MACULAR PIGMENT - ANOMALY OR USEFUL RETINAL FEATURE?

JOHN MELLERIO  
School of Biosciences  
University of Westminster  
London, W1M 8JS  
email: mellerj@wmin.ac.uk

Since the nineteenth century it has been known that there is a patch of yellow pigment in the macula which can easily be seen in a dissected eye (figure 1). The question was what does it do - why is it there? There are three possible roles for the macular pigment (MP) which need to be described.

![Figure 1](image)  
**Figure 1** View of macula of a monkey retina clearly showing the yellow pigment extending from the foveal pit. (Courtesy of Prof John Marshall, London)

**First Function**

The first suggested function derives from a consideration of physiological optics. The macular pigment is found mainly concentrated in the fibre layer of Henle in the fovea so it acts as a pre-receptoral absorber and, as it is yellow, it absorbs blue light. It is well known that the optics of the eye, although good, display chromatic aberration. Thus a yellow filter before the tightly packed cones of the fovea will absorb the short wavelength light and reduce the extent of the coloured fringes of the retinal image hence improving visual acuity. However, the extent of any improvement in acuity has been queried by Hammond et al. (2001). The argument goes like this. As figure 2 shows, the spectral absorption curve for MP has a maximum absorption for blue light of 462 nm wavelength. The average optical density of MP in adults is about 0.4 log units, i.e. it absorbs about 60% of the incident blue light, so the blue fringes would not be completely eliminated. Also, in the foveola there are no blue sensitive or S cones and it is functionally tritanopic. The MP will not, therefore, affect the blue channel of the trichromatic colour vision system at the very centre of gaze and its effect on the M and L cones (green and red absorbing, respectively) will be small, as figure 2 shows. Thus partially removing the blue light in an area not very sensitive to blue light might not be expected to be a very effective mechanism. It remains to be shown how important for vision is the aberration correction function of MP, but it is probably small.
Second Function

Macular pigment, acting as a blue light absorber, has a second role. It has been shown that short wavelength light, because of its relatively high photon energy, more readily damages the retina than yellow or red light which is less energetic (Mellerio, 1994). Determination of the action spectrum for light damage to the retina by showing which specific components of the retina/RPE/choroid complex are first damaged at threshold, produced inconsistent results. However, Kremers and van Norren (1988) noted that there was a dichotomy of tissue damage type and action spectrum shape at an exposure time of about 12 hours (Mellerio, 1994). For the relatively more powerful exposures below 12 hour duration, the photochemical damage probably arises initially in the RPE and the action spectrum peaks somewhere in the blue or ultraviolet (see figure 3), and various cellular enzyme systems have been suggested as the initial site of light action. Exposures over 12 hours duration showed initial damage in the photoreceptor outer segments and the action spectrum followed the shape of the photopic sensitivity curve, i.e. photopigment absorption. These two types of damage are sometimes called Ham damage and Noell damage after the two authors who first described the damage profiles (Noell et al., 1966, Ham et al., 1976). Figure 3 also shows the spectral absorption curve of the lens of a young adult and of macular pigment. To a first approximation it appears that the lenticular absorption protects the retina against the Ham damage mechanisms. The MP, though, extends this protection towards 500 nm and would also protect the photoreceptors, especially the S-cones. The lens protection will be present across the whole retina whereas that from the MP will be limited to the macula around the optical axis of the eye, where the intensity of the retinal image is greatest in this on-axis area (Mainster, 1988).

Third Function

The third role for MP depends upon its chemistry rather than its spectral absorbing properties. MP is a mixture of two carotenoids, lutein and zeaxanthin (L and Z). Carotenoids in general are known for their antioxidant and free radical scavenging properties (Krinsky, 1989; Jacob & Burri, 1996). Structurally very similar (see figure 4) L and Z are not synthesised in the body and are derived solely from the diet. The best food sources of L and Z are not the same as for β-carotene which is perhaps the most famous carotenoid. Whilst dark green vegetables...
(spinach and so on) were recommended as sources of L and Z, it seems that maize and orange pepper are better respectively for L and Z (Sommerberg et al, 1998).

When radiation such as UV and short wavelength (blue) light interact with tissues, especially with molecules called photosensitisers, there is formed a range of excited singlet state molecules. These are very reactive and are short lived: they lose the energy they gained in the excitation process by forming photoproducts, by fluorescing or by generating so-called triplet state molecules (Mellerio, 1991). These excited triplet state molecules are longer lived and may react with the molecules found in the tissues, especially with oxygen, to produce free radicals such as the oxygen free radical superoxide and the hydroxyl radical, or they may give rise to the destructive singlet oxygen. These various radicals are not good news as they can in turn oxidise tissue molecules. At especial risk are polyunsaturated fatty acids (PUFA) which enter a chain reaction called lipid peroxidation. Any cellular structure that is rich in PUFA's is at risk, and the photosensitive outer segments of rods and cones are obviously vulnerable (Marshall, 1985). Figure 5 shows a cone outer segment in the first stages of light damage - the regularity of the discs is interrupted by centres of lipid peroxidation and the picture is reminiscent of a wooly sweater after a visitation by moths.

![Graph showing action spectra for Noell and Ham type damage](image)

**Figure 3** Action spectra for Noell and Ham type damage. The dashed line is the \( V'_{\lambda} \) curve representing the absorption of the visual pigments. Also shown are the absorption curves of the lens of a young adult and of macular pigment. Note, the curves have been moved vertically by arbitrary amounts to produce a clearer graph.
The two important protective properties of carotenoids, namely singlet oxygen quenching and the scavenging of reactive oxygen species, vary across the range of carotenoids and with the conditions used to measure these properties (Schalch et al, 1999). For example, in vitro, zeaxanthin has about twice the capacity to quench singlet oxygen than lutein and five times the ability to repair the α-tocopheryl radical cation. Whether these effectiveness ratios apply in vivo is not known, but it is interesting to see that L and Z are not equally distributed across the retina. In the fovea the ratio of L concentration to Z concentration is 0.7 and about 1.3 in the outer macular zone and higher still in the retinal periphery. Indeed, L and Z occur in many retinal tissues but in much smaller amounts than in the fovea - free radicals are not only produced by the interaction of radiation and tissues, but are formed as by-products of normal cellular metabolism and all cells contain systems to protect against the destructive actions of these radicals.

![Figure 4](image)

**Figure 4** Structure of lutein and zeaxanthin, the two carotenoids that make up the macular pigment. The difference in structure is shown in red.

The interest in the antioxidant properties of L and Z in MP arises because of laboratory experiments which show that prolonged exposure to light can induce damage to the retina and that the damage can resemble certain aspects of AMD. Epidemiological research has suggested many factors that might predispose a person to AMD (Evans, 2001) but there is no universal consensus on all of these. One factor that the lab light-exposure experiments points to is chronic exposure to light, especially blue light and UV radiation. Oxidative stress is high in the retina, especially so in the fovea where the metabolic rate and the oxygen tensions are high, and where the incident light is most intense and there is a plethora of PUFA's awaiting peroxidation (Beatty et al, 2000; Marshall, 1985). A good supply of carotenoid pigment in the macula would be a useful sight-preserving component to have throughout life to inhibit the slow destruction of retinal cellular components. The idea that macular pigment is protective to retinal function (Haegerstrom-Portnoy, 1988) and AMD (Snodderly, 1995) is now firmly established but not at all confirmed.

If it is the antioxidant function of MP that is most important in ocular physiology, then one might expect evidence from both laboratory investigations and from epidemiological studies that the amount of MP a person has correlates inversely with the age of onset and the severity of macular degenerative disease. Indeed, there is evidence from lab measurements that supports this idea. Bone et al. (2001) measured the MP in normal and AMD donors eyes and showed that the latter have significantly less MP and this, of course, corroborates the protective hypothesis. However, one could always suggest that the lower MP is the result of the pathological changes
in the macula and not a precursor to that pathology. Support for the protective hypothesis comes, though, from other papers. Beatty et al. (2001) showed that the healthy eyes of patients who had AMD in the fellow eyes possessed significantly less MP. Werner et al. (2000) reported a reduced sensitivity in the S wavelength cones of subjects with less MP compared to normals. They were not 100% behind the protection hypothesis as they continued by arguing that the difference in MP density could be explained by the life-long action of short wavelength light on the S cones reducing their sensitivity - a kind of evolutionary or adaptive change misinterpreted by those keen on a role for MP in the AMD story. This view notwithstanding, Berendschot et al. (2002) have recently shown no difference in the retinal levels of MP between normals and those with AMD. So it seems there is some contradictory evidence from lab studies for the idea that MP protects for AMD. But at a recent conference (ARVO, 2002) a number of authors (e.g. Nieto, Pelosini, Koh Feldhamer) presented communications that support the protection idea but suggest that the shape of the spatial distribution of the pigment across the macula, which is complex, may be a better predictor than the peak MP density. Currently, the balance is for the protective hypothesis but more confirmatory evidence is urgently needed.

Figure 5  Part of the outer segment of a pigeon cone that had been exposed to a domestic fluorescent lamp for 6 hours. Note the punctate disruption of the disc membranes (Courtesy J Marshall)
Two epidemiological studies (Taylor et al., 1992, Cruickshanks, Klein and Klein, 1993) have shown that increased exposure to sunlight is associated with an increased incidence of AMD, but the relationships were not simple ones. They are, however, support for the MP protective hypothesis. Additional back up for the hypothesis comes from lab studies that show that in people with greater exposure to sunlight the amount of MP is decreased (Mellerio et al. 2002) and that light coloured irides are also associated with less pigment (Hammond, Ful & Snodderly, 1996). The consensus seems to be that MP may be protective and it would be a good thing if people had a good quantity of it in their retina.

**Prophylaxis**

The protective hypothesis leads fairly logically to consideration of increasing MP levels as a prophylactic move. As the body does not synthesise lutein or zeaxanthin, the source of these carotenoids is the diet so it would make sense to eat a diet rich in L and Z. So perhaps people should eat lots of maize and orange peppers (Sommerberg et al., 1998) and, indeed, Hammond et al. (1997) have shown that dietary modification with these vegetables can increase MP levels.

If you do not like maize or orange peppers, the idea of supplementation of the diet by taking L and Z is attractive. Those companies that manufacture dietary supplements agree and L has been available for some years, sold on-line as a blindness preventative! A number of trials of supplementation with L have reported positive results, e.g. Landrum et al. (1997), Aleman et al. (2001), but zeaxanthin, which might be the preferred carotenoid as its concentration is highest in the central macula, is not yet commercially available though supplementation trials are underway and one small trial has reported (Garnett et al., 2002). One finding that intrigues those who hope that dietary enrichment of L and Z will increase MP is that not everybody benefits. Subjects may be “responders” or “non-responders” (Hammond et al. 1997) and it would be interesting to know why as this has potentially serious implications for anybody who seeks to promulgate a supplementation policy.

**Screening**

Although L and Z seem devoid of toxic side affects, it may not be wise to suggest everybody takes L and Z pills. These should be reserved for those with low MP levels who might eventually benefit in their senior years from supplementation. To achieve this requires some way of conveniently measuring MP in a clinic or optometrist’s office. There are a number of techniques to measure MP objectively, such as special scanning laser ophthalmoscopy, retinal autofluorescence or Raman spectroscopy. Description of these techniques is beyond this article, but see Werner et al (2000) and Delori et al (2001) for more details. All these methods are complicated and expensive and are currently found only in research laboratories. There exist three or four psychophysical techniques for determining MP and one, heterochromatic flicker photometry (HFP), has become popular and lends itself to use in small, portable instruments that fit in well in a busy office or clinic. The first reported was by Mellerio et al (1998, 2002) but Wooten and his colleagues have described a sophisticated instrument (Wooten et al. 1999) as have Beatty et al. (2000). Versions of these instruments are available and are now involved in supplementation trials, screening of large populations and other investigations. It is to be expected that many uncertainties in the macular pigment and eye disease story will soon be resolved - only to open up fresh questions. This is the well established pattern of scientific enquiry.
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