ANALELE UNIVERSITĂŢII "DUNĂREA DE JOS" GALAŢI
MEDICINĂ
FASCICULA XVII, nr. 2, 2013

REVIEW ARTICLE

MACULAR PIGMENTS AND VISUAL FUNCTION

Sanda Jurja[1], Mihaela Hîncu[2], Liliana Nistorescu[3], Mălina Coman[4]

[1]Department of Ophtalmology, Faculty of Medicine, "Ovidius" University Constanţa, Romania
[2] Department of Histology, Faculty of Medicine, "Ovidius" University Constanţa, Romania
[3] Médica Oncologica S.C., Mexico DF.
[4]Department of Histology, Faculty of Medicine, "Dunărea de Jos" University Galaţi, Romania

jurjasanda@yahoo.com

ABSTRACT

In 1980 lutein and its structural isomer zeaxanthin were identified, as being specific xanthophylls pigments of the retina, located in the layer of Henle fibers in primates. In recent years, the authors have demonstrated an inverse relationship between AMD (Age – related Macular Degeneration) and the level of macular pigment, using the analysis of retinas kept in organ banks.A considerable body of scientific evidence has built up, highlighting the central role of macular pigments in protection against degenerative eye diseases, particularly in AMD. Each year brings its batch of new studies that arouse worldwide enthusiasm and optimism in ophthalmology researchers.The present document proposes a detailed review of current knowledge about these compounds that look increasingly like a future hope for the prevention, and perhaps even the treatment, of AMD.

KEYWORDS*: retina, macular pigments, AMD.*

The macular pigments consist of two xanthophylls from the carotenoid family: lutein and zeaxanthin, and the products of their transformation in the body, notably meso-zeaxanthin.

The carotenoids are a series of natural carbohydrate pigments derived from carotene. More than 600 carotenoids have been isolated and characterized. About fifty of them are found in our food, and about twenty have been identified and measured in human plasma and tissues. They have many different properties: they are vitamin A precursors, free radical trapping molecules, photoprotectors, regulators of intercellular communication and, immunomodulators.

Most carotenoids are markedly hydrophobic, and soluble only in lipids. The xanthophylls stand out by having hydrophilic groups that result in some degree of polarity and allow them to integrate into cell membranes.

Lutein and zeaxanthin are isomers with the formula C40H56O2.

They have some minor differences, which do however have some important biological consequences: the relative orientations of their hydroxyl radicals is a factor that may allow each isomer to be specifically recognized by proteins and may thus influence their selective affinity for certain sites.

Furthermore, both of these molecules have 2 ionone rings; these are both, (β-type rings in zeaxanthin, but lutein has a (β and an e ring. Hydroxyl groups in the (β position are located axially, whereas the ε group is aligned equatorially relative to the plane of the ring.

Thus, lutein and zeaxanthin interact differently with the cell membranes, which allow us to suppose that they may have distinct local actions. Experimentally zeaxanthin is known to lie perpendicularly to the plane of the phospholipids membrane bilayer.

However the position of lutein remains controversial: according to some authors it lies at an angle of between 42 and 23°, whereas others believe it is split between two positions, one of them being the same as that of zeaxanthin, and the other parallel to the membrane; this phenomenon remains to be explained and could be linked to a partial chemical transformation.

It is the numerous double bonds in the polyene chain that give the carotenoids their ability to absorb light.

Finally, it should be noted that, despite their structural similarity to the carotenes, lutein and zeaxanthin have no provitamin A activity.

Macular pigments cannot be synthesized by the body in primates, thus they are obtained entirely from dietary intake.

Lutein is present in yellow and pale green foods: yellow vegetables (corn, yellow peppers, carrots, mustard seeds), vegetables with green leaves (green cabbage, curly kale, spinach, sorrel, fresh parsley, broccoli), and edible flowers such as marigolds. The latter is the source from which lutein is usually extracted for use in dietary additives and supplements. Lutein is also found In milk, poultry, egg yolk derived from animals fed with xanthophyll-rich feed.

Lutein is dominant in most of these sources. Zeaxanthin can also be found in egg yolk, orange juice, spinach juice, cauliflower, corn, millet, and marrow.

Eating 5 portions of fruit and vegetables per day may result in an intake of 5 to 6 mg/day of carotenoids, which is lower than the doses used in studies of the prevention of degenerative ocular diseases.

Lutein and zeaxanthin are absorbed from the duodenum via the chylomicrons. This process requires the presence of bile and pancreatic salts.

The absorption of carotenoids is influenced by the conditions of preparation and storage of food, and by numerous genetic and nutritional factors including sex, body mass index, oxidative stress, dietary fat, and probably others that are still unknown. For instance, carotenoid absorption is increased by a high-fat diet, and reduced by a high intake of fiber or by competition with ß-carotene.

The macular pigments are concentrated in the central region of the macula, to which they impart its characteristic yellow color, their density declining by a factor of 2 around the edge. Lutein dominates around the edge of the macular, whereas zeaxanthin predominates in the foveola, its concentration declining with the distance from this zone.

The concentration of macular pigments is very variable from one individual to another, the amount of carotenoids in the diet being only one of the factors implicated in this variability.

In addition, it is clear that subjects with AMD, who tend to be elderly, have a lower macular pigment density although nothing tells us whether this is the cause or consequence of the disease [1].

Functional properties: protecting the retina

Various observations suggest that the conditions identified as being likely to lower the macular pigment density have also been identified as risk factors for AMD [2].

An accelerated selective loss of visual

sensitivity at short wavelengths has been reported in elderly subjects with a low macular pigment density, suggesting that these pigments may have a protective effect against this functional deterioration, which is known to precede the onset of AMD [3]. It has also been demonstrated that subjects over 60 years of age who have a high macular pigment density, have visual sensitivity (incremental phototopic sensitivity) that is markedly better than that of subjects of the same age with a low density, and comparable to that of young subjects.

It has been known since the 19th century that macular pigments are able to filter light with the highest energy, and therefore the wavelengths that are most dangerous. Thus the macular pigments act as natural optical filters. The absorption spectrum of the pigments ranges from 400 to 550 nm, peaking at 446 nm (blue light) [4].

The filtration of blue and ultraviolet light may have several optical functions: attenuation of dazzle, reduction of chromatic aberrations, better vision of details, heightened contrast. Indeed, light at short wavelengths seems to dominate in the atmosphere, and this leads to a visual veiling effect when objects are viewed from a distance [5].

In addition, blue light generates considerable oxidative stress, and therefore also generates free radicals. The size of the retinal lesions induced by the light increases exponentially as the wavelength decreases. The distribution of the macular pigments means that they reach their highest concentrations in the pre¬receptor axonal bundles, and therefore they absorb the blue light before it reaches the photoreceptors. It has been estimated that the macular pigments attenuate the incident light by 40% [6].

As a result of their long polyunsaturated chains and their hydroxyl radicals, the carotenoids act as excellent traps for free radicals.7

The retina is particularly favorable for the production of reactive species of oxygen. Its external part is rich in polyunsaturated fatty acids, the double bonds of which are sensitive to photo-oxidation; the partial pressure of oxygen is high, similar to that in the plasma (70 mmHg).

A vulnerable substrate in an environment rich in oxygen and absorbing highly energetic blue light constitutes the ideal conditions for oxidative lesions.

The lipid peroxidation of the fatty acids leads to damage of the DNA, the oxidation of the transmembrane proteins and glycoproteins and, more generally, to cellular dysfunction, tissue damage and organic lesions.

The ability of lutein and zeaxanthin to trap the superoxide anion and the hydroxyl radical has been measured by chemiluminescence and by spin resonance.

Vascular effects of xanthophylls

Vascular insufficiency has been reported in both the wet and dry forms of AMD. The protective role of lutein against the progression of early-onset atherosclerosis has been identified in two major epidemiological studies, which have demonstrated a relationship between the levels of xanthophylls in the circulation, and the thickness of the intima and media of the artery walls [8].

All the studies made during these last 30 years since macular pigments were identified, demonstrate the unquestionable effects of supplements or of a high lutein and zeaxanthin diet on the macular pigments, and on visual function in individuals suffering from AMD [9]

However, even though all the studies provide convergent indications, for the moment none provides a definitive answer to the main question: does supplementation with lutein and with zeaxanthin prevent or slow the progress of AMD?

The “gold standard’’ in the assessment of supplementation is the AREDS study (Age-Related Eye Disease Study), a controlled, randomized clinical trial started in 1990 by the National Eye Institute in

the USA, which has enrolled about 5000 patients at 11 centers [10]. This trial has demonstrated a 25% reduction in the risk of the progress after 5 years of AMD towards more advanced stages, and a 19% reduction in the risk of visual deterioration, as a result of a combination of zinc and of antioxidants. Unfortunately, lutein and zeaxanthin were not available in the form of dietary supplements when the study was being designed, and AREDS focused on (β-carotene, which we now know can result in excess mortality in smokers.

Since AREDS, numerous studies already cited have shed light on the role of the carotenoids, xanthophylls, and omega-3 fatty acids in retinal metabolism, allowing us to hope that the combination of these molecules with the antioxidants of AREDS 1 could further improve the results in AMD. This led the US health authorities to implement the AREDS 2 study.

AREDS 2 is as ambitious as its predecessor, and will include 4000 patients between 50 and 85 years of age. All, eyes investigated must have at least some serous drusen or neovessels.

As the "AREDS formula" was demonstrated to be efficacious, this formula will be proposed to all the patients, including the controls in order to avoid any unethical loss of chance. However, β-carotene (15 mg) will be excluded for the smokers, and the subjects will subsequently be randomised to receive in a first level of randomization, either the same dose of zinc as the original AREDS 1 formula (80 mg), or a lower dose (25 mg).

The subjects will then undergo a second randomization into 4 groups, and in addition to the AREDS or modified AREDS formula, will receive new study treatments: lutein, zeaxanthin and/or omega-3.

The results of AREDS 2 will not be available for another few interminable years, and we can be sure that before then, numerous studies will add to the optimism regarding xanthophyll pigments and AMD.

Contribution note:

All the authors have equal contribution to the paper.

References

1.National BPM drugs monograph. Age-Related Eye Disease Study Research Group. A randomized, placebo- controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol 2001; 119 (10): 1417-36.

2. Dwyer JH, Paul-Labrador MJ, Fan J, Shircore AM, Merz CN, Dwyer KM., Progression of carotid intima-media thickness and plasma antioxidants: the Los Angeles Atherosclerosis Study. Arterioscler Thromb Vase Biol 2004 24 (2): 313-9.

3.Hammond BR Jr, Wooten BR, Snodderly DM., Preservation of visual sensitivity of older subjects: association with macular pigment density. Invest Ophthalmol Vis Sci 1998; 39 (2): 397-406.

4.Junghans A, Sies H, Stahl W., Macular pigments lutein and zeaxanthin as blue light filters studied in liposomes. Arch Biochem Biophys 2001; 391 (2): 160-4.

5.Krinsky Nl, Landrum JT, Bone RA., Biologic mechanisms of the protective role of lutein and zeaxanthin in the eye. Annu Rev Nutr 2003; 23: 171 -201.

6.Kvansakul J, Rodriguez-Carmona M, Edgar DF, Barker FM, Kopcke W, Schalch W, Barbur JL., Supplementation with the carotenoids lutein or zeaxanthin improves human visual performance. Ophthalmic Physiol Opt 2006; 26 (4): 362-71.

7.Nolan JM, Stack J, O'Donovan O, Loane E, Beatty S., Risk factors for age related maculopathy are associated with a relative lack of macular pigment. Experimental Eye Research 2007: 84 ,61-74.

8.O'Connel E, Neelam K, Nolan J et al., Macular carotenoids and age-related maculopathy. Ann Acad Med Singapore 2006 ; 35 : 821-830.

9.Ribaya-Mercado JD, Blumberg JB., Lutein and zeaxanthin and their potential roles in disease prevention. J Am Coll Nutr 2004; 23 (6 Suppl): 567S-587S.

10.Whitehead AJ, Mares JA, Danis RP., Macular pigment: a review of current knowledge. Arch Ophthalmol 2006; 124(7): 1038-45.