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Lutein, zeaxanthin, and *meso*-zeaxanthin: The basic and clinical science underlying carotenoid-based nutritional interventions against ocular disease

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ABSTRACT

The human macula uniquely concentrates three carotenoids: lutein, zeaxanthin, and *meso*-zeaxanthin. Lutein and zeaxanthin must be obtained from dietary sources such as green leafy vegetables and orange and yellow fruits and vegetables, while *meso*-zeaxanthin is rarely found in diet and is believed to be formed at the macula by metabolic transformations of ingested carotenoids. Epidemiological studies and large-scale clinical trials such as AREDS2 have brought attention to the potential ocular health and functional benefits of these three xanthophyll carotenoids consumed through the diet or supplements, but the basic science and clinical research underlying recommendations for nutritional interventions against age-related macular degeneration and other eye diseases are underappreciated by clinicians and vision researchers alike. In this review article, we first examine the chemistry, biochemistry, biophysics, and physiology of these yellow pigments that are specifically concentrated in the *macula lutea* through the means of high-affinity binding proteins and specialized transport and metabolic proteins where they play important roles as short-wavelength (blue) light-absorbers and localized, efficient antioxidants in a region at high risk for light-induced oxidative stress. Next, we turn to clinical evidence supporting functional benefits of these carotenoids in normal eyes and for their potential protective actions against ocular disease from infancy to old age.

Abbreviations: ABCA1, ATP-binding cassette sub-family A member 1; ABCA4, ATP-binding cassette sub-family A member 4; A2E, N-retinyl-N-retinylidene ethanolamine; AFI, Autofluorescence imaging; AMD, Age-related macular degeneration; AREDS, Age-Related Eye Disease Study; AREDS2, Age-Related Eye Disease Study 2; BCO1, β-carotene oxygenase 1 (also known as β-carotene-15′,15′-monoxygenase); BCO2, β-carotene oxygenase 2 (also known as β,β-carotene-9′,10′-dioxygenase); cHFP, Customized heterochromatic flicker photometry; cSLO, Confocal scanning laser ophthalmoscope; DHA, Docosahexaenoic acid; DMAPP, Dimethylallyl pyrophosphate; EDCC, Eye Disease Case-Control; EPA, Eicosapentaenoic acid; EFSA, European Food Safety Authority; GGPP, Geranylgeranyl pyrophosphate; GRAS, Generally recognized as safe; GSH, Glutathione; GSTs, Glutathione-S-transferases; GSTP1, Glutathione S-transferase P1; GWAS, Genome-wide association studies; HDL, High-density lipoproteins; HFP, Heterochromatic flicker photometry; HPLC, High pressure/performance liquid chromatography; I/R, Ischemia/reperfusion; IRBP, Interphotoreceptor retinoid-binding protein; ISX, Intestine-specific homeobox; IPP, Isopentenyl pyrophosphate; LC–MS, Liquid chromatography–mass spectrometry; LC–MS/MS, Liquid chromatography–tandem mass spectrometry; LDL, Low-density lipoprotein; MacTel, Macular telangiectasia type II; MP, Macular pigment; MPOD, Macular pigment optical density; NOAEL, No observed-adverse-effect-level; ROS, Reactive oxygen species; ROP, Retinopathy of prematurity; RP, Retinitis pigmentosa; RPE, Retinal pigment epithelium; SR-BI, Scavenger receptor class B member 1; StARD3, Steroidogenic acute regulatory domain protein 3; VEGF, Vascular endothelial growth factor; WHAM, Wisconsin hypoalpha mutant.

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Contents

1. Introduction

Carotenoids are phytochemicals that are classified as carotenes if they are exclusively hydrocarbons, but if they contain oxygen as a result of oxidation or enzymatic addition, they are known as xanthophylls. Carotenes are structurally characterized by a $C_{40}H_{56}$ conjugated polyene backbone chain that allows electrons in their double-bonds to easily delocalize (Willstätter and Mieg, 1907), lowering the ground state energy of the molecule. This core system of conjugated carbon–carbon double-bonds makes them efficient quenchers of reactive oxygen species (ROS) and absorbers of potentially damaging visible light (Britton, 1995a), and their functions are determined by their physical and chemical properties, functional groups, geometry, and varied structures. In general, carotenoids are present in all organisms of the food chain, but in widely varying amounts (Maoka, 2011), and recent evidence indicates that carotenoid pigments are responsible for brilliant plumage color in birds (Shawkey and Hill, 2005), bright coloration in fish, shrimp, sea sponges and bivalves (Maoka, 2011), as well as essential components of plants' photosynthetic apparatus (Dall'Osto et al., 2006) and for the diverse colors of many fruits and vegetables. In humans, one of their most remarkable and unique functions is as the pigment of the *macula lutea*, the yellow spot centered on the fovea (Bone et al., 1985; Handelman et al., 1992). The macular pigment carotenoids (MP), lutein, zeaxanthin, and *meso*-zeaxanthin are widely recommended as dietary supplements for the prevention of visual loss from age-related macular degeneration (AMD) and other ocular diseases, but the basic and clinical science supporting such recommendations is underappreciated by clinicians and vision scientists. Here, we provide a comprehensive review of the chemistry, biochemistry, biophysics, and clinical studies underlying the ocular protective and functional roles of these remarkable pigments throughout the lifespan.

2. Basic science of the macular pigment carotenoids

2.1. Carotenoid chemistry and analysis

2.1.1. Carotenoid chemistry

Carotenes are hydrophobic, with little or no solubility in water, while the xanthophylls have modestly better aqueous solubility. Hence, these carotenoids are generally restricted to the lipophilic areas in the cell such as the inner core of the cell membranes or else bound to proteins (Britton, 1995a). Polar functional groups alter the polarity and solubility of the carotenoids and affect their interactions with other molecules (Woodall et al., 1997a, 1997b). The antioxidant properties of different carotenoids vary based on their chemical and physical properties. For example, β-carotene and zeaxanthin have different dynamic behavior in a model membrane system (Cerezo et al., 2013), while lutein and zeaxanthin orient differently in phospholipid bilayers (Sujak and Gruszecki, 2000; Sujak et al., 2000). Of all the carotenoids, a few carotenoids have