The Whitehall-Robins Report
June 2007 - Volume 16, Number 2

Protective Effects of Lutein, Zeaxanthin and Related Dietary Carotenoids

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Dietary carotenoids are present in many colorful fruits and vegetables. Some provide the necessary precursors for our bodies to make vitamin A (for vision), and others contribute in ways that we are still trying to understand. The antioxidant ability of carotenoids has been well established from a variety of laboratory studies. Proving that this effect also occurs in the body is more complex. Further, different carotenoids such as lutein and zeaxanthin are localized in different and specific regions of the body. A detailed examination of these follows.

Different carotenoids play specialized physiological roles[1]. Vitamin A, required for vision, comes from dietary β-carotene. Zeaxanthin and lutein (isomeric dihydroxycarotenoids) are the major constituents of the retinal macular region[2]. The macula contains the highest density of cone photoreceptors in the retina and it is responsible for central (not peripheral) vision[3]. The macula appears as a bright yellow spot in the center of the typical primate retina, and deteriorates in some elderly humans (a condition called age-related macular degeneration, AMD or ARMD), reducing or eliminating central vision[4]. The supplementation with β-carotene, antioxidant vitamins C and E, zinc and copper has been reported to decrease the progression of advanced AMD, suggesting a role for antioxidants in reducing risk of AMD[5].

The xanthophylls zeaxanthin and lutein are present throughout the neural retina of humans (from prenates through adult), although the relative amounts vary[2]. Studies using HPLC analysis have shown that the fovea, the center of the macula, has the greatest zeaxanthin concentration, out to a radial distance of 2.5 mm, beyond which lutein is found in greater abundance[2]. Bone and Landrum reported the total amount of carotenoids per unit of area decreased from 13 ng/mm^2 in the center of the fovea to 0.05 ng/mm^2 at a radial distance of 8.7 to 12.2 mm^2.

The function of carotenoids in the macula has not yet been determined, although it is generally believed that pigments may selectively absorb blue light[4,6], thereby protecting the retina against the formation of free radicals from the high energy photons of blue light. Recent work suggests that in addition to the absorption of blue light and quenching of reactive oxygen species (ROS), such as singlet oxygen and peroxyl radical, the carotenoids may play an important role in scavenging superoxide and hydroxyl radicals[7]. Although carotenoids are generally ascribed poor superoxide scavenging ability (while reacting much more readily with hydroxyl, alkoxyl and peroxyl radicals[8], the primary literature is sparse. The general statement that carotenoids do not scavenge superoxide is based on studies of crocin[9] a carotenoid with only seven conjugated double bonds, which is certainly not a representative sample of all carotenoids.

Lycopene, β-carotene and zeaxanthin, have similar hydroxyl radical scavenging abilities and contain 11 conjugated double bonds. Lutein, containing only 10 conjugated double bonds, scavenges hydroxyl radicals less effectively than the others. The two retinal carotenoids, zeaxanthin and lutein, and lycopene and β-carotene all scavenge hydroxyl radicals. While zeaxanthin is the most powerful hydroxyl radical scavenger, above β-carotene, lycopene, and lutein (in that order) the differences between them are within the standard deviations of the relatively noisy signals. The best scavenger of these four, zeaxanthin, predominates in the centre of the fovea (responsible for central vision). Perhaps the centre of the fovea has sufficient hydroxyl radical production that this powerful scavenger (of all the available carotenoids) is directed *in vivo* to the retina. In support of this possibility, we have previously reported that rat retina contains a high concentration of superoxide anion, which increases with age[10]. The source of such reactive oxygen species in the retina is probably the mitochondria of the retinal photoreceptor cells. Mitochondria are known to produce superoxide as a result of leakage of electrons from the electron transport chain by way of coenzyme CoQ_{10}, and damage to mitochondria which can occur with age can result in increased production of reactive oxygen species[11], when superoxide is converted to hydroxyl radical, by the Haber-Weiss and Fenton reactions. In addition to the well-known protective absorption of blue light by the carotenoids in the macula[2], their radical scavenging activities would provide important protection to the fovea.

DIETARY SOURCES, ABSORPTION AND TISSUE DELIVERY

The best sources of lutein and zeaxanthin are vegetables and fruits, particularly yellow and orange ones[12]. A useful website is www.luteininfo.com. Among the green vegetables spinach and broccoli[13] are good sources, but sweet corn and even carrots contain lutein although carrots have β-carotene as their main carotenoid[14]. Surprisingly eggs are an excellent source of lutein[15]. Smokers have much lower plasma concentrations of lutein, possibly because they are in an oxidatively stressed state, which would use up this important dietary component[16]. Because lutein is a carotenoid, multivitamin supplements containing lutein should be taken along with the main meal of the day, which will have the highest fat content. This will facilitate its absorption along with the fats in the diet. Lutein appears to be absorbed after hydrolysis of lutein esters by gut esterases[17], and transported as lipoproteins and chylomicrons[18] to the cellular site where they can be re-esterified and stored. There is some controversy about the proteins in the cell that bind lutein. Several papers have suggested that lutein can be bound to the microtubule protein tubulin[19] at the paclitaxel binding site[20], while other authors have suggested that lutein is bound to the cellular enzyme glutathione-S-transferase[21], and this may protect against oxidation of the macular retinal cell membranes[22].

EFFECTS ON THE EYE:

In addition to the protective effect of lutein and its closely related isomer, zeaxanthin, on the macula, recent studies have shown that lutein in the diet can reduce the risk of aging cataracts by approximately 20%[23,24]. Although these studies used dietary questionnaires to estimate the dietary lutein intakes, and were not prospective studies of lutein supplementation, they support the protective effect of lutein on the eye lens cells shown in some tissue culture experiments[25]. Cataracts are associated with aging, and the prevalence of cataract increases from about 5% of the population aged 55 years old to almost half of the population aged 75 or more[26]. Similar to case-control studies which show reduced risk of cataract by vitamins E and C, lutein may act as an anti-oxidant in slowing the oxidative changes which form part of the pathology of cataract[26].

Snodderly, Bone and Landrum, and Nolan and co-workers have shown that dietary supplementation with lutein is able to increase the concentration of the macular pigment[27-33]. This would offer dual protection to the photoreceptor cells of the macula: (1) protection by absorption of blue light which can generate free radicals in the retina, and (2) scavenging of free radicals generated by the blue light. In addition to this, the lens of the eye is also protected against risk of cataract by elevated dietary lutein[34].

SKIN

In hairless mice, which are used to model human sunscreen protective effects, dietary lutein/zeaxanthin has been shown to decrease UVB-induced hyperproliferation and acute inflammation[35]. Mixed carotenoids containing lutein also showed a protective effect on human UV-induced erythema[36,37]. A large study[38] was not able to show any protective effect of caroteinoids or lutein in particular in decreasing the risk of skin cancer, squamous cell carcinoma. Wingerath[39] has found lutein as an ester form in human skin, suggesting that the lutein is re-esterified after its transport in plasma. It is known that, because of the possibility that light can generate tocopheryl radicals, the skin and eye have almost tenfold lower concentrations of vitamin E than internal organs. This would suggest that lutein esters in the skin may play an important and as yet little recognized protective role against sunburn damage and potential subsequent skin cancer.

CARDIOVASCULAR

Although Voutilainen et al.[40] concluded in a review that "the consumption of carotenoids in pharmaceutical form for the treatment or prevention of heart disease cannot be recommended", there are several reports which indicate that lutein and related carotenoids are inversely related to factors associated with increased risk of cardiovascular disease[41-44], such as C-reactive protein, F2-isoprostanes, sICAM1,or microalbuminuria[43]. The Los Angeles Atherosclerosis Study, looking at early stages of atherosclerosis, found that the carotid intima-media thickening (IMT) was inversely correlated with plasma oxy-carotenoids lutein, zeaxanthin, and β-cryptoxanthin and a hydrocarbon carotenoid, α-carotene[45,46]. A Costa Rican study found a positive association between the concentration of lutein and zeaxanthin in adipose tissue and myocardial infarct[47] but a protective association with β-carotene, while US investigators found a positive association between CVD risk and lutein/zeaxanthin[48] in plasma, or no effect[49,50] in separate studies. No association between lutein/zeaxanthin concentration and microalbuminuria was noted for Australian aboriginals[51], however, these authors did note a strong inverse correlation between C-reactive Protein and lutein[52].

CANCER RISK REDUCTION

The literature dealing with cancer risk reduction or prevention is rather sparse, and is based on dietary information, but not related to supplementation with lutein. A southeast Chinese study found a significant reduction in risk of prostate cancer for lutein and zeaxanthin dietary consumption[53,54]. For malignant melanoma, persons in high versus low quintiles of energy-adjusted lutein, had significantly reduced risk for melanoma (Odds Ratios < or = 0.67)[55]. A study of prostate cancer used California avocados. These were extracted with acetone to obtain a mixture of carotenoids and tocopherols[56]. This extract inhibited the growth of both androgen-dependent (LNCaP) and androgen-independent (PC-3) prostate cancer cell lines, by a mechanism involving G2/M cell cycle arrest as well as increased p27 protein. Lutein alone did not reproduce these effects. Lutein/zeaxanthin appeared to be protective against lung cancer in a Singapore study[57].

For breast cancer, diets containing lutein and zeaxanthin showed reduction in risk. Compared to the lowest quartile of intake, adjusted ORs for the highest quartile of intake for specific nutrients were as follows: lutein + zeaxanthin (OR=0.47; 95% CI=0.28.0-77)[58]. The authors were not able to definitely attribute cause to a single factor such as lutein, because diets rich in vegetables and fruit contain a mixture of carotenoids and tocopherols.

AGING

In addition to macular degeneration and cataract, lutein may be of benefit in reducing risk of other aging conditions. For instance, women aged 70-79 with higher carotenoid plasma concentration, including lutein/zeaxanthin, had higher grip, hip and knee strength comparing the highest to lowest quartiles of total plasma carotenoids[59]. A similar association was found for frailty in older women[60]. This area is however, quite controversial. The FDA concluded that no credible evidence exists for a health claim about the intake of lutein or zeaxanthin (or both) and the risk of age-related macular degeneration or cataracts. In contrast to this, Seddon[61] suggests that a healthy lifestyle with a diet containing foods rich in antioxidants, particularly lutein and zeaxanthin, as well as ω-3-fatty acids, appears beneficial for AMD and possibly cataract. Based on their observational studies, this group is embarking on a second phase of the Age Related Eye Disease Study that had initially used β-carotene as the carotenoid component of the treatment regimen, and are replacing it with lutein. A number of studies have suggested that addition of lutein either as a supplement or in the form of dietary components would result in an increase in the macular pigment[61].

IMMUNE SYSTEM EFFECTS

Chew et al showed that lutein was able to stimulate the immune response in dogs[62], and reviewed the role of lutein in inducing apoptosis in tumour cells in experimental animals[63].

SUMMARY

Many colorful fruits and vegetables are an excellent source of dietary carotenoids. The widely ranging beneficial contributions of carotenoids to our overall health are still being uncovered. As such, it is important to ensure that our diets incorporate carotenoids. We have detailed lutein and zeaxanthin here because of their importance to eye health, although their benefits extend throughout the human body. Supplements containing lutein should be taken with major meals in order to facilitate its digestion and absorption.

ACKNOWLEDGEMENTS

The authors would like to express our thanks to the Robert Church, the Editor of Molecular Vision, for permission to reprint portions of our paper *The retinal carotenoids zeaxanthin and lutein scavenge superoxide and hydroxyl radicals: a chemiluminescence and ESR study*[7] from Molecular Vision, as portions of the introductory section of this review.

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