HHS Public Access

Author manuscript

Arch Ophthalmol. Author manuscript; available in PMC 2016 May 11.

Published in final edited form as:

Arch Ophthalmol. 2010 February ; 128(2): 244–245. doi:10.1001/archophthalmol.2009.399.

Intense Cyclic Light–Induced Retinal Degeneration in Rats

Jacque L. Duncan, MD and **Matthew M. LaVail, PhD**

Departments of Ophthalmology (Drs Duncan and LaVail) and Anatomy (Dr LaVail), University of California–San Francisco, San Francisco

Retinal degenerations, including retinitis pigmentosa and age-related macular degeneration (AMD), affect the sight of nearly 10 million people in the United States, and treatment options for those affected are limited to nonexistent. The understanding of retinal degenerations has been greatly enhanced through the use of environmental exposures that result in damage to photoreceptors or the Bruch membrane. Environmentally induced retinal degenerations, such as exposure to intense constant light or laser photocoagulation, in normal rodents[1] have provided useful models for the study of retinal degeneration and choroidal neovascularization. Studies of light exposure in rodents with mutations that cause photoreceptor degeneration have provided further insight into the complex relationship between light exposure and retinal degeneration (reviewed by Wenzel et al[2] and Paskowitz et al[3]).

Albert and colleagues[4] present a study describing photoreceptor degeneration in normal Wistar and Sprague-Dawley (SD) rats exposed to intense levels of light on a cyclic basis (12 hours on, 12 hours off). The authors are to be commended for their characterization of a new model of environmentally induced retinal degeneration and the clear identification of strain differences in the susceptibility to light-induced damage. In their article, the authors describe the development of photoreceptor degeneration after exposure to cyclic bright light (3000 lux) for periods ranging from 1 to 6 months. The intensity of the light used exceeds the control exposure by a factor of about 43-fold (standard exposure is about 70 lux). The novel aspect of this method is the use of cyclic rather than constant light. The article describes loss of the photoreceptor outer nuclear and inner and outer segment layers beginning as early as 1 month after the onset of intense cyclic light exposure in Wistar rats. After 3 months, the Wistar rats exposed to intense cyclic light demonstrated complete loss of the photoreceptor layers as well as loss of part of the inner nuclear layer and frequently developed neovascularization beneath the retina (Figure 2B), while by 6 months, neovascularization was observed to extend from the subretinal space to anastomose with the retinal vessels (Figures 2E and F). Less extensive damage was observed in SD rats exposed to intense cyclic light for 6 months (Figures 5A–C). The authors demonstrate oxidative damage using immunochemical stains, including 4-hydroxy-2-nonenal– and nitrotyrosine-modified proteins. This new model of environmentally induced retinal degeneration may be effective

Correspondence: Dr Duncan, University of California–San Francisco, 10 Koret Way, Room K301, San Francisco, CA 94143, (duncanj@vision.ucsf.edu).

Financial Disclosure: None reported.

for the study of cyclic intense light on photoreceptor survival and may also provide insight into retinal neovascularization.

However, the authors argue that intense cyclic light–induced retinal degeneration provides a useful model of AMD, the leading cause of irreversible blindness in the United States. Vision loss in patients with AMD often results from choroidal neovascularization, in which new vessels originating from the choriocapillaris extend through the Bruch membrane beneath the retinal pigment epithelium (RPE) or retina, causing hemorrhage, subretinal fluid, subretinal fibrosis, and subsequent death of the overlying photoreceptors. Rats exposed to intense cyclic light initially develop degeneration of the photoreceptors, followed by subsequent development of new vessels in the subretinal space. The development of abnormal retinal vessels following extensive photoreceptor degeneration has been described in histological studies of human eyes with retinal degeneration[5] as well as in many rodent models of retinal degeneration in which neovascularization of the RPE was from retinal capillaries and not the choroid.[6–8]

The current study provides a well-characterized example of neovascularization in eyes with extensive photoreceptor loss. However, the authors refer to the abnormal vessels as *choroidal* neovascularization throughout the article, but do not convincingly demonstrate that the new vessels originate from the choroid. In fact, subretinal neovascularization (of the RPE) is shown in the presence of an intact Bruch membrane in Figure 1F and in Figure 5A (as described in the legend to Figure 5A), suggesting that the new subretinal vessels did not originate from the choriocapillaris through the damaged Bruch membrane. It is presumptive to refer to these new vessels as choroidal neovascularization if they cannot be shown to originate from the choroid. Techniques such as those used by Wang et al,[9] which use serial semi-thin plastic sections to trace the origin of individual blood vessels from the choroid through breaks in the Bruch membrane, are necessary to demonstrate the choroidal origin of choroidal neovascularization. The 8-μm paraffin-embedded sections shown in the present article are insufficient to distinguish the origin of these vessels being from either the choroid, as the authors state, or from the deep capillary plexus of the retina, demonstrated by others to be the origin of subretinal neovascularization after photoreceptor death in inherited models of retinal degeneration using 0.5- or 1-μm plastic histological sections. Most of the illustrations in the article are similar to those published in many inherited and light-induced retinal degenerations where retinal capillaries invade the RPE.[6–8]

The authors contend that because epidemiological studies have demonstrated a possible association between light exposure and AMD[10] and because many studies suggest that there is a relationship between oxidative damage and AMD,[11–13] retinal degeneration induced by intense cyclic light exposure provides an appropriate model for AMD. However, AMD is characterized by the subretinal accumulation of lipofuscin, a lipid-containing, autofluorescent substance within and beneath the RPE. Lipofuscin deposits form drusen, the hallmark of AMD, and are felt to play an important role in the pathogenesis of vision loss in AMD. It is therefore concerning that the model described by Albert and associates does not appear to be associated with lipofuscin accumulation. Although the discussion refers to the “sub-RPE deposition of amorphous material similar to basal laminar deposits described in the literature,” the deposits are not shown in the figures. In summary, the model Albert and

colleagues described is not associated with the hallmark feature of AMD—lipofuscin accumulation— and the neovascular changes described do not convincingly originate from the choroid. Therefore, although intense cyclic light exposure likely will provide another useful model of environmentally induced retinal degeneration, the model has features that may limit its relevance to the study of human exudative AMD.

REFERENCES

1. Tobe T, Ortega S, Luna JD, et al. Targeted disruption of the FGF2 gene does not prevent choroidal neovascularization in a murine model. Am J Pathol. 1998; 153(5):1641–1646. [PubMed: 9811357]
2. Wenzel A, Grimm C, Samardzija M, Reme CE. Molecular mechanisms of light-induced photoreceptor apoptosis and neuroprotection for retinal degeneration. Prog Retin Eye Res. 2005; 24(2):275–306. [PubMed: 15610977]
3. Paskowitz DM, LaVail MM, Duncan JL. Light and inherited retinal degeneration. Br J Ophthalmol. 2006; 90(8):1060–1066. [PubMed: 16707518]
4. Albert DM, Neekhra A, Wang S, et al. Development of choroidal neovascularization in rats with advanced intense cyclic light–induced retinal degeneration. Arch Ophthalmol. 2010; 128(2):212–222. [PubMed: 20142545]
5. Milam AH, Li ZY, Fariss RN. Histopathology of the human retina in retinitis pigmentosa. Prog Retin Eye Res. 1998; 17(2):175–205. [PubMed: 9695792]
6. Burns MS, Tyler NK. Selective neovascularization of the retinal pigment epithelium in rat photoreceptor degeneration *in vivo*. Curr Eye Res. 1990; 9(11):1061–1075. [PubMed: 1710178]
7. Nishikawa S, LaVail MM. Neovascularization of the RPE: temporal differences in mice with rod photoreceptor gene defects. Exp Eye Res. 1998; 67(5):509–515. [PubMed: 9878212]
8. Pennesi ME, Nishikawa S, Matthes MT, Yasumura D, LaVail MM. The relationship of photoreceptor degeneration to retinal vascular development and loss in mutant rhodopsin transgenic and RCS rats. Exp Eye Res. 2008; 87(6):561–570. [PubMed: 18848932]
9. Wang F, Rendahl KG, Manning WC, Quiroz D, Coyne M, Miller SS. AAV-mediated expression of vascular endothelial growth factor induces choroidal neovascularization in rat. Invest Ophthalmol Vis Sci. 2003; 44(2):781–790. [PubMed: 12556414]
10. Cruickshanks KJ, Klein R, Klein BE. Sunlight and age-related macular degeneration: The Beaver Dam Eye Study. Arch Ophthalmol. 1993; 111(4):514–518. [PubMed: 8470986]
11. Beatty S, Koh H, Phil M, Henson D, Boulton M. The role of oxidative stress in the pathogenesis of age-related macular degeneration. Surv Ophthalmol. 2000; 45(2):115–134. [PubMed: 11033038]
12. Hollyfield JG, Bonilha VL, Rayborn ME, et al. Oxidative damage-induced inflammation initiates age-related macular degeneration. Nat Med. 2008; 14(2):194–198. [PubMed: 18223656]
13. Winkler BS, Boulton ME, Gottsch JD, Sternberg P. Oxidative damage and age-related macular degeneration. Mol Vis. 1999; 5:32. [PubMed: 10562656]