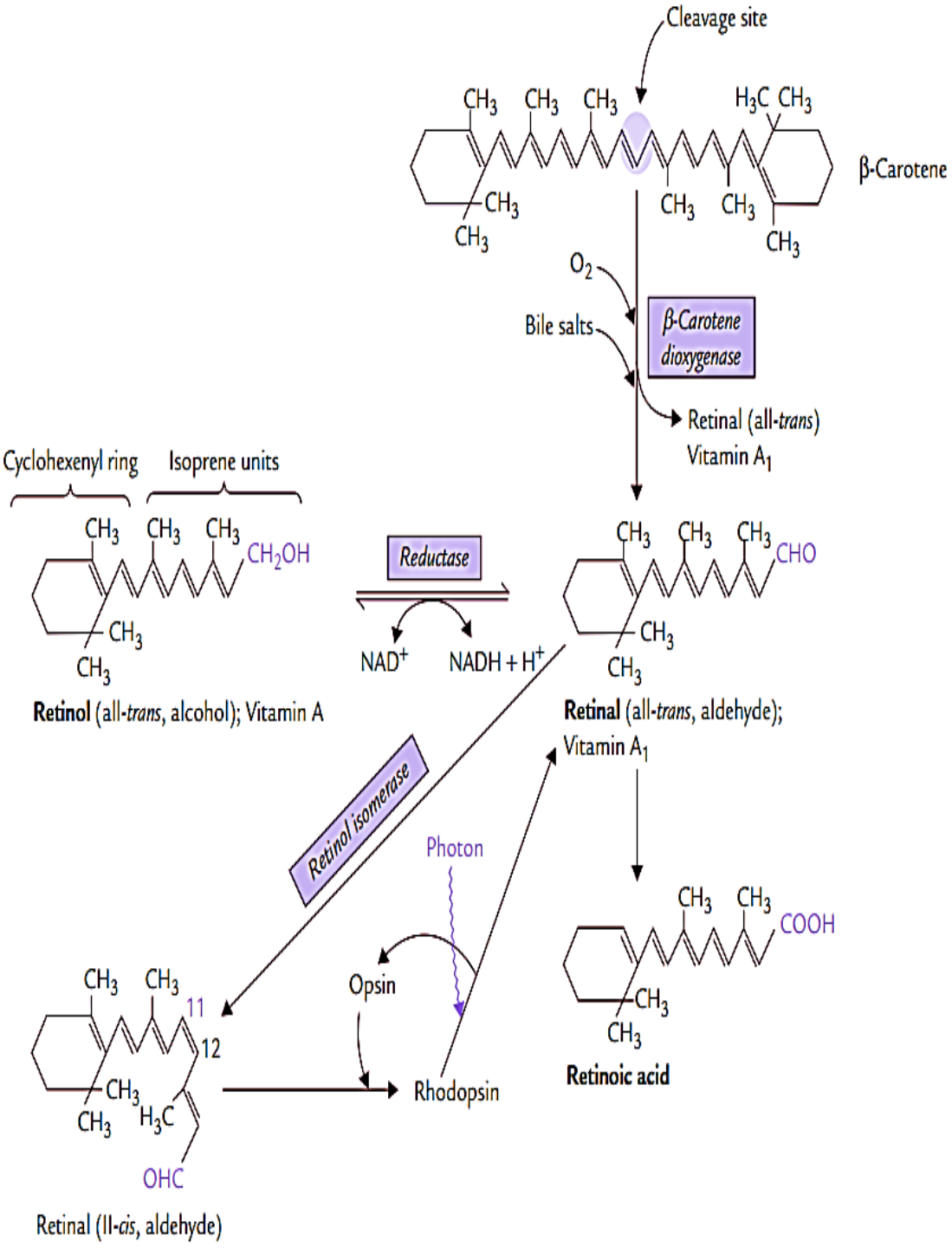


Fig. 18.12. Structures and interconversions of various members of the vitamin A family.

Metabolism of vitamin A and pro-vitamin A carotenoid

Lipid-dissolved retinol is absorbed from the small intestine. The absorption of 70–90% of dietary retinol is typical. 5–60% of dietary carotene is absorbed, depending on food type and cooking method. Retinol and carotene absorption are inhibited in diets with less than 10% fat, and particularly low-fat diets are linked to vitamin A insufficiency.

Absorption

Carotenes and retinol esters are treated differently.

(a) β-carotene is absorbed in small intestine and enters mucosal cells where it is cleaved into two molecules of trans-retinal by a **dioxygenase** and **molecular oxygen; bile salts facilitate the reaction.** Retinal is reduced to retinol **by an NADH or NADPH-dependent retinal reductase.** Retinol is esterified with a fatty acid, incorporated into chylomicrons together with dietary lipids, and secreted into lacteals (Fig. 18.13).

Note: Chylomicrons are composed of a main central lipid core that consists primarily of triglycerides,

(b) Retinol esters of animal foods are treated differently. They are hydrolyzed in the intestinal lumen **by a pancreatic enzyme (carboxylic ester hydrolase).** then generated of free retinol is transferred across the intestinal mucosal cell. It is then esterified, incorporated into chylomicrons and secreted into lacteals. The presence of

lipids in the intestine ensures efficient absorption of retinol, up to 80% of the intake. Carotenoid absorption is less efficient, about 40% of the intake. Its activity is 1/6th that of retinol.

Note: Lacteals are small lymphatic vessels located in the lining of the small intestine. They are responsible for absorbing dietary fats and fat-soluble vitamins from the intestine and transporting them to the bloodstream. This process is essential for proper nutrient absorption and overall health.

Transport

The liver parenchymal cells hydrolyze retinol esters after chylomicrons transport it into circulation. In a one-to-one ratio, the released retinol is reversibly bound to RBP and released into the circulation for delivery to other organs. RBPspecifi c receptors help target cells absorb retinol-RBP, which binds to CRBP. It may then be oxidised to retinal or retinoic acid (Fig. 18.13).

Note: In the liver, parenchymal cells (i.e., mainly hepatocytes) utilize autophagy to provide amino acids, glucose, and free fatty acids as sources of energy and biosynthesis functions, but also for recycling.

Chylomicrons carry the absorbed retinol into the circulation and then to liver parenchymal cells where the retinol esters are hydrolyzed. The retinol so released is reversibly bound to retinol-binding protein (RBP) in a one-to-one proportion and released into the circulation for transport to other organs. The target cells take up the retinol-RBP by a RBPspecifi c receptor-mediated process, and the retinol is bound to cellular retinol-binding protein (CRBP). Subsequently it may be oxidized to retinal or retinoic acid (Fig. 18.13).

What is the Retinol-binding protein (RBP)?

Retinol-binding protein (RBP) in human plasma is a monomeric polypeptide which has a single binding site. Being of low molecular weight (MW 20,000), RBP (**Retinol-**

binding protein (RBP) can be cleared by kidneys, so it circulates after being reversibly complexed with a plasma protein. Retinoic acid is transported in association with albumin.

Storage

The hepatocytes not only dispatch retinol with RBP, they can also store the surplus in the form of retinol esters. More than 90% of the body's supply of vitamin A is usually stored in the liver cells, which contain a year's supply of the vitamin.

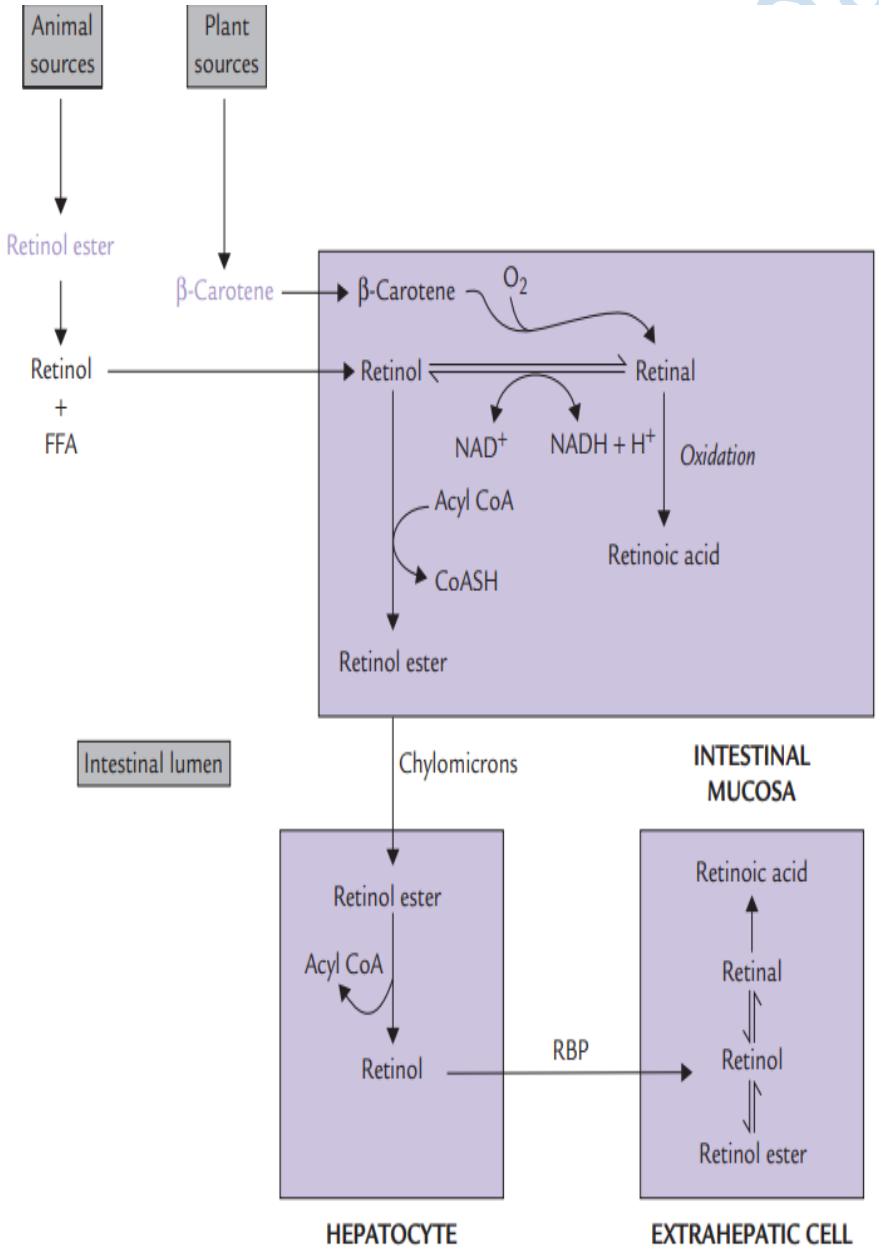


Fig. 18.13. Absorption, transport and metabolism of retinoids (RBP = retinol-binding protein, FFA = free fatty acid).

Functions of vitamin A

The role of vitamin A in vision has been known. Also, its importance in various other cellular functions, unrelated to visual process is also being recognized:

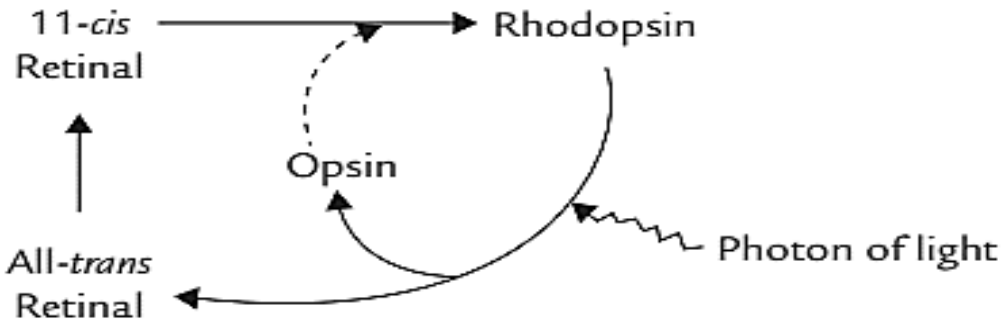
1. Retinal is involved in vision.
2. Retinoic acid is involved in growth and cellular differentiation.
3. Retinol is necessary for the reproductive system.
4. Carotenoids have an antioxidant role per se (not through their conversion into vitamin A).

1- Vitamin A and Vision:

Vitamin A is the prosthetic group of rhodopsin, the light sensing protein in retinal rod cells. Rhodopsin is located in a membrane system in the outer segment of the rod cell.

(a) Rhodopsin synthesis: Rhodopsin is made up of the protein opsin and 11-cis-retinal. The 11-cis retinal serves as the light absorbing part of rhodopsin, and opsin is an integral membrane protein with seven transmembrane helices. In the pigment epithelium of retina, all trans-retinal is isomerized to 11-cis retinal. The aldehyde group of the 11-cisretinal then spontaneously links with a lysyl residue in the apoprotein to form **rhodopsin.** This rhodopsin reaction places the 11-cis-retinal at the center of the molecule.

Note: In the cone cells, opsin is somewhat different and the rhodopsin equivalent is iodopsin



(b) Wald's visual cycle:

Rhodopsin is a photosensitive pigment, which plays a central role in the dim light vision. Exposure to light of wavelength centered around 500 nm on the rod cells induces isomerization of 11-cis-retinal (Fig. 18.14). This photo-isomerization switches rhodopsin to a series of unstable intermediates in the following sequence:

Opsin 11-Cis-Retinal: Rhodopsin, then Batho-rhodopsin then, then……..Meta-rhodopsin-II

The last one (meta-rhodopsin-II) is an activated" photo-excited conformation" referred to as **active rhodopsin (R*).** The Schiff-base between the all-trans-retinal and the active rhodopsin R* then hydrolyzes, and all-trans-retinal dissociates from the active rhodopsin R*.

(c) Regeneration of 11-cis-retinal:

Conversion of all-transretinal (released following dissociation of R*) back to 11-cis-retinal **is the final event of the Wald's visual cycle.**

This reaction can occur in the retina itself, or it may require participation of an enzyme system located in liver (Fig. 18.14).

A-In retinal cells: The trans- to cis-isomerization reaction is catalyzed in the dark by the enzyme **retinal isomerase.** The 11 cis-isomer then combines with opsin to regenerate rhodopsin, as discussed earlier.

B- In liver: The all-trans-retinal is released into blood circulation and transported to liver. Following uptake by hepatocytes, it is reduced to all-trans-retinol **by alcohol dehydrogenase,** an NADH-dependent, zinc containing, enzyme. The all-trans-retinol is isomerized to 11-cisretinol and carried to retina by blood where it is oxidized to 11-cis-retinal.

This completes the Wald's visual cycle.

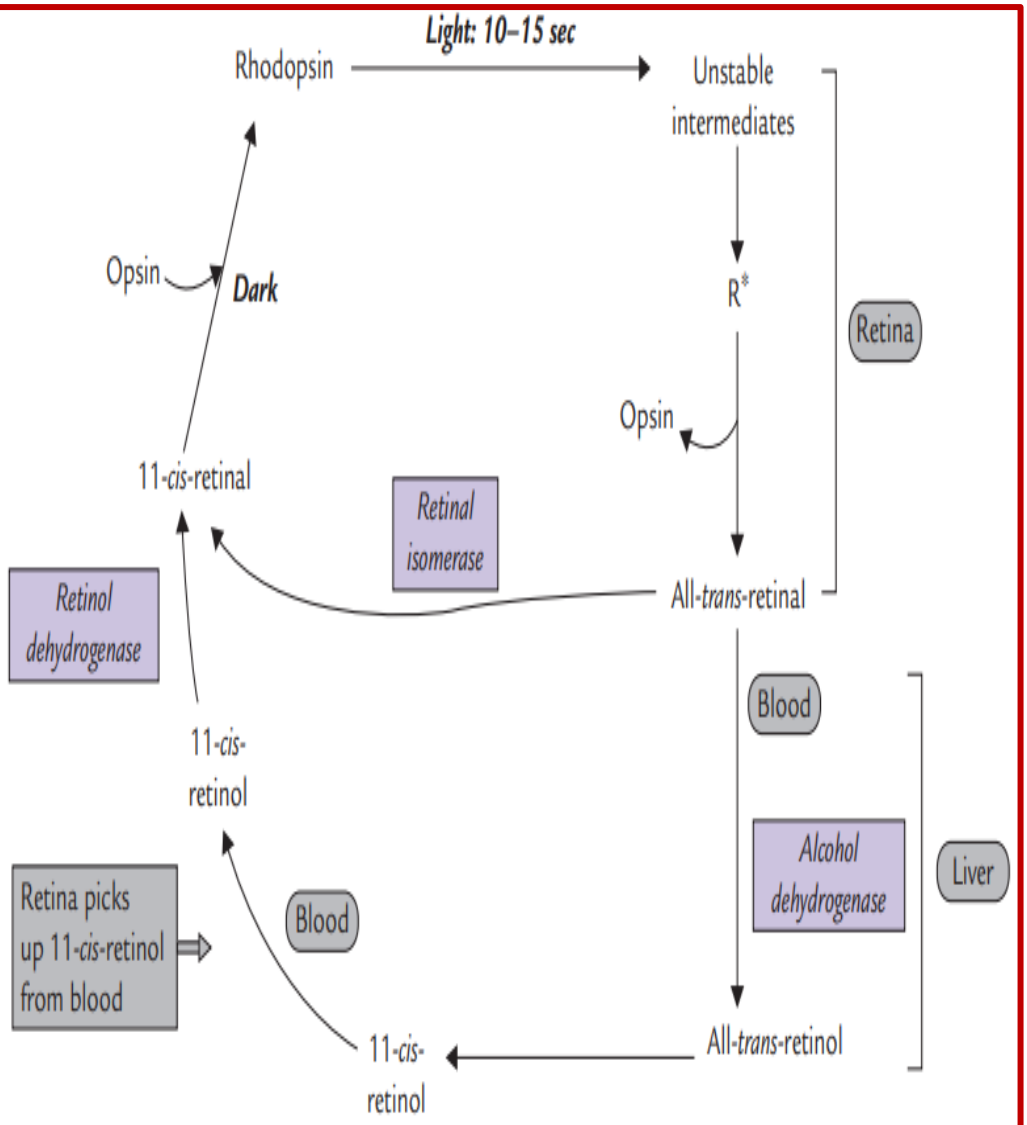


Fig. 18.14. Wald's visual cycle (rhodopsin cycle); R* activates transducin based cascade.

(d) Dark adaptation mechanism: The time taken for regeneration of rhodopsin (following light induced depletion of rhodopsin) is known as **dark adaptation time.** It is a common experience that when a person shifts from bright light to dark, there is difficulty in seeing (e.g. in cinema hall), and after a few minutes the vision improves. During these few minutes' rhodopsin is resynthesized, and the time taken is referred to as the dark adaptation time. It depends on vitamin A status of the person. It is prolonged in the vitamin A deficiency state.

Mechanism of Vision:

Rhodopsin is a transmembrane protein located in rod cells, bound to membranous structures in the outer segment.

Rod cell physiology: The rod cell consists of outer and inner segments connected to each other by a narrow cilium (Fig. 18.15). The outer segment has membranous disc structures while the inner section has mitochondria. Next comes cell bodies with axons to nerve endings and synapses.

About 1000 closed membranous 16 nm discs are placed within each outer segment. These discs contain light-sensitive rhodopsin. Sodium channels allow Na to enter the outer segment's rod plasma membrane.

Sodium is later pumped out of the cell by an ATPase located in the inner segment. Such movement of sodium ions is called the dark current because it takes place in dark (absence of light).

The sodium channels are kept open by the intracellular nucleotide, cGMP. When light strikes the rhodopsin, these sodium channels close, and the dark current ceases. This leads to polarization of the cell membrane and consequent generation of an electric current which results in a visual impulse.

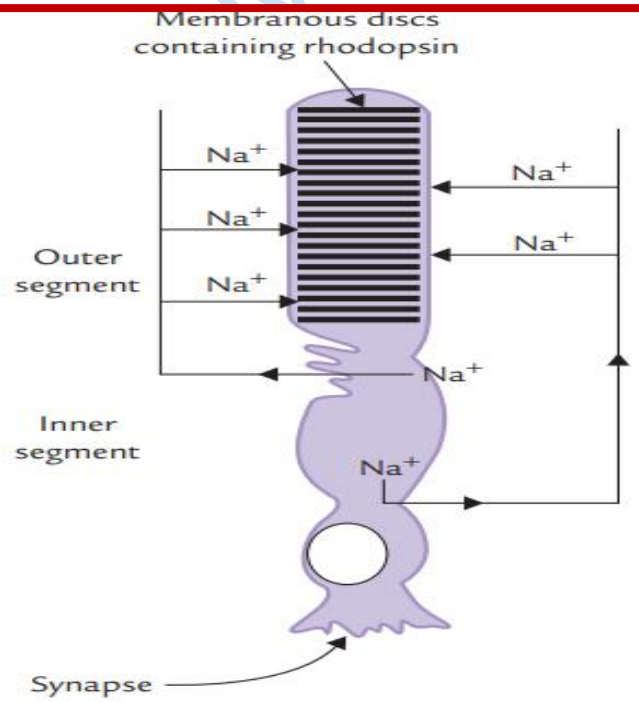


Fig. 18.15. A rod cell showing the dark current: the sodium ions enter the outer segment through cGMP-sensitive channels and are actively pumped out from the inner segment by an *ATPase*.

Other Functions of Vitamin A

2- Regulation of gene expression: Retinoic acid is an important regulator of gene expression. It is transported to the nucleus bound to intracellular proteins: cellular retinoic acid-binding protein (CRABP)-I and -II. In nucleus, retinoic acid binds to and activates two families of nuclear receptors, which regulates gene expression by binding to response elements on the DNA.

Note: Action of retinoic acid resembles that of steroid hormones, and the retinoic acid receptors (like the thyroid and steroid hormone receptors) belong to a large super-family of ligand-regulated transcription factors (Chapter 29).

3- Growth and differentiation: Because retinoic acid regulates gene expression, several processes associated with growth and differentiation depend on retinoic acid. These include maintenance of healthy epithelial cells, cell differentiation in spermatogenesis, and the differentiation of epithelial cells, among others. Severe vitamin A deficiency leads to production of abnormal epithelial tissues (keratinization).

4- Glycoprotein synthesis: Retinyl phosphates, obtained from retinol play a role in glycoprotein synthesis. Its hydrophilic portion serves as an anchor for growing oligosaccharide chains. This function appears analogous to that of dolichol phosphate (Chapter 5).

5- Role in reproduction: Retinol is required in reproduction. This function is mediated by control of expression of certain genes by retinol bound to cellular retinolbinding protein. Retinol, and to a lesser extent the retinal, support spermatogenesis in males and prevents fetal resorption in females.

6- Antioxidant role of vitamin A: The antioxidant properties of the carotenoids at low oxygen partial pressures in tissues have been reported. It is in this role that carotenoids are thought to prevent the development of diseases in which the action of free radicals is implicated, such as cancer and cardiovascular diseases.

7- Others: Retinoic acid exerts a number of metabolic effects on tissues, such as control of the biosynthesis of proteoglycans, particularly sulphation of the latter.

Requirements and Dietary Sources:

Vitamin A requirement is difficult to calculate because of the different forms in which it is present. It is usually expressed in terms of international units (IU: one IU is the activity present in 0.3 g of retinol, 0.344 g of retinol acetate or 0.6 g of -carotene).

Clinical Deficiency:

Vitamin A deficiency may be primary (dietary) or secondary.

Causes of secondary deficiency include:

1. Fat malabsorption.
2. Failure to synthesize chylomicrons into which vitamin A is normally incorporated after absorption (mostly due to inability to synthesize apoB48).
3. Failure to cleave -carotene because of an enzyme defect.
4. Impaired storage in hepatic cells in liver disease.
5. Failure to synthesize retinol-binding protein (RBP), thus impeding transport from liver to target tissues.

The deficiency of vitamin A leads to the following clinical manifestations (Symptoms)

1. Vision impact: Retinal is important for the pigment rhodopsin, which is responsible for low light vision. Thus, retinal insufficiency may impede of the 'dark adaptation'. Long-term deprivation kills visual cells permanently. Retinoic acid is essential for epithelium formation and maintenance, therefore chronic deficiency causes dryness of the conjunctival and corneal. Vitamin A (retinal) is necessary for vision mediated by the rod cells, so deficiency often presents as night blindness, dry eyes, and more serious consequences if untreated.therefore, Vitamin A supplementation is needed immediately to avoid this hazard.

2. Failure of bone remodeling occurs leading to thick and solid bones in the skull with an increase in the cerebrospinal fluid pressure.

3. Gonadal dysfunctions occur in deficiency of the vitamin A. also deficiency of vitamin A lead to testicular degeneration in males and an increased incidence of miscarriage.

4. Follicular hyperkeratosis (gooseflesh) : is the transformation of columnar epithelium into heavily keratinized squamous epithelia. Follicular hyperkeratosis is an important sign, developing early stage of in the disease.

5. Nerve lesions: often occurring with bone lesions.

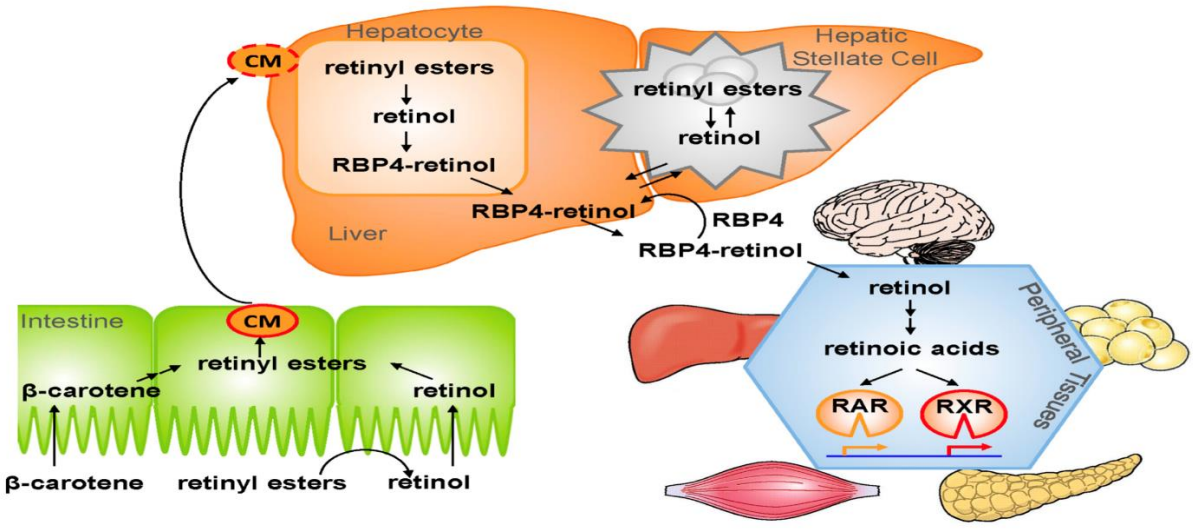
6. Certain forms of skin diseases are also common in vitamin A deficiency.

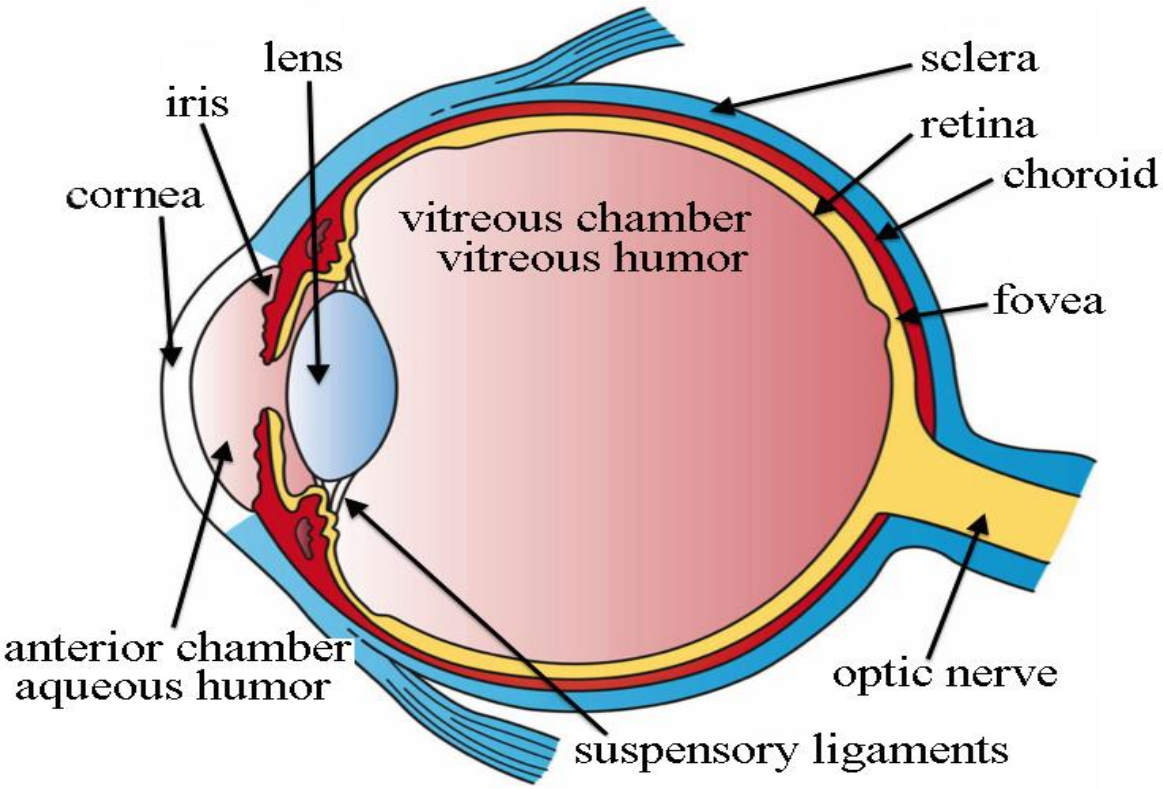
Vitamin A Toxicity (Hyper-vitamin A):

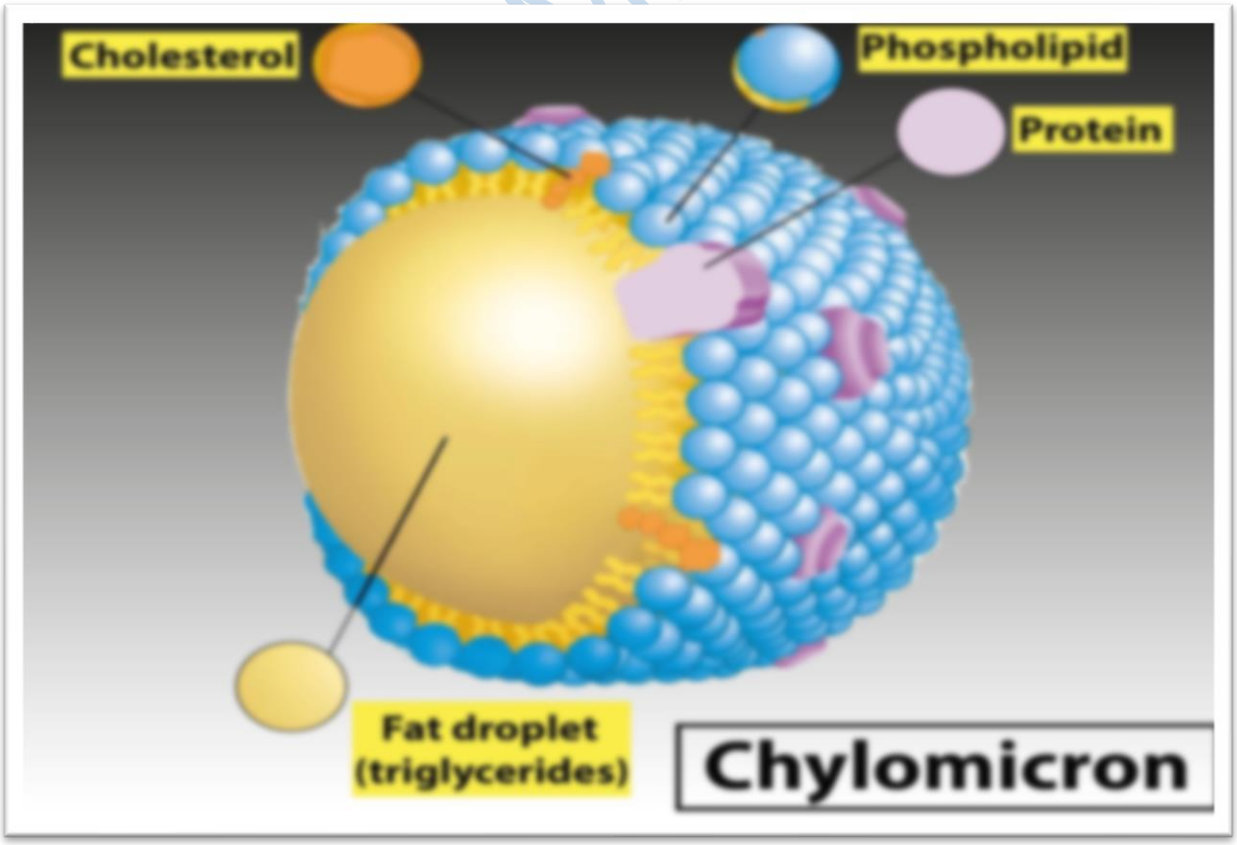
The earliest reports of vitamin A poisoning were among arctic explorers who devoured polar bear liver, which has high levels of the vitamin.

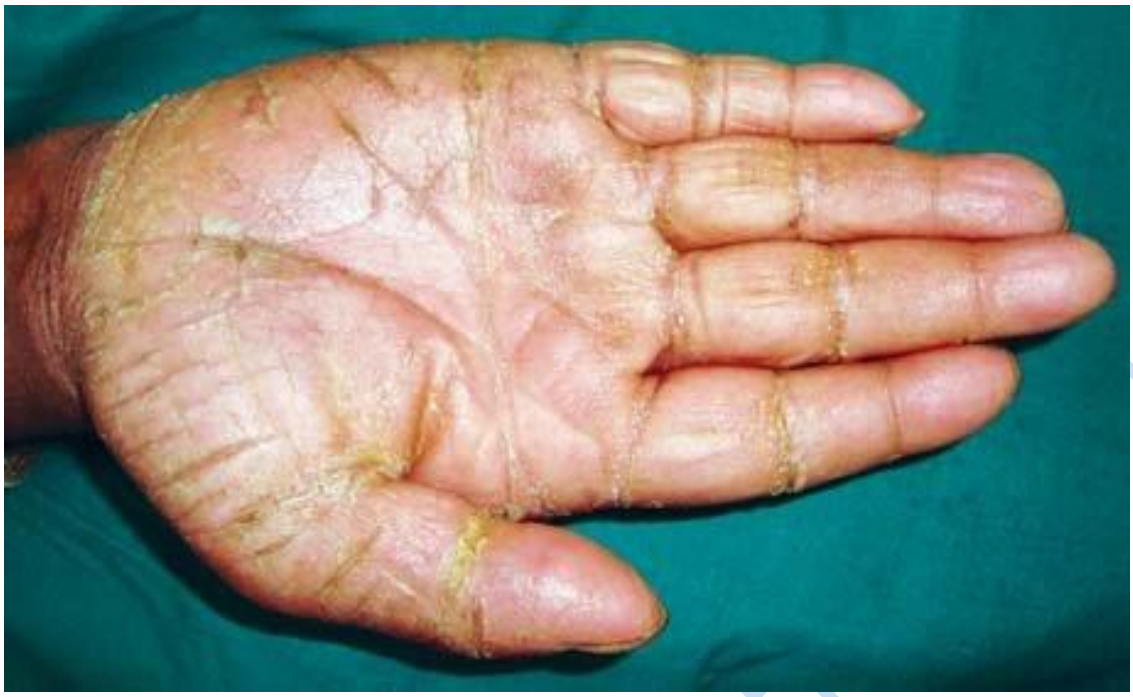
Vitamin A toxicity is rare with typical diets unless the patient self-medicates or takes pharmaceutical doses.

A single intake of more than 300 mg, or prolonged consumption of excessive quantities, causes hyper-vitaminosis, a hazardous disease. It causes dry, pruritic skin, hepatomegaly, and high intracranial pressure, which might simulate a brain tumor. Excessive consumption of vitamin A may cause congenital deformity. These dangers should be avoided by pregnant women.




lens
iris
cornea
sclera
retina
choroid
vitreous chamber
vitreous humor
fovea
anterior chamber
aqueous humor
optic nerve
suspensory ligaments


Cholesterol
Phospholipid
Protein
Fat droplet
(triglycerides)
Chylomicron



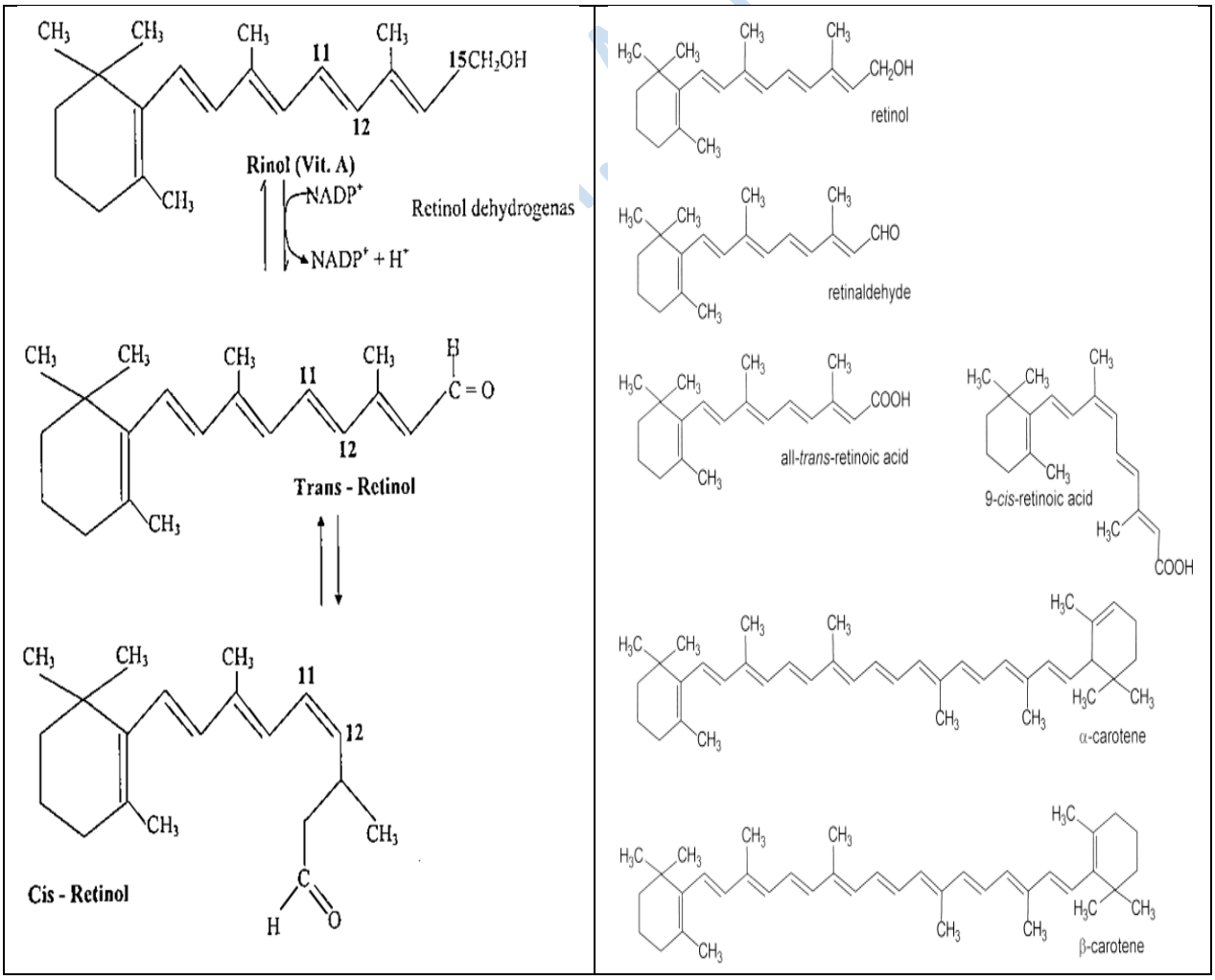


Figure 11.2 Vitamin A – retinoids and pro-vitamin A carotenoid