

The Institute of Biomedical Engineering, George Washington University.

Model of Chronic Photodamage to the Macular and Photoprotective Glasses" or *What sunglasses should you wear?*

RF Bonner, Medical Biophysics, LIMB, National Institutes of Health

The associations of age-related macular degeneration (AMD) with cataracts, prior cataract surgery, cumulative exposure to sunlight, and pigmentation all support the hypothesis that chronic photochemical injury drives macular changes with age and AMD progression. Lipofuscin accumulates with age in the retinal pigment epithelium (RPE) and colocalizes with acute photosensitization of reactive oxygen intermediates (ROI) in the primate retina. Lipofuscin granules contain at least 10 different fluorescent photochemical products including A2E (N-retinylidene-N-retinylethanolamine), its epoxides, and other as yet chemically unidentified A2E-related fluorophores. The precursors of these fluorophores originate from reactions of all-trans-retinal within rod outer segment (ROS) discs during periods associated with significant rhodopsin bleaching (i.e., normal daylight). Although RPE lysosomal processing digests over 99% of the shed ROS contents, A2E and related fluorophores are not digested but are concentrated in lipofuscin granules. By age 60 years, the average concentration of A2E within RPE cells reaches ~400 micromolar in normal eyes. However, A2E is toxic to cellular membranes at much lower concentrations. We hypothesize that segregation of A2E into lipofuscin granules and prevention of its redistribution into critical membranes is required for RPE health.

We sought to model the normal accumulation of potentially damaging photoproducts with age in the RPE as well as changes induced by external spectral filtering of light reaching the macula. We developed a biophysical model using normal values of pupil size, lens transmission, and rod dark adaptation to determine average retinal spectral irradiance and resulting production of A2E-related species in the ROS and in the RPE as a function of age and ambient light intensity. Our model predicts a decline of about one third in the action spectra-weighted short-wavelength macular irradiance with each decade of life and a nearly constant production rate of A2E-related fluorophores in the RPE during the first 60 years (falling significantly thereafter). A similar age dependence of total lipofuscin granule volume and total fluorescence per RPE cell has been reported in human cadaver eyes. With age, the rate of lipofuscin increase is slower than the rate of decrease in short-wavelength macular irradiance in the phakic eye, consequently ROI photosensitization in the RPE should also fall with increasing age. Photo-oxidative stress in the outer retina might arise from the smaller amounts of A2E-related fluorophores observed in critical membranes of the RPE/BM complex. However, if the RPE/BM complex were the site of photo-oxidative injury driving AMD progression, the magnitude and rate of this oxidative injury would be expected to increase dramatically following cataract removal and intraocular lens (IOL) implantation.

Consequently, we propose a novel hypothesis that photochemically-induced singlet oxygen generation within RPE lipofuscin granules induces the chemical alteration of accumulating A2E, thereby limiting the steady-state levels of A2E ($[A2E]_{ss}$) in the RPE, the redistribution of A2E into retinal membranes, and A2E chemical toxicity. Singlet oxygen reacts with its A2E to form A2E epoxides which then react to form increasingly complex cross-linked molecules. As short-wavelength macular irradiance falls with age, the rate of A2E photo-oxidation falls approximately up to 20-fold, causing $[A2E]_{ss}$ in the normal phakic eye to increase even as rod bleaching and A2E production decrease. Our theoretical model of macular aging reproduces the normal age dependence of lipofuscin and A2E. It provides a primary cytotoxic mechanism in which, once A2E reaches a threshold concentration in the RPE cell, A2E redistribution into critical membranes causes damage with or without additional photo-activation. The model also predicts that in normal eyes nearly constant levels of A2E are maintained at a given age and lens color, irrespective of total ambient light exposure. It is primarily the yellowing of the lens with age that distorts the original spectral balance between rate of production and rate of photo-oxidation found in youth, and allows the $[A2E]_{ss}$ to rise with age. If our model is correct, then restoring or optimizing the spectral balance by wearing external spectrally selective sunglasses could significantly lower A2E levels and may prevent associated macular degenerations.

Noninvasive, quantitative imaging of retinal autofluorescence associated with A2E levels could permit clinical validation of our predictions of both the photochemical changes associated with lens status and the benefits of specific spectral photo-protective filters. We have designed vermilion sunglasses which should optimally reduce both rod activation in bright ambient light and the accumulation of toxic photoproducts in the RPE. In collaboration with the NEI and the Eye Institute of the Russian Academy of Medicine, we are designing clinical studies of the effects of such filters on A2E levels in the RPE and on progression of both early and moderate AMD following cataract surgery and IOL implantation and in young patients with Stargardt's macular dystrophy.

Meyers SM, Ostrovsky MA, Bonner RF (2004) A model of spectral filtering to reduce photochemical damage in age-related macular degeneration. *Transactions of American Ophthalmological Society*. 2004;102:83-95.

The seminar will take place in room 738, Phillips hall, Academic Center, 801 22nd St. Washington, DC. Friday October 21st, At 1:00 pm.