The role of macular pigment in the health of the eye

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The presence of macular pigment in the human retina, other than as a postmortem artifact, was in dispute as late as the middle of the 20th century. Since then, the dispute has evaporated and the role of macular pigment in the health of the retina is rapidly gaining acceptance in the ophthalmic community. In this article, I will describe the composition and distribution of the pigment, its purported function, particularly in relation to age-related macular degeneration (AMD), and its response to dietary intervention.

Fig. 1 Structures of the macular carotenoids. Note that lutein and meso-zeaxanthin differ only in the position of one double bond (indicated).

Nearly 200 years after the discovery of the *macula lutea*, or yellow spot, by Francesco Buzzi in 1782 [1], the associated "macular pigment" (MP) was identified as a mixture of the oxygenated carotenoids, or "xanthophylls," lutein, zeaxanthin, and meso-zeaxanthin [2, 3]. Lutein and zeaxanthin are yellow pigments found in green, leafy vegetables as well as orange and yellow fruits and vegetables, and their presence in the eye can be attributed solely to the diet. Meso-zeaxanthin is not present in commonly consumed foods and its presence in the eye is due to conversion of lutein, possibly under enzymatic control, primarily in the foveal region. The structures of the three carotenoids are shown in Fig. 1. The distribution of MP in the retina, and the corresponding xanthophyll ratios that reflect the conversion process, are shown in Fig. 2. The concentration of MP in the center of the retina is higher than in any other tissue, e.g. ~ 3 and ~ 4 orders of magnitude higher than in the liver and blood serum, respectively. Spectroscopy of transverse sections of the retina reveals the majority of MP in the receptor axon layer (Henle fibers) and inner plexiform layer, thereby providing the central photoreceptor outer segments with a blue-light-absorbing filter. MP is also present in rod outer segments, and we can speculate that it is probably present in cone outer segments too.

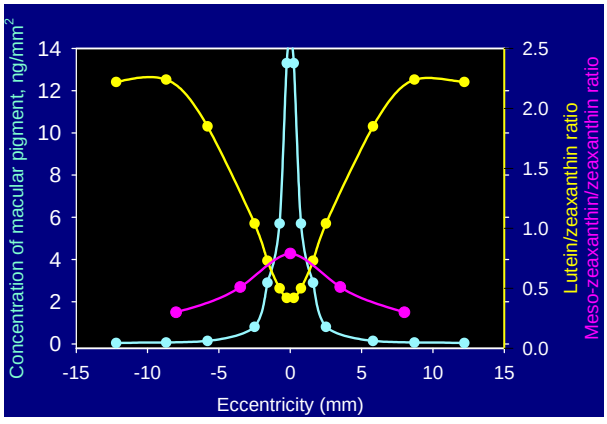

Fig. 2 Concentration of MP (blue), lutein:zeaxanthin ratio (yellow) and meso-zeaxanthin:zeaxanthin ratio (magenta) versus distance from the center of the fovea. The inverse relationship between these ratios reflects the conversion of lutein to meso-zeaxanthin in the foveal region,

The key to understanding how MP may be protective against AMD is to understand the processes that are implicated in the etymology of the disease. Photoreceptor disks in the outer segments are continuously being shed as part of the outer segment renewal process. RPE cells are responsible for digesting the disk material and eliminating it through the choroidal circulation. Probably owing to the RPE cells' inability to completely catabolize membrane components in the disks, such as oxidized polyunsaturated fatty acids, deposits of lipophilic material called drusen can form between the RPE cell layer and Bruch's membrane. Ultimately this can lead to complete separation of the RPE cells from the photoreceptors, and the latter begin to die causing associated vision loss in the affected areas. In some cases, the formation of drusen may be accompanied by neovascularization in the sub-retinal space, with fluid from the new capillaries accumulating between the choroid and retina. The occurrence of AMD is, of course, dependent on age, but also on genetic factors such as family history of AMD, race, sex and eye color, and environmental factors such as smoking, diet and light exposure. It is truly a multifactorial disease though underlying many, if not all, of the factors may be photooxidative damage and the resulting occurrence of drusen. Consequently, epidemiological studies on the role of the macular carotenoids in the development of AMD have not been completely consistent. However, there are many large-scale studies that support the protection hypothesis. These include the early studies by the Eye Disease Case-Control Study Group which reported that subjects with higher dietary intakes, or higher plasma levels, of lutein and zeaxanthin had a lower risk of developing advanced neovascular AMD [4, 5]. More recently, the Age-Related Eye Disease Study (AREDS) reported that subjects with a high dietary intake of lutein and zeaxanthin had significantly lower risk of developing both the wet and dry forms of AMD [6]. The current AREDS II will specifically examine the efficacy of lutein in AMD.

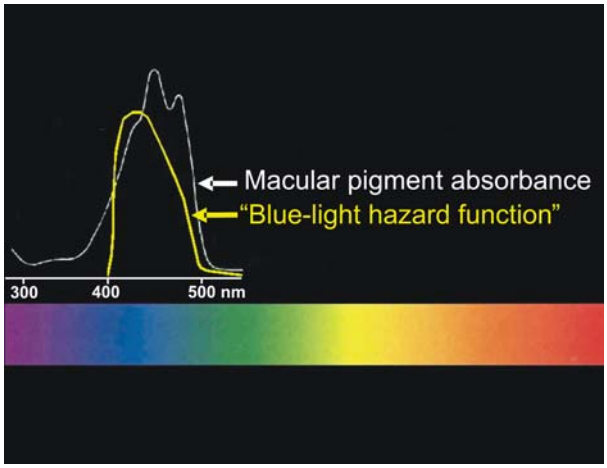

Fig. 3 The macular pigment absorbance spectrum (white) and the blue light hazard function (yellow) occupy the same region of the visible spectrum.

The absorbance spectrum of MP, together with its location in the Henle fiber and inner plexiform layers (which are anterior to the outer segments), provide an effective shield against photooxidation of the readily oxidized polyunsaturated fatty acids with which the outer segments are well endowed. MP absorbs blue light in the wavelength range ~ 400 to 500 nm, coinciding with the spectral region responsible for the majority of light-induced damage. See Fig. 3. Photooxidation is promoted by the presence of photosensitizers, as well as the fact that retinal tissue is highly oxygenated and subjected to focused light. One of the more studied photosensitizers is A2PE, formed in the outer segments and a precursor of lipofuscin in RPE cells. The photosensitizer molecule is excited by the absorption of a photon to a singlet state from which it rapidly decays to an excited triplet state. From here it is able to

interact with oxygen, for example, producing highly reactive singlet oxygen, one of the so-called reactive oxygen species (ROS). Oxidation of polyunsaturated fatty acids can then follow. Depending on an individual's MP density, the amount of blue light reaching the vulnerable tissues may be attenuated by up to 90% in some individuals, with a substantial effect on the rate of ROS production and resulting oxidative damage. The average attenuation of light by MP in the center of the macula is ~ 40% for a wavelength of 460 nm.

Additionally, carotenoids are antioxidants. Energy transfer from the triplet excited state photosensitizer to the carotenoid, rather than to oxygen, eliminates the formation of singlet oxygen. In the case where singlet oxygen has been formed, carotenoids are efficient quenchers, able to absorb the energy of the singlet oxygen and return it to the ground state. In both cases, the energy absorbed by the carotenoid is dissipated harmlessly as thermal energy. Chemical quenching of singlet oxygen by carotenoids, in which the carotenoid becomes oxidized, represents only a tiny fraction of the overall quenching process, so the turnover of carotenoids in the retina need only be very small. In the outer segments, an intimate association between the protective macular pigment molecules and the easily oxidized polyunsaturated fatty acid molecules would be desirable. In fact this is the case for zeaxanthin and meso-zeaxanthin, which appear to be incorporated in the cell membranes in a transverse fashion and therefore lie alongside the fatty acid chains. Lutein, on the other hand, appears to adopt a more variable orientation within the membrane.

The density of MP can be modified by diet. Monkeys raised on a carotenoid-free diet lack MP and, significantly, exhibit signs of early maculopathy – drusen and macular hyperfluorescence. In 1997, my colleague John Landrum and I reported the results of the first supplementation study with lutein. Thirty milligrams per day over a 180 day period resulted in ~ 20 and 40% increases in MP optical density in the two participating subjects respectively. Furthermore, the optical density remained elevated long after supplementation ceased. Since then, we and others have obtained similar results when supplementing with zeaxanthin or meso-zeaxanthin, or with foods that are rich sources of lutein and zeaxanthin. MP distributions in some individuals, unlike that shown in Fig. 2, are characterized by a dip in the very center of the fovea where meso-zeaxanthin concentration is normally maximum. In a recent supplementation study using all three carotenoids, but predominantly meso-zeaxanthin, subjects exhibiting this dip at the beginning of the study had a more normal MP distribution, like that in Fig. 2, at the conclusion of the study. Anecdotally, there have been a number of reports recently of regression of drusen accompanied by improvement in visual function in AMD patients taking this type of supplement.

Lutein and zeaxanthin have also been detected in the human lens, and their occurrence in this tissue may be related to the observation of a lower incidence of cataract among both men and women having a relatively high dietary intake of these carotenoids [7, 8]. Thus we may conclude that these colorful compounds truly are "vitamins" for the eye.

References

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