Spare the Rods, Save the Cones in Aging and Age-related Maculopathy

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A ge-related maculopathy (ARM) is the leading cause of untreatable new vision loss among older adults in the United States and other industrialized countries.\(^1\) ARM is a heterogeneous disorder affecting the retinal pigment epithelium (RPE), Bruch’s membrane, and choriocapillaris (the RPE/Bruch’s membrane complex).\(^2\) Early ARM is characterized by minor-to-moderate vision loss associated with focal or diffuse sub-RPE debris and changes in RPE pigmentation. Late ARM is characterized by severe vision loss associated with extensive RPE atrophy with or without the sequelae of choroidal neovascularization. Better understanding of early ARM will help guide development of better treatments or prevention for late ARM.\(^3\) As reviewed elsewhere,\(^4\) recent progress has been made in understanding the demographics and natural history of early ARM and identifying genetic mutations that produce degeneration of the macula in young adults.

In this review we focus on recent studies of visual function in elderly persons and in patients with ARM\(^5\) that complement previous histopathologic studies of photoreceptor loss in these conditions.\(^6\) The RPE, Bruch’s membrane, and the choroid are vitally important for the well-being of photoreceptors. It is the dysfunction and death of photoreceptors, through an atrophic process or a neovascular event, that account for the vision loss associated with ARM. Therefore, photoreceptor health, assessed functionally in living patients, is the most direct bioassay of the significance of changes in the RPE/Bruch’s membrane complex, which may not be revealed by standard imaging techniques such as fundus photography and fluorescein angiography until late in ARM or not at all. The functional studies reviewed herein were facilitated by the development of standard fundus grading systems, which permit comparison of results from patients at similar stages of ARM across disciplines,\(^7\) and a better understanding of the mechanisms underlying normal human dark adaptation,\(^8\) which informs the interpretation of age- and disease-related changes.

For the purposes of discussion, we consider the human macula an area 6 mm in diameter, or 21.5° of visual angle, centered on the fovea.\(^9\) The small cone-dominated fovea, only 0.8 mm (2.75°) in diameter, is surrounded by a rod-dominated parafovea.\(^10\) In young adults, rods outnumber cones in the macula by 9:1. In the entire eye, rods outnumber cones 20:1, so the macula can be considered cone-enriched but not cone-dominated. In maculas of older adults lacking grossly visible drusen and pigmentary change (i.e., they do not have ARM), the number of cones in the cone-dominated part of the macula is stable at approximately 32,000 through the ninth decade.\(^11\) In contrast the number of rods in the macula of the same eyes decreases by 30%. The greatest loss occurs in the parafovea (1-3 mm from the fovea or 3.5-10° from fixation), with loss at more peripheral locations uncertain. The location of age-related rod loss differs from the region where rod density is maximal (4-6 mm from the fovea) and from the region where the cell loss associated with retinitis pigmentosa typically begins (8-10 mm from the fovea). With respect to photoreceptor topography at different stages of ARM, the foveal cone mosaic of eyes with large drusen and thick basal deposits appeared surprisingly similar to that of age-matched controls,\(^12\) and the total number of foveal cones was normal. In contrast, in the parafovea, cones appeared large and misshapen, and few rods remained. Furthermore, in eyes with late ARM, virtually all surviving photoreceptors in the macula were cones, a reversal of the normal predominance of rods. Preferential loss of rods over cones was found in 3 of 4 of early and late ARM eyes examined (Medeiros NE, Curcio CA, unpublished results, April 2000).

Psychophysical studies of photopic and scotopic sensitivity have identified functional correlates to the histopathologic findings that rods are at risk for degeneration in aging and ARM. Older adults with good macular health, as assessed by grading of fundus appearance, have reduced rod-mediated light sensitivity, and the magnitude of this scotopic sensitivity impairment is similar throughout the parafoveal region.\(^13\) Scotopic impairment is greater than photopic impairment in 80% of older adults evaluated, and, furthermore, scotopic sensitivity declines throughout adulthood faster than photopic sensitivity declines.\(^14\) With respect to ARM patients, mean scotopic sensitivity within 18° of fixation was significantly lower in early ARM patients as a group than in age-matched controls without ARM.\(^15\) The topography of sensitivity loss in the central 36° of the visual field varied considerably among individual patients with early ARM. Of the patients with reduced light sensitivity in this region, 59% showed reduced scotopic sensitivity, 27% showed both reduced scotopic and photopic sensitivity, and only 14% had reduced photopic sensitivity. Thus, in almost all (87%) of these patients, the magnitude of mean scotopic sensitivity loss exceeded the magnitude of mean photopic sensitivity loss. The ARM-related deficit in scotopic sensitivity was most severe within 9° of fixation, suggesting that the emergence of regional sensitivity impairments within the parafovea may be an early sign of ARM.

In addition to the reduced sensitivity of the rod system, the kinetics of rod function also change with aging and...
The classic dark adaptation function describes the recovery of sensitivity after a bright flash of light and consists of an early portion exclusively mediated by cones, a transition to rod function (rod-cone break), and a later portion exclusively mediated by rods. In older adults with good macular health, as assessed by grading of fundus appearance, the rod-mediated portion of dark adaptation is significantly slower than younger adults. During adulthood, the time constant of the rod-mediated component of dark adaptation increases by approximately 8 seconds per decade. Rod-mediated dark adaptation is not correlated with scotopic sensitivity in these patients, indicating that the mechanisms underlying these two aspects of rod vision are not identical. In early ARM patients, rod-mediated dark adaptation is much slower (13 minutes on average) than in normal age-matched controls. Consistent with the pattern of scotopic sensitivity loss described above, delays in rod-mediated dark adaptation are greater than those for cone-mediated dark adaptation in ARM. Delayed rod-mediated dark adaptation occurs in AMD patients with normal scotopic sensitivity, whereas the opposite pattern, normal dark adaptation with poor scotopic sensitivity, is rare.

Taken together, these new functional studies extend the earlier histopathologic results indicating that photoreceptor degeneration and loss occurs well before disease in the RPE/Bruch's membrane complex progresses to late ARM. Further, the loss in aging, early ARM, and late ARM is greater for rods than for cones. We emphasize that understanding how visual function changes during ARM progression will require prospective studies to complement the cross-sectional studies described here, as well as determination of the most meaningful fundus feature(s) for monitoring the rate of progression. We also emphasize that subsets of ARM patients differing by their relative impairment of rod and cone vision are likely to emerge.

Even disorders involving single gene defects can produce multiple clinical entities with different effects on rods and cones, and ARM doubtlessly involves an even more complex interplay of genetic and environmental factors.

Nevertheless, our data suggest three phenomena that need to be understood mechanistically: the slowing of rod-mediated dark adaptation in aging and ARM, the qualitative similarity of aging and ARM effects on photoreceptor function, and the earlier involvement of rods relative to cones. How could aging and disease-related changes in the RPE/Bruch's membrane complex affect photoreceptor function and survival in this manner?

The rod-mediated portion of dark adaptation is thought to represent the regeneration of rhodopsin and other aspects of recovery during the visual cycle. The visual cycle comprises biochemical reactions in the RPE and photoreceptors that produce the vitamin A derivative 11-cis-retinal from all-trans precursors delivered across Bruch's membrane by plasma proteins. Not only is 11-cis retinal required to regenerate the photoreceptor pigment after bleaching by light, but retinoids are also required for photoreceptor survival. Vitamin A deprivation leads to outer segment degeneration and photoreceptor death in vivo and accelerated degeneration of photoreceptors with mutant rhodopsins in vitro. Lack of vitamin A affects primarily rods but eventually impacts cones as well. Cones have a different retinoid delivery pathway, demonstrated by the normal cone electroretinogram in mice lacking a key visual cycle component (RPE65 gene product) and measurable rod sensitivity.

According to a recent theoretical model of dark adaptation, slowed rod-mediated recovery implies limited availability to the rods of 11-cis-retinal, resulting in the accumulation of intermediates that actively desensitize the retina. Delayed dark adaptation is a hallmark of systemic vitamin A deficiency and genetic disorders affecting visual cycle components or the retinoid transport system. It is therefore possible that age- or disease-related changes in photoreceptor or RPE-based components of the visual cycle alter precursor uptake, enzyme activity, or substrate availability, resulting in a localized scarcity of 11-cis retinal to the photoreceptors. Alternatively, but more likely on the basis of current data, localized scarcity of 11-cis-retinal could result from reduced retinoid transfer from the blood to the RPE. Characteristic debris accumulates within Bruch's membrane from early adulthood through senescence, accompanied by reduced collagen solubility and deposition of neutral lipids. Additional material accumulates between the RPE and Bruch's membrane in older adults and in ARM patients. Together, these processes are hypothesized to slow the transfer of fluids and essential nutrients across Bruch's membrane.

Our detailed analysis of photoreceptor function suggests that an essential nutrient reduced in aging and ARM eyes is a retinoid derivative.

Thus, the retinoid deficiency hypothesis potentially explains slowing of the rod-mediated component of dark adaptation and the earlier involvement of rods relative to cones in aging and ARM. It also links photoreceptor degeneration with age-related changes in Bruch's membrane and the characteristic lesions of ARM. The plausibility of this mechanism is reinforced by findings that rod dysfunction and degeneration occur in various late-onset conditions with sub-RPE deposits and dark adaptation improves in patients with Sorsby's fundus dystrophy, characterized by thick sub-RPE deposits, who received vitamin A supplements. Clearly, there are still significant gaps in our knowledge that warrant further study. The long-term effects of partial vitamin A depletion, which is more relevant to aging and disease than complete deficiency, are unknown. The retinoid delivery system to cones is poorly understood, but should it involve the neurosensory retina, cones may be less vulnerable to reduced transport across Bruch's membrane and the RPE than rods. Finally, it is possible that changes elsewhere in the visual cycle exacerbate problems due to changes in Bruch's membrane barrier properties. For example, missense mutations in single alleles of the Stargardt's disease-causing ABCR gene are hypothesized to increase susceptibility to ARM. Perhaps an abnormality in the ABCR gene product, a photoreceptor-based retinoid transporter, results in the accumulation of desensitizing intermediates in addition to those resulting from insufficient 11-cis retinal.

The hypothesis that local retinoid deficiency contributes toward photoreceptor loss is not incompatible with other hypotheses regarding the pathogenesis of ARM, which is a complex, multifactorial disease. For example, smoking, family history, antioxidant status, cardiovascular disease, and apolipoprotein genotype have been identified as risk factors for late ARM. These factors as well as others may operate in concert with local retinoid deficiency to produce retinal degeneration. Regardless of the specific disease mechanism proposed, we propose that early selective rod vulnerability in ARM is a salient feature that theories of pathogenesis should attempt to explain. Current model systems include early onset macular degenerations that like ARM feature sub-RPE deposits, RPE atrophy, and choroidal neovascularization and mice bear-
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ing the causative genetic mutations in these conditions. The relative rates of rod and cone dysfunction, a signature characteristic for any disease affecting photoreceptors, should be among the criteria for determining the appropriateness of these models for ARM research.

Although mechanistic studies are still underway, our results have immediate implications for the choice of clinical tests and for the timing of interventions in ARM patients. Early detection of ARM is an important goal, because it will permit intervention at early stages when the prognosis for preservation or restoration of function is best. The data gathered so far are consistent with the hypothesis that tests of rod function, particularly those that probe dynamic properties, will permit detection of ARM at earlier stages than tests of cone function in many patients. Conversely, tests of visual acuity, currently the standard clinical assessment for the elderly and ARM patients, may underestimate the degree of visual dysfunction by using high contrast stimuli presented in bright light to foveal cones. Therefore, developing a test of rod kinetics that is more practical and less time-consuming than classic dark adaptation for use in a clinical setting should be a priority. Our results also have implications for timing of interventions to maximize the survival of both cones and rods. Rod photoreceptors not only serve as an early indicator of impending cone dysfunction, but they also contribute in important ways to daily visual behavior and therefore are worth saving in their own right. Although clinical assessment emphasizes foveal cone vision, older patients including those with ARM report difficulty with activities performed at night and under low illumination (e.g., driving, reading). An early intervention may not only save the carrierc-degenerating rods but also indirectly contribute to preserving the later-degenerating cones, because rods produce a diffusible substance essential for cone survival. Sparing the rods may thus be the right strategy for saving the cones.

References

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