The possibility that the macular carotenoids, lutein (L), and zeaxanthin (Z), could retard age-related changes in the eye and prevent the eye diseases that result from such changes (namely, cataract and macular degeneration) has been carefully studied. A role for the carotenoids very early in life, however, has received far less attention. Nevertheless, an influence on visual development is likely. Retinal L and Z, for instance, would influence the development of the visual system if they (1) altered input during a critical/sensitive period of visual development and/or (2) influenced maturation and/or (3) protected the retina during a period when it was particularly vulnerable. The available evidence indicates that the pigments may play a role in all three of these areas.

INTRODUCTION

The dietary carotenoids lutein (L) and zeaxanthin (Z) are the only carotenoids that are normally found in the human eye. The uptake of these xanthophylls by the eye appears to be quite specific. The other carotenoids in the sera (20 or so) are normally excluded. Throughout the visual system, L and Z have been found in most tissues (e.g., visual cortex) including the many tissue types in the eye such as the epithelium of the crystalline lens, iris, photoreceptor outersegments, and retinal pigment epithelium. Where L and Z reach their highest concentration by far, in fact the highest concentration of carotenoids in the body, is the central retinal region often referred to clinically as the macula (hence the term for the pigments in this area, the macular pigments).

Of course, the macula has great importance in vision. This small area (~5–6 mm), for instance, is greatly magnified by the visual cortex. Looking at an object (e.g., reading text) essentially means lining up that object with the central macula (~1.5 mm), the cone-rich fovea. The fact that the visual system displays such selectivity by concentrating just these specific carotenoids in such a vital region suggests that these pigments play a special role in human vision. Many roles have been proposed. Most of them, however, can be classified as either prophylactic (e.g., Ahmed et al.) or directly optical (e.g., Wooten and Hammond). The most data and attention, by far, has been with respect to the former. Expressed simply, L and Z, at the site of the retina, are believed to prevent damage, largely actinic and oxidative in origin, leading to age-related macular degeneration (AMD). Similarly, L and Z in the crystalline lens are thought to prevent oxidative damage leading to acquired cataracts (e.g., Hammond et al.). Since these diseases are so prevalent, and are increasing with the aging of the American population, L and Z represent an important preventive approach.

The epidemiological data on AMD and serum and dietary L and Z, however, is somewhat mixed. Some studies have found relations, while others have not. For example, the most recent AREDS study (2007) found that those individuals that were in the highest quintile of dietary intake of L and Z had a 27%, 35%, and 55% lower probability of developing large or extensive intermediate drusen, neovascular AMD, or geographic atrophy, respectively. One difficulty with the epidemiological data, of course, is that AMD is a degenerative disease. Hence, it reflects many decades of irreversible neuronal damage. Assessments at the end of life are probably not a good indicator of a lifetime of behavior. As such, however, we cannot definitively answer whether the magnitude of MP’s protective effects are significant enough over time.
to meaningfully reduce the risk of acquired retinal disease. Such a question can really only be answered by longitudinal study. This is particularly difficult, however, when considering that degenerative diseases like age-related macular degeneration (AMD) reflect the accumulation of damage accrued over an entire lifespan. This process likely begins at birth.

Focusing on the role of L and Z at the end of life may, in fact, have distracted us from the important role it may play at the beginning. Indeed, it is unlikely that the mechanisms responsible for MP accumulation evolved to protect from a disease that manifests well past reproductive age. Carotenoids, in general, are known to have many functions, both active and passive, other than just preventing degeneration. One likely suspect would be influences on the development of the retina.10 L and Z are, after all, found in an area of the retina that is the most immature at birth (i.e., they are in the correct location to have an influence). There are at least three means by which MP could influence the developing visual system: 1) if MP altered input during a critical/sensitive period of visual development and/or 2) influenced maturation and/or 3) protected the retina during a period when it was particularly vulnerable.

**EVIDENCE THAT MP COULD ALTER VISUAL INPUT DURING A CRITICAL/SENSITIVE PERIOD DURING VISUAL DEVELOPMENT**

MP is a yellow filter found in the inner layers of the retina.11 It therefore screens shortwave (i.e., “blue”) light before that light is processed by the photoreceptors. The magnitude of this screening, however, is highly variable across individuals, ranging from very low levels (e.g., nearly 100% transmission) to very high levels (e.g., transmitting only 2–3% at peak absorbance).12 Wide variation in screening of the foveal cones can be found as early as infancy.13,14 It is reasonable to expect that such significant filtration of such a large part of the visible spectrum could influence visual function. As such, a number of hypotheses have been advanced that MP might improve vision through purely optical mechanisms (for a review see Wooten and Hammond15). There is significant empirical data to support such hypotheses.

Richer et al.,14 for example, tested the effects of lutein supplementation on visual performance in a double-blind placebo-controlled study of veterans (average age = 65 years) with early-stage AMD. He found that the lutein-treated group showed functional improvements (e.g., Snellen acuity) that were consistent with their measured increases in MP density. Olmedilla et al.,15 tested the visual effects of lutein supplementation on cataract patients using a double-blind placebo-controlled design and also found improvements in visual acuity in only those patients supplemented with L. Similar to Richer et al.,14 the cataract subjects in the Olmedilla et al. study also showed reductions in glare sensitivity after the 2-year L supplementation period. Given the careful experimental design, these studies provided strong evidence that the MP carotenoids could improve visual performance.

Such effects, however, could be due to either biological or optical changes. For example, the veterans in the Richer et al.14 study may have been somewhat malnourished and therefore responded to a nutritional intervention due to correcting deficiencies. To test optical effects, Stringham and Hammond16,17 measured changes in photostress recovery and glare disability that resulted from supplementing only young healthy subjects (n = 39) with 12 mg L and Z per day for 6 months. MP density at baseline was strongly related to photostress recovery time and glare disability (r’s ~ 0.80) when using broadband light strongly filtered by MP but not when using narrow-band light that was not filtered by MP. By varying the wavelength composition of their glare source, Stringham et al.16 showed that the mechanism responsible for their results was based on simple filtration. Supplementation led to direct improvements in glare disability and photostress. Previous studies18,19 demonstrated that MP strongly reduces visual discomfort for centrally viewed sources containing SW light. Wenzel et al.,20 for instance, showed that daily supplementation with 30 mg/L significantly decreased acute discomfort glare (photophobia) as a linear function of MP increases.

This combination of experimental data shows that MP improves visual function through optical mechanisms and as a linear function of amount. In the case of glare, MP improves the visibility of a target by absorbing the intraocular scatter that otherwise would veil the target. Such veiling, however, does not need to only be produced by scatter within the eye (entoptic). Wooten and Hammond21 conducted a detailed analysis of how MP might be expected to improve visibility outdoors due to reducing the veiling effects of blue haze. They found that, theoretically, an individual with 1.0 log unit of MPOD could see about 30% farther through the atmosphere compared to someone with little or no MP.

Would such effects be meaningful to the developing infant? Would wearing yellow goggles in infancy influence later visual development? Of course, we have no data to address this question directly. We do know that alteration of visual input is accompanied by an alteration in the corresponding brain mechanisms (e.g., anisometropic or strabismic amblyopia). Sugita,21 for instance, demonstrated that varying ambient illumination (an effect similar to filtering) could significantly alter the development of color vision mechanisms of macaque monkeys (an animal model with color vision similar to our own). It is certainly possible that the optical effects of MP that are
known to influence adult vision are also meaningful to infants. The magnitude of the effect, however, is likely to be small. After all, there are decades of children now that have been raised on formulas containing no or only trace amounts of xanthophylls and who have relatively normal vision. Any deficits are likely to be subtle for two reasons. The first is that all babies are probably exposed to some level of L and Z in utero (amounts varying according to their mother’s intake). Second, even formula-fed babies are probably exposed to foods containing L and Z after their first year. Babies with very little or very high retinal L and Z might show some color vision differences, which would be interesting from a scientific point of view but would likely have only small effects on their daily vision.

**EVIDENCE THAT MP COULD INFLUENCE MATURATION**

Maturation refers very specifically to the anatomical and physiological changes that accompany the differentiation of cells, tissues, and organs. With respect to the retina, it is the central portion, the fovea, that changes the most dramatically after birth.\(^\text{22}\) For example, the adult fovea is composed of an array of tightly packed cones that tend to be relatively long and skinny. In contrast, the packing of cells within the infant fovea is relatively sparse and the cones are significantly less differentiated (see Table 1). It is in the first year that most of the maturational changes to the fovea occur. Lutein is the dominant carotenoid in this rapidly changing area (e.g., the adult Z to L ratios across the retina are approximately reversed\(^\text{13}\)) and is well-placed to influence maturation. Of course, direct experimental evaluation of L & Z deprivation on foveal maturation is not possible on humans. Some non-human primates, however, (like macaques) also have maculas and macular pigment and have been experimentally evaluated.

Malinow et al.\(^\text{23}\) originally studied macaques raised on normal or xanthophyll-free diets. These authors found that, in addition to simply lacking macular pigment, the xanthophyll-free monkeys had more drusen-like bodies within their retinal pigment epithelium (RPE), increased macular hyperfluorescence, and retinal abnormalities.\(^\text{24}\) At issue, however, was the fact that these monkeys had diets that were unusual in other ways that could influence retinal health (such as a lack of taurine; originally noted by Snodderly\(^\text{20}\)). A follow-up study,\(^\text{26}\) also on macaques, that more specifically depleted just L and Z (and the n-3 status of some groups), found that it was primarily the RPE that was most influenced by the absence of L and Z. The RPE is the lysosomal-tissue (immediately posterior to the retina) that supports the very metabolically active overlying retina and is often affected by duress (e.g., it is the tissue that is actually diseased in patients with AMD). Leung et al.\(^\text{26}\) raised monkeys on normal chow and chow lacking L and Z (and low in n-3 fatty acids). They found that the xanthophyll-depleted monkeys showed distinct morphological changes (a proliferation of cells and other structural differences, such as a central decrease in cell density) compared to controls raised normally (see Table 1). Such changes could be largely reversed in a third group that received supplementation later in life (matu- rational changes can often be reversed by later exposures if the nervous system is still plastic).

**EVIDENCE THAT MP PROTECTS THE RETINA WHEN IT IS PARTICULARLY VULNERABLE TO DAMAGE**

The rapid maturation of the fovea increases the metabolic activity of a tissue that is already very metabolically active. It is, therefore, perhaps not surprising that the retina is particularly susceptible to the stressors that accompany this increased activity. For example, studies using animal models (reviewed by Hardy et al.\(^\text{27}\)) indicate a relative lack of autoregulation of blood flow within the choroid of the newborn (the primary blood supply posterior to the retina), which leads to hyperoxygenation and concomitantly higher levels of lipid peroxidation. Restricted blood flow (ischemia) is known to induce cellular degeneration within the retina. Choi et al.\(^\text{28}\) used high intraocular pressure to induce ischemia in rat retinas. This manipulation results in numerous changes such as increases in the production of nNOS (neuronal nitric oxide synthase), which generates nitric oxide, a promoter of oxidative stress. Lutein reduced the production of nNOS in a dose-dependent manner. Similarly, in rat models, zeaxanthin supplementation has been shown to inhibit oxidative damage to the retina produced by inducing diabetes.\(^\text{29}\)

Of course, L and Z are both known to be potent lipid-based antioxidants, and empirical evidence has shown that the infant retina and RPE “ages” rapidly due to increased oxidative stress. For example, Wing et al.\(^\text{30}\) and Feeney-Burns et al.\(^\text{31}\) have shown that the accumulation of lipofuscin (peroxidized lipids) is most rapid in the first years of life (see Table 1). Rapid aging of the infant retina is probably due to both increased oxidative and actinic stress. With respect to the latter, shortwave (blue) light is a likely culprit. Light lower than about 400 nm (e.g., ultraviolet) is certainly energetic enough to produce photochemical damage. Such light, however, does not tend to reach the retina since it is largely absorbed by the cornea and crystalline lens. Light longer than about 500 nm easily reaches the retina but is not energetic enough to convert inert oxygen into reactive oxygen species (although, of course, increasing retinal temperature can predispose the retina to photochemical damage so excessive that exposure can cause harm). It is really the waveband between about 400 and 520 nm that appears to be
Table 1  The visual system of the infant versus adult.

<table>
<thead>
<tr>
<th>Adult</th>
<th>Infant</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
<tr>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
</tr>
</tbody>
</table>

The infant orbit is about 30% smaller than the adult and the crystalline lens is relatively transparent.\(^{34}\)

Newborns lack a distinct foveal pit. (Images adapted from Snodderly, 1995\(^{25}\)).

Macular cone density increases by about 80% from birth to 4–5 years of age.\(^{45}\)

The cone outer segments of infants are thin and short in relation to the inner segments, which are quite broad. Nonetheless, visual capabilities that are largely mediated by receptor processes (such as absolute sensitivity) tend to develop very early. In contrast, visual capabilities that rely on postreceptoral processes (like Snellen acuity) mature much later (e.g., Vernier acuity does not reach adult levels until 4–5 years). (Images derived from Banks and Bennet, 1988\(^{46}\)).

Infants have low cortical synaptic density followed by a period of rapid synaptogenesis followed by synaptic pruning. (Images derived from Goldstein, 2007\(^{47}\)).
particularly harmful (this waveband is often termed the “blue-light hazard”).\textsuperscript{32,33} The infant retina may be more susceptible to the blue-light hazard due to the relative clarity of the crystalline lens.\textsuperscript{34} As crystallin proteins oxidize, the aging lens becomes increasingly yellowed and blocks shortwave light. In contrast, the relatively transparent infant lens transmits much higher levels. The lens focuses this high-energy light on a tissue saturated with oxygen. Such factors probably enhance the need of the retina for antioxidant and actinic protection. Indeed, mother’s milk contains many antioxidants including lutein (as opposed to most infant formulas, which contain only trace amounts),\textsuperscript{35} perhaps reflecting this need.

How can the role of L and Z in protecting the infant retina be empirically evaluated? The primary defense against senescence used by most of the body is simply biological renewal. This incessant mechanism replaces damaged or degenerated cellular and molecular structures by replacing them with newly formed molecules synthesized according to genetic instruction. For example, in the retina, about 50% of the proteins are replaced weekly; rod outer segments last about 2 weeks, etc. Since the actual receptors themselves are neural and therefore do not undergo mitosis, the retina (and nervous system in general) has enormous redundancy to allow for anatomical loss that does not appear as functional loss. For example, there are about 90 million rod photoreceptors in the eye at 20 years of age but only about 60 million at the age of 60 years. This loss, however, 30 million rods, is accompanied by minimal loss in scotopic (i.e., rod) sensitivity over the same time period.\textsuperscript{35} The visual system compensates for the loss\textsuperscript{36} to maintain function as long as

$\text{Table 1 Continued}$

<table>
<thead>
<tr>
<th>Adult</th>
<th>Infant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipofuscin accumulates relatively rapidly during the first few years of life. (Images derived from Wing et al., 1978\textsuperscript{30}).</td>
<td>Lipofuscin accumulates relatively rapidly during the first few years of life. (Images derived from Wing et al., 1978\textsuperscript{30}).</td>
</tr>
</tbody>
</table>

Breastfeeding and/or infant formula are the sole sources for L and Z prior to solid foods.

RPE cell density of monkeys raised on normal chow compared to monkeys raised on diets containing no L and Z and low omega-fatty acid content. (Images derived from Leung et al., 2004\textsuperscript{26}).

Monkeys: no L+Z, low N-3

Control monkeys: Normal diet

L dominates in the fovea during infancy, Z dominates afterwards.\textsuperscript{13}
CONCLUSION

Bone et al. originally showed that MP density was highly variable in the infant retina. Although all of the factors responsible for the wide variation in infant MP have not been studied, dietary intake of L and Z is clearly necessary. One obvious concern with infants is that food options are limited to breast milk or manufactured infant formulas, which often do not contain L and Z in other than trace amounts. In contrast, breast milk contains L and Z in concentrations that are approximately proportional to maternal intake of these carotenoids. Johnson et al. showed that breastfed infants and formula-fed infants had the same levels of plasma L and Z at birth. After 1 month, however, plasma L and Z increased significantly for the breastfed infants and decreased in the formula-fed infants. This implies that retinal levels in formula-fed infants are also low, analogous to the xanthophyll-deprived monkeys in the study of Leung et al. What is the long-term effect of such deprivation?

Of course, it is possible that L and Z actually have no function within the human retina (the null hypothesis) and therefore their absence is inconsequential. This is unlikely. L and Z are highly concentrated within the fovea, making the fovea the most carotenoid-dense region within the body. The foveal region of the retina has exaggerated importance in vision. This small area (measuring only several millimeters, about 2–3% of the whole retina) is greatly magnified by the striate cortex, and most human visual information processing originates from the sensory input initiated from this small retinal region. The fovea is also the most rapidly maturing area within the human retina. MP is an optical filter. If such selective filtering had no purpose, it would only serve to reduce the amount of useful light available to this very critical region of the retina. It is probably also not purely incidental that L and Z are antioxidants found within lipid-rich receptoral outer segments, a region that suffers greatly from oxidative damage, particularly in infants, due to circulatory issues, the resulting oxygen saturation, and increased lenticular transparency. These factors appear to drive a very rapid accumulation of lipofuscin early in life (e.g., L and Z have been shown to prevent photooxidation of A2-PE/A2E, a major and toxic component of lipofuscin), underscoring that early prevention is necessary to prevent disease later.

In addition to preventing cumulative damage that could result in late-stage retinal disease, it is possible that L and Z could have a role in ameliorating retinal diseases that manifest earlier in life (e.g., clinical trials have just begun investigating whether L can help prevent retinopathy of prematurity, formally, retrolental fibroplasias). The question of whether L and Z can actually influence the disease process is just now beginning to be studied. For example, in rodent models, lutein has been shown to linearly decrease the expression of COX-2, which is a pro-inflammatory protein. Local inflammation has been linked to AMD development. For example, recent data suggests that a variant of the gene that encodes complement factor H (an inflammatory regulator) may account for as much as 50% of the AMD cases in the United States. A recent experimental study using rodents found that lutein could significantly suppress choroidal neovascularization. Zeaxanthin, also in rodent models, has been shown to directly inhibit oxidative damage and the production of vascular endothelial growth factors and adhesion molecules induced by diabetes. Macular pigment, measured in vivo in adults, has been shown to be related to reduced retinopathy in diabetic patients.

In general, a very good case can be made for the important role of L and Z in visual development. A large confluence of data, from a variety of sources, supports such a role. Nonetheless, there is, at present, no data on humans showing directly that L and Z do, in fact, influence retinal/visual development. Such data will be difficult to acquire. Obviously, any long-term benefit in
preventing age-related eye disease is going to be challenging to assess (e.g., longitudinal studies covering an entire lifetime are obviously exceedingly difficult). Morphological changes to the retina or RPE that could occur in the absence of L and Z (e.g., for infants fed formulas lacking L and Z) require anatomical study or extremely high-resolution imaging (e.g., spectral domain ocular coherence tomography), which is possible but also difficult. Behavioral testing of visual function (or EEG recordings as the criterion response) could be informative but, as noted, the visual system is able to compensate for many anatomical/physiological changes in order to maintain normal function. Nonetheless, the question is of sufficient importance that even complex and expensive studies are warranted. A possible role of L and Z in influencing pathological processes in the infant retina (e.g., preventing retinopathy of prematurity) appears to also be feasible.

Acknowledgment

Declaration of interest. The author has received speaker’s fees from Wyeth Pharmaceuticals, which manufactures infant formula containing lutein.

REFERENCES


