NUTRITION AND RETINAL DEGENERATIONS

Vitamin A, Taurine, Ornithine, and Phytanic Acid

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Retinal degenerations represent a significant cause of visual loss to people from all over the world.[1-4] In the United States an estimated 200,000 to 300,000 people have macular degenerations with juvenile onset or onset in later life. Figure 1A illustrates the fundus of a patient with a juvenile form of macular degeneration; depigmentation of the pigment epithelium and white deposits are present in the macula. These patients usually have severely reduced central vision with preserved peripheral vision. Some 50,000 to 100,000 people in this country have degenerative retinal diseases grouped under the heading of retinitis pigmentosa. Figure 1B shows the fundus of a patient with a moderately advanced stage of retinitis pigmentosa; characteristic intraretinal pigment deposits in a bone spicule configuration are distributed around the midperiphery. These patients characteristically have night blindness and decreased peripheral vision in the early stages; eventually, almost all will lose central vision as well. Patients with retinitis pigmentosa can now be detected in early life on the basis of an abnormal electroretinogram (ERG) at a time when minimal, if any, abnormalities are visible on ophthalmoscopic examination.[5,6] Macular degenerations and retinitis pigmentosa, taken together, account for approximately 30% of the legal blindness in the United States. The problem is magnified further when we consider that no treatments are known for practically all types.

Outside of the United States xerophthalmia is a major cause of blindness in 73 countries and territories.[7] The term xerophthalmia or dry eyes is now applied to all of the ocular manifestations of vitamin A deficiency, including conjunctival and corneal xerosis, Bitot's spots, corneal ulcerations, keratomalacia, corneal scarring, night blindness, and retinal degeneration.[8,9] In the mid-1960s the annual incidence of blindness due to xerophthalmia was estimated to be 100,000 people; this estimate was based on a global survey sponsored by the World Health Organization[10] together with an intensive investigation in Jordan.[11] A recent survey in Indonesia with projections to the whole of Asia (Table 1) has led to an estimate that as many as 250,000 people become blind each year while millions suffer from partial signs of vitamin A deficiency.[7] Severe vitamin A deficiency is associated with a mortality rate that may be as high as 60% in children under 5 years of age. Vitamin A deficiency is not the sole cause of death as protein-energy malnutrition and infection are often present.[7,12,13]

Treatment of night blindness with diet appears to have originated with the ancient Egyptians who recommended the eating of liver for this affliction.[14] In 1917 the factor in liver that can cure nutritionally induced night blindness was identified as "fat soluble

PRECURSOR: All-trans-β-Carotene

ISOMERIC FORMS:

All-trans   11-cis

CHEMICAL FORMS:

Retinol: R = CH₂OH
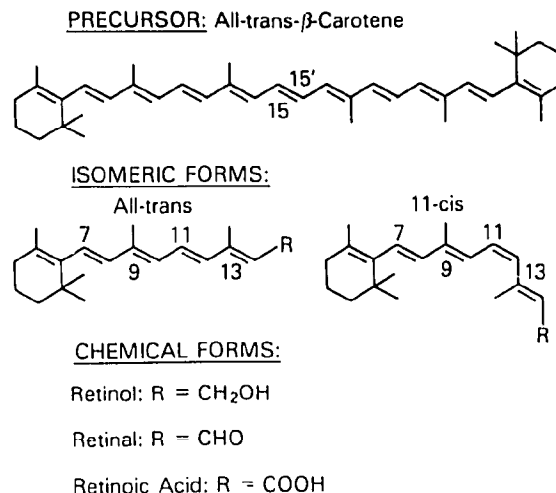
Retinal: R = CHO

Retinoic Acid: R = COOH

Fig. 2. Structures of B-carotene, retinol (vitamin A), retinaldehyde (retinal), and retinoic acid.

A,"[15] later called vitamin A. The chemical structure of carotene was determined in 1930[16] and that of vitamin A, or retinol, in 1931,[17] thereby clarifying the relationship between vitamin A in animals and the provitamin A, carotene, in plants. Vitamin A is important not only for vision but also for reproduction, growth, the maintenance of differentiated epithelia, and mucous secretion. It participates in glycoprotein synthesis[18,19] and appears to influence DNA and RNA synthesis[20] but the exact mechanisms of action by which it subserves all of its biologic functions remain to be clarified.

Through research largely conducted in the past 15 years, we now know that vitamin A can be used in the treatment of a hereditary disease involving the retina, namely the Bassen-Kornzweig syndrome. We also have discovered that dietary deficiency of taurine can result in a retinal degeneration in animals. Treatment trials with special diets are being conducted to determine whether lowering of plasma ornithine in gyrate atrophy or serum phytanic acid in Refsum's disease will alter the course of the retinal degenerations in these human diseases. The purpose of the present report is to provide an overview of some of the recent advances made in our understanding of these retinal degenerations.

Vitamin A and the Bassen-Kornzweig Syndrome

Major natural sources of vitamin A (eg, retinol) in the diet include β-carotene, which is found in yellow and green leafy vegetables, and long-chain retinyl esters, which are found in animal tissues. β-carotene is converted to retinol primarily in the intestinal mucosa. β-carotene 15,15′ deoxigenase catalyzes the cleavage of β-carotene at the central double bond (Fig. 2),

Fig. 1. *Top,* Fundus photograph from an 18-year-old man with juvenile macular degeneration and *bottom,* a 44-year-old man with retinitis pigmentosa. Patient (top) has best-corrected vision of 20/200 with intact peripheral vision; patient (bottom) has 20/20 with night blindness and substantial loss of peripheral vision. Photograph (top) includes left disc and macula; photograph (bottom) shows right disc and nasal midperiphery.

Table 1. Estimations of Annual Incidence of Xerophthalmia in Asia Based on Indonesian Data*

Ocular Sign	Annual Incidence Preschool	Population at Risk	Cases Per Year
Indonesia			
Corneal	4/1,000	12 million	48,000
Noncorneal	104/1,000	12 million	1,250,000
Asia			

Corneal xerophthalmia, annually: 500,000; about 250,000 go blind

Noncorneal, annually: 8–9 million

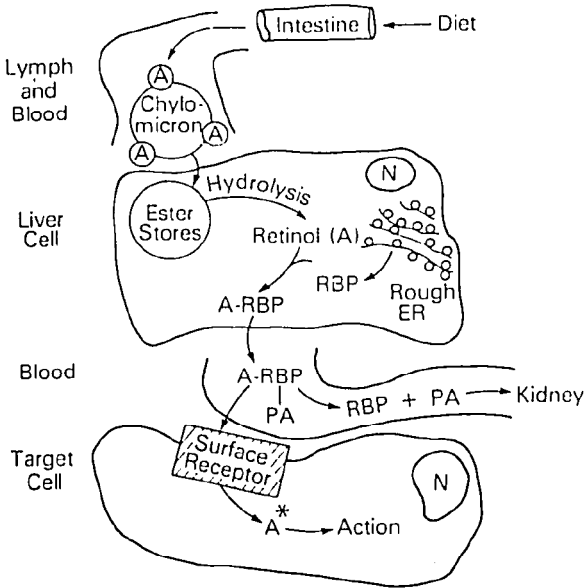* From the International Vitamin A Consultative Group (IVACG).[7]

Fig. 3. Vitamin A transport to a model target cell. A designates vitamin A; RBP, retinol-binding protein; A-RPB, holo-RBP; PA, prealbumin; ER, endoplasmic reticulum; N, nucleus. (From Chader G. Retinoids in ocular tissues: binding proteins, transport and mechanism of action. In: McDevitt DS, ed. Cell Biology of the Eye. New York: Academic Press, 1982, 377–433.)
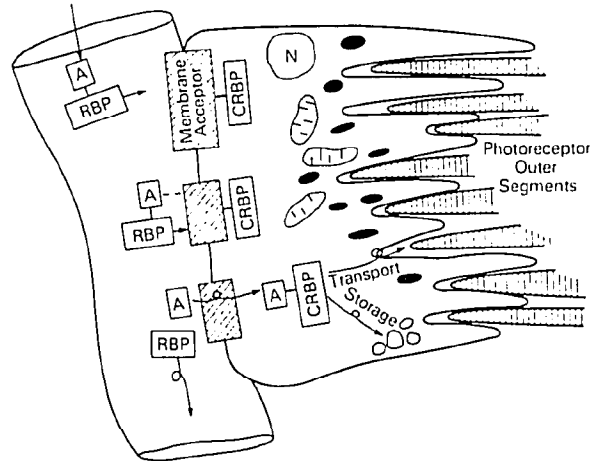

Fig. 4. Pathway of vitamin A transport from plasma to photo-receptor outer segments. A designates vitamin A; RBP, retinol-binding protein; CRBP, cytosol retinol binding protein; N, nucleus. (From Chader G. Retinoids in ocular tissues: binding proteins, transport and mechanism of action. In: McDevitt DS, ed. Cell Biology of the Eye. New York: Academic Press, 1982, 377–433.

yielding two molecules of retinaldehyde (eg, retinal) and then retinaldehyde is reduced to retinol by retinaldehyde reductase. Dietary retinyl esters are hydrolyzed in the intestine, and the resulting retinol is then absorbed into the mucosal cells. In the mucosal cells retinol (designated as A in Fig. 3), either newly absorbed or newly synthesized from carotene, is re-esterified mainly as the palmitate, complexed with other lipids and proteins in the form of chylomicra, and transported via the lymph and blood to the liver. Chylomicra are removed from the circulation almost entirely by the liver.[21] After uptake of the chylomicra retinyl esters, hydrolysis and re-esterification occurs in the liver, and the resulting retinyl esters, mainly retinyl palmitate, are stored in association with lipid droplets, either in the hepatic parenchymal cells or in "fat-storing cells," sometimes referred to as Ito cells.[22] From these liver stores, vitamin A is mobilized as the free alcohol, retinol, bound to a specific retinol-binding protein (RBP)[23] and secreted as holo-RBP (designated as A-RBP in Fig. 3). The secreted complex of vitamin A and retinol-binding protein then forms a 1:1 molar complex with prealbumin (designated PA) in the plasma. The RBP-prealbumin complex serves to reduce glomerular filtration and renal catabolism of RBP. Vitamin A mobilization from the liver is highly regulated by factors that control the rates of RBP production and secretion by the liver.[24] Delivery of vitamin A to peripheral tissues appears to involve

specific cell surface receptors (Fig. 4) for the RBP.[25,26] The vitamin A so delivered enters the target cell, eg, the pigment epithelium, where it may become associated with an intracellular cytosol retinol-binding protein (designated CRPB, Fig. 4).[27] In the pigment epithelium, vitamin A is esterified and again stored primarily as the palmitate.[28,29] Upon demand it is hydrolyzed and transported to the photoreceptor outer segments apparently bound to one or more
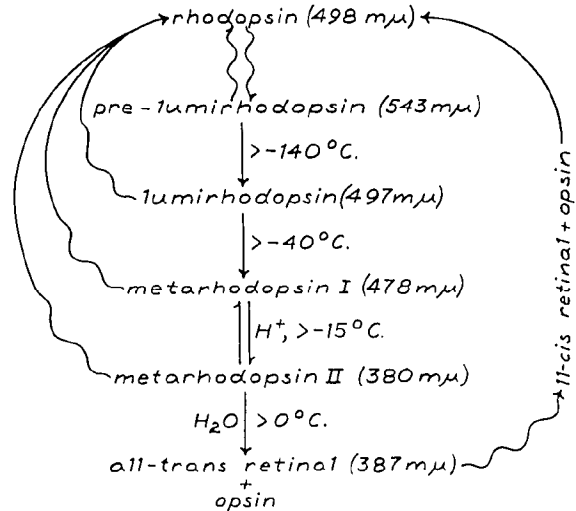

Fig. 5. Stages in the bleaching of rhodopsin. Photochemical reactions are denoted by wavy lines, thermal (dark) reactions by straight lines. Reactions arrested at designated temperatures. Absorption maxima in parentheses. (From Matthews RG, Hubbard R, Brown PK, Wald G. Tautomeric forms of metarhodopsin. J Gen Physiol 1963-1964;47:215–220, by copyright permission of The Rockefeller University Press).

Fig. 6. Retinal histology of rats raised on vitamin A-free diets and supplemented with vitamin A (A) or retinoic acid (B, C, and D). In contrast to normal structure (A), rats raised on vitamin A-free diets and supplemented with retinoic acid show less intensely stained outer segments at two months (B), almost complete disappearance of outer segments with loss of about half the inner segments and visual cell nuclei at six months (C), and disappearance of visual cells except for one irregular row of visual cell nuclei at ten months (D). Other parts of the retina and pigment epithelium appear normal. (From Dowling JE, Gibbons IR. The effect of vitamin A deficiency on the fine structure of the retina. In: Smelser G, ed. The Structure of the Eye. New York: Academic Press, 1961;89).

proteins.[20,30] Along the way, oxidation and isomerization convert vitamin A to 11-cis retinaldehyde. Binding is thought to occur between 11-cis retinaldehyde and the lysine in opsin at position 53 from the C-terminus by a Schiff-base linkage between the aldehyde group and the epsilon-amino group of lysine.[31,32] Light results in isomerization of 11-cis retinaldehyde to all-trans retinaldehyde and opsin through a series of intermediates (Fig. 5)[33] and results in visual excitation[34] by mechanisms still to be defined completely.

Vitamin A supports growth and the visual cycle while vitamin A acid or retinoic acid supports growth but does not support the visual cycle. Photoreceptors of weanling rats fed a vitamin A-free diet supplemented with retinoic acid show the effects of vitamin A deprivation within two months. Figure 6A shows the normal control retina of a rat raised on a vitamin

Fig. 7. Recovery from vitamin A deficiency. In a typical experiment litter mates were raised on vitamin A-free diets for about six months; one rat was supplemented wth vitamin A (A), the other two with retinoic acid. Sixteen days prior to the end of the experiment the recovery animal was fed a large dose of vitamin A (500 μg) and then periodically fed further vitamin A for 16 days (C), while the deficient animal (B) was continued on retinoic acid. For description of histology see text. (From Dowling JE, Gibbons IR. The effect of vitamin A deficiency on the fine structure of the retina. In: Smelser G. The Structure of the Eye, New York: Academic Press, 1961;95).

A-free diet supplemented with vitamin A. In contrast, rats raised on a vitamin A-free diet supplemented with retinoic acid show changes in the outer segments at about two months (Fig. 6B) and loss of outer segments, inner segments, and about half the photoreceptor nuclei at about six months (Fig. 6C). At ten months (Fig. 6D) the photoreceptors have disappeared except for one row of nuclei. In rats on vitamin A-free diets plus retinoic acid, the level of rhodopsin declines to 5–10% of normal after two months, while the concentration of the visual protein opsin decreases more slowly, with 50% remaining after two months. Loss of ERG function and loss of outer segments precede loss of photoreceptor cells, and this provides an opportunity for therapeutic intervention. In fact, reversal of function and structure can be achieved with refeeding vitamin A in early stages. Figure 7 illustrates the retina of a control rat (A), that of a vitamin A-deficient rat at six months with loss of outer segments and half the photoreceptors (B), and the retina of a rat depleted for about six months and then given vitamin A for 16 days (C). No increase in the thickness of the outer nuclear layer occurs (Fig. 7C compared with Fig. 7B), but new outer segments (Fig. 7C) with normal length and width regenerate within 16 days.[35,36]

Light is required to produce this sequence of events as vitamin A-deficient rats supplemented with retinoic

Fig. 8. Representative sections from midperipheral retina of vitamin A-depleted 13-lined ground squirrel kept in cyclic dim illumination (0.1–10 ft-C) for 45 weeks (top) and from midperipheral retina of vitamin A-depleted 13-lined ground squirrel kept in cyclic dim illumination (0.1–10 ft-C) for 38 weeks and then cyclic moderate illumination (50–500 ft-C) for eight weeks. The upper section appears normal whereas the lower section shows abnormal deposits at the photo-receptor pigment epithelial cell interface that extend into inner segment layer. Largest deposit is $20 \times 40 \mu$ (From Berson EL. Experimental and therapeutic aspects of photic damage to the retina. Invest Ophthalmol 1973; 12:37).

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