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Major review

Retinoic acid and the ocular surface

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ABSTRACT

Retinoic acid is known to improve cutaneous wound healing and, in recent years, its application in ophthalmology has been investigated. This review looks at the role of retinoic acid on the ocular surface. Retinoic acid can be produced synthetically, and its mechanism of action includes both nuclear and non-nuclear receptor mediated pathways. It has been shown to improve full and partial thickness corneal lacerations as well as corneal epithelial defects. Retinoic acid plays a critical role in cell differentiation at the cornea, conjunctiva, and limbus, and may have an anti-tumor role. Its positive effect is only achieved at the correct concentration, however; excess concentrations of retinoic acid have a deleterious effect. The main limiting factor of retinoic acid use is its detrimental effect on meibomian glands, resulting in cell death, atrophy of acini, hyposecretion of oils, and altered gene expression, eventually resulting in dry eye symptoms. This effect is reversible on discontinuation of the drug.

1. Introduction

Vitamin A has long been known to improve cutaneous wound healing. Numerous studies demonstrate that vitamin A accelerates epithelial migration, granulation tissue formation, and reversal of the retardation of healing induced by corticosteroids.[33,65,127] This review will explore the international literature on the ophthalmic use of retinoic acid on the ocular surface.

2. Production of retinoic acid

2.1. *Natural production in the human body*

Retinoic acid is produced in the body by two sequential oxidation steps: first from retinol to retinaldehyde and then from retinaldehyde to retinoic acid, which is the active form of vitamin A. Retinol (vitamin A), ingested in food and absorbed by intestinal mucosal cells, is bound to the serum

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retinol-binding protein and transported into target epithelial cells by a membrane receptor encoded by the gene stimulated by retinoic acid 6. Additionally, a second enzyme, lecithin retinol acyltltransferase, is required for the uptake of retinol into cells.[112] Once inside the cell, enzymes such as alcohol dehydrogenase, short-chain dehydrogenase, and retinol dehydrogenase of the microsomal fraction catalyze the oxidation of retinol to retinaldehyde via a reversible reaction. This is followed by the non-reversible oxidation of retinaldehyde to retinoic acid by retinal dehydrogenase (RALDH 1, 2, 3 and 4).[107,117] Most organs have the capacity for retinoic acid biosynthesis, including corneal epithelial cells.[117,135] Vitamin A is transported to the eye via the ocular surface blood vessels and tears.[175]

2.2. *Synthetic production*

Retinoic acid is produced synthetically for both therapeutic and research purposes. There are two main methods described in the literature. In one, the reaction products of β-ionone and γ-bromocrotonic ester are dehydrated and subsequently saponified to produce ionylidene crotonic acid III. Using lithium methyl, ionylidene crotonic acid III is transformed into C_{18} ketone IV. Subsequently, the C_{18} ketone IV reacts with methylbromoacetate, producing all-trans-retinoic acid.[177]

The second method consists of the condensation of β-ionylideneacetaldehyde with an ester of β-methylglutaconic acid under alkaline conditions to form 4-carboxyvitamin A acid. This is decarboxylated by heating the solution in an organic base containing small amounts of copper powder. The resulting neovitamin A is isomerized with iodine to produce all-trans retinoic acid.[133]

All-trans-retinoic acid is inherently unstable because it undergoes photoisomerization. As a result, synthetic retinoic acid, which remains stable to degradation, has been investigated.[29] Though it is meant to have comparable activity, synthetic retinoic acid may not exert all the biological effects of all-trans-retinoic acid.[24] Further studies are needed.

Retinol/retinyl palmitate, another derivative of vitamin A with increased stability compared to all-trans-retinoic acid, is the precursor and storage form of vitamin A[181] and has similar effects to retinoic acid in certain conditions such as dry eyes.[162] Briefly, vitamin A is dissolved in a mixture of ethylene chloride and pyridine. Palmityl chloride is then added. Finally, all unesterified vitamin A and remaining palmitic acid is removed from the resultant mixture.[7]

3. Vitamin A deficiency

Ocular manifestations of vitamin A deficiency remain the leading cause of childhood blindness in developing countries,[154] though these also occur in developed nations.[23,128,136,150] A deficiency of this fat-soluble vitamin or its metabolites (e.g., retinoic acid) manifests in two ways—night blindness (nyctalopia) and a spectrum of ocular disease known as xerophthalmia. Retinoic acid promotes incorporation of glucosamine into specific glycoproteins, which is significantly reduced in xerophthalmia.[49,156] Ocular changes include epidermal keratinization and squamous metaplasia of the cornea and conjunctiva, corneal ulceration, night blindness, and retinopathy.[144] This spectrum of pathology provides an insight into the various mechanisms by which vitamin A and its metabolites exert their ocular effects.

The initial and most common ocular manifestation of vitamin A deficiency is nyctalopia, because the visual pigments of the photoreceptors are derived from vitamin A. When light strikes the retina, the 11-cis configuration is converted to the trans form, which is released by the photoreceptors to enter the retinal pigment epithelium. Here it is reconverted to the cis form.[31] Throughout this process of phototransduction, some retinal (both cis and trans) is lost; therefore, a constant source of vitamin A is required for optimal photoreceptor function.[144] Retinal electrophysiology can assist in the diagnosis and follow-up of vitamin A deficiency.

Conjunctival pathology typically follows nyctalopia, but can also occur without concurrent clinical night blindness.[150] The first sign is xerosis (dryness) caused by a marked decrease in mucous-secreting goblet cells.[81] Epidermal keratinization and squamous metaplasia of mucous membranes results to a degree inversely proportional to serum vitamin A levels.[51,169,185] Clinically, the conjunctiva appears thickened and wrinkled with loss of transparency. Occasionally present are Bitot spots—triangular, perilimbal foamy gray plaques of keratinized conjunctiva overlying an area of dryness.[31] Although Bitot spots are said to be pathognomonic of current vitamin A deficiency, they may not reverse with replacement therapy.

As the deficiency worsens, the cornea becomes involved. Instability of the precorneal tear film leads to punctate keratopathy, which progresses to epithelial defects, keratinization, and stromal edema.[147,183] Left untreated, corneal epithelial defects progress to partial or full-thickness ulceration and may develop bacterial infection. Keratomalacia is full-thickness liquefactive necrosis of the cornea and, in conjunction with vitamin A deficiency, is often associated with a preceding systemic stressor such as measles or severe protein malnutrition. The corneal stroma can slough, either leaving a descemetocoele or, in severe cases, causing corneal perforation.[21,31,144]

Lastly, there is an uncommon condition known as the xerophthalmic fundus, characterized by numerous small yellow dots representing loss of pigment from the retinal pigment epithelium. These may be accompanied by scotomas.[21]

Replenishment of vitamin A stores typically results in the reversal of night blindness and the conjunctival and retinal pathology.[50,63,125,148,149,178] Keratopathy without severe ulceration also responds favorably to vitamin A replenishment,[144] whereas severe corneal ulceration leads to permanent vision loss from corneal scarring, particularly if complicated by secondary infection.

4. Mechanism of retinoic acid action

The mechanisms by which retinoic acid produces its actions can be classified into two broad categories: nuclear receptor