PERSPECTIVE

Light and inherited retinal degeneration

D M Paskowitz, M M LaVail, J L Duncan

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Light deprivation has long been considered a potential treatment for patients with inherited retinal degenerative diseases, but no therapeutic benefit has been demonstrated to date. In the few clinical studies that have addressed this issue, the underlying mutations were unknown. Our rapidly expanding knowledge of the genes and mechanisms involved in retinal degeneration have made it possible to reconsider the potential value of light restriction in specific genetic contexts. This review summarises the clinical evidence for a modifying role of light exposure in retinal degeneration and experimental evidence from animal models, focusing on retinitis pigmentosa with regional degeneration, Oguchi disease, and Stargardt macular dystrophy. These cases illustrate distinct pathophysiological roles for light, and suggest that light restriction may benefit carefully defined subsets of patients.

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I t was first suggested over a century ago that light exposure might modify the course of disease in patients with retinal degeneration,[1] implying a possible therapeutic benefit of light deprivation. Four small studies have investigated this hypothesis in patients with retinitis pigmentosa (RP), a group of hereditary retinal dystrophies characterised by progressive photoreceptor degeneration, night blindness, visual field constriction, and electroretinographic (ERG) abnormalities, with rods affected earlier than cones. Berson[2] used an opaque scleral contact lens to occlude one eye for 6–8 hours per day for 5 years in two young adults with RP. Progression of disease was symmetrical in both patients.[2] A shorter trial using monocular sunglasses worn by three children with RP for 3 months also showed no protection.[1]

A third report described a man with RP who had sustained trauma to the anterior segment of the right eye at age 7, resulting in occlusion of the pupil by a thick membrane. Surgical correction and physiological testing 42 years later revealed that the retina had been protected by a 1.2 log unit filter. Fundus examination and ERG offered no evidence that degeneration had been slowed in the occluded eye.[3] In the fourth study, 13 RP patients wore a brown contact lens with low transmission on one eye for 1–3 years. In eight patients, the rate of visual field loss was reported to be slower in the light restricted eye.[4] However, other measures of visual function were not used, and these data await confirmation.

No benefit of light deprivation has been convincingly demonstrated in patients with RP.

However, the underlying genetic defect was not defined for any of the patients in these trials. It is now known that RP exhibits extraordinary genetic heterogeneity (http://www.sph.uth.tmc.edu/Retnet), and it remains possible that light deprivation could be beneficial for patients with certain mutations. This idea has received considerable support in recent years from animal studies. For some models of retinal degeneration, the progression of disease is indeed slowed by darkness, accelerated by bright light, or both. Several of these animal models carry mutations also found in patients.

Table 1 lists mammalian animal models of inherited retinal degeneration for which the effects of light have been assessed in peer reviewed studies. For three well characterised groups of models, the animal data are discussed in detail below, together with studies of patients carrying mutations in the corresponding genes. The literature on retinal damage by constant light in wild type albino rodents has been reviewed recently[5][6] and will not be discussed further. Mutations that cause light dependent retinal degeneration in the fruit fly *Drosophila melanogaster*[7] are also outside the scope of this paper.

AUTOSOMAL DOMINANT RP: RHODOPSIN MUTATIONS ASSOCIATED WITH REGIONAL DEGENERATION

Rhodopsin (*RHO*) mutations are a common cause of autosomal dominant RP (ADRP), accounting for some 25% of families in the United States.[76][77] The change of proline to histidine at codon 23 (Pro23His, P23H) is found in the most common American mutant allele.[35][78] Several mutations including P23H cause a distinctive phenotype classified by Cideciyan and colleagues as class B1.[79] Typical features include slower progression and better visual function compared to other forms of ADRP; more rapid degeneration in the inferior than in the superior retina, correlating with earlier loss of the superior visual field; and delayed dark adaptation.[79–90] However, some patients with the P23H mutation have a more uniform distribution of relatively mild degeneration, possibly representing an early stage of disease.[79]

It has been proposed that the faster progression of disease in the inferior retina may result from a modifying effect of light. This argument

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See end of article for authors' affiliations

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Correspondence to:
Jacque L Duncan, MD,
Beckman Vision Center,
UCSF School of Medicine,
San Francisco, CA
94143–0730, USA;
duncanj@vision.ucsf.edu

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Abbreviations: ADRP, autosomal dominant retinitis pigmentosa; ERG, electroretinography; *N*-ret-PE, *N*-retinylidene-phosphatidylethanolamine; *RHO*, rhodopsin; RK, rhodopsin kinase; RmP, rim protein; RP, retinitis pigmentosa; RPE, retinal pigment epithelium; STGD, Stargardt disease

Table 1 Effects of light exposure on animal models of retinal degeneration

Gene product (symbol)	Mutation	Species	Findings*	Human counterpart†
Modified by light				
Arrestin (Sag)	Knockout[8]	Mouse	Protection by DR[9] Exacerbation by light[9][10]	Oguchi disease,[11] ARRP[12]
ATP/GTP binding protein 1 (Agtpbp1, Nna1)	Putative regulatory mutation (pcd[1J])[13]	Mouse	Exacerbation by light[14]	Unknown
Crumbs homologue 1 (Crb1)	Knockout[15]	Mouse	Exacerbation by light[15]	LCA, RP12, RPCEV,[16] PPCA[17]
Mertk (Mertk)	Deletion[18]	Rat	Protection by DR[19–21] Exacerbation by light[21–23]	ARRP[24]
Rds/peripherin (Rds)	Insertion[25]	Mouse	No protection by DR[26] Exacerbation by light[26]	Several forms of retinal dystrophy[27]
Rhodopsin (RHO)	Thr4Arg (T4R)[28]	Dog	Exacerbation by light[29]	ADRP[30][31]
Rhodopsin (Rho)	Val20Gly, Pro23His, Pro27Leu (VPP)[32]	Mouse (tg)	Protection by DR[33] Exacerbation by light[34]	ADRP[35]
Rhodopsin (Rho)	Pro23His (P23H)[36][37]	Rat (tg)	Protection by DR[38] Exacerbation by light[38–42]	ADRP[35]
Rhodopsin kinase (Grk1, Rhok)	Knockout[43]	Mouse	Protection by DR[43] Exacerbation by light[10][43]	Oguchi disease[44]
Rim protein (Abca4, Abcr)	Knockout[45]	Mouse	Prevention of A2E accumulation by DR[46]	Stargardt disease and other retinal dystrophies[47]
RPE65 (Rpe65)	Knockout[48]	Mouse	Protection by DR[49] Resistance to light damage[50]	LCA, early onset severe retinal dystrophy[51]
Solute carrier family 6, taurine transporter (Slc6a6, Taut)	Knockout[52]	Mouse	Protection by DR[53]	Unknown
Tubby (Tub)	Splice donor site mutation[54][55]	Mouse	Protection by DR[56]	ARRP,[57][58] LCA[59]‡
Unknown	Nervous mutation (nr)[60]	Mouse	No protection by DR[61] Exacerbation by light[14]	Unknown
Not modified by light				
Ceroid lipofuscinosis, neuronal 8 (Cln8)	Frameshift[62]	Mouse	No protection by DR[63]	NCL-8,[62] vLINCL[64]
Microphthalmia associated transcription factor (Mitf)	Asp222Asn (D222N)[65]	Mouse	No protection by DR[66]	Waardenburg syndrome type II,[67] Tietz syndrome[68]
Rhodopsin (Rho)	Lys296Glu (K296E)[69]	Mouse (tg)	No protection by DR[69]	ADRP[70]
Rhodopsin (Rho)	Ser334ter[71]	Rat (tg)	No protection by DR[38][72] No exacerbation by light in most experiments[38][41][73]	ADRP§
Rhodopsin (Rho)	Knockout[74]	Mouse	Resistance to light damage[50]	ARRP[75]

ADRP, autosomal dominant retinitis pigmentosa; ARRP, autosomal recessive retinitis pigmentosa; DR, dark rearing; LCA, Leber congenital amaurosis; NCL, neuronal ceroid lipofuscinosis; PPCA, pigmented paravenous chorioretinal atrophy; RP12, retinitis pigmentosa type 12; RPCEV, retinitis pigmentosa with Coats-like exudative vasculopathy; tg, transgenic; vLINCL, Turkish variant late infantile neuronal ceroid lipofuscinosis.

*''Protection'' does not necessarily imply complete rescue. Light exposure protocols vary among studies, but ''exacerbation by light'' refers to accelerated degeneration in light brighter than that used for routine animal housing in a given study. Because sufficiently bright light can cause retinal damage in wild type animals,[6] only cases in which exacerbation of degeneration significantly exceeds the damage produced in wild type controls by the same light regimen are included.

†Except where noted, the listed human diseases arise from mutations in genes orthologous to those mutated in the respective animal models. Phenotypes may not correspond precisely. Where more than one human disease is listed, these represent alternative phenotypes arising from mutations in the same gene.

‡These phenotypes are associated with mutations in the human gene TULP1 (Tubby-like protein 1), which is related to mouse Tub, but not orthologous.

§Ser334ter transgenic rats exhibit dominant retinal degeneration, but this mutation has not been reported in human RP.

holds that since most light sources are located in the superior visual field, the inferior retina experiences greater exposure, accelerating the degeneration.[29][79][80][90–92] Additional clinical evidence for this hypothesis has come from a case series describing two families with the P23H mutation.[80] In one family, a 28 year old man with an 8 year history of bright light exposure as a lifeguard and ski instructor had more advanced disease than his 52 year old mother. In the other family, one patient had atypical disease, with preferential loss of the inferior visual field and more advanced fundus changes in the superior retina. This patient had served in the navy, and had a history of bright light exposure in the inferior visual field from sunlight reflected from water and welding repairs to flooring.

Studies of three animal models of class B1 RP have demonstrated modification of degeneration by light. ''VPP mice'' carry a murine opsin transgene with the P23H mutation, together with two other mutations (Val20Gly and Pro27Leu) not known to be pathogenic. Like class B1 patients, they exhibit dominantly inherited retinal degeneration,[32] more rapid photoreceptor loss in the inferior retina

when housed with overhead lighting,[33] and delayed dark adaptation.[93] Rearing VPP mice in the dark slows, but does not completely prevent, the degeneration. Dark rearing also eliminates the difference between superior and inferior retina, supporting the conclusion that this difference is due to greater light exposure in the inferior retina.[33] A 24 hour exposure to bright light that has no effect on wild type littermates accelerates the degeneration in VPP mice.[34]

Analysis of rats carrying a murine opsin transgene with the P23H mutation has yielded results similar to those from the VPP mice. Dark rearing slows the rate of degeneration in P23H rats,[38] while exposure to bright light accelerates it.[38–41] Degeneration is slower in very dim light compared to moderate room light.[42]

The third animal model offers a particularly dramatic example of the effects of light. A naturally occurring dominant retinal degeneration in English Mastiff dogs is caused by a RHO mutation that changes threonine to arginine in the fourth codon (Thr4Arg, T4R).[28] This mutant is likely to have properties similar to Thr4Lys (replacing threonine with lysine, which like arginine is positively charged at

physiological pH), a mutation identified in human ADRP with regional degeneration.[30][31] The T4R dog resembles human class B1 RP in having delayed dark adaptation after bright flashes, and regional photoreceptor loss.[28] Cideciyan and colleagues used this large animal model to ask whether light exposure at levels routinely encountered in ophthalmological clinical settings could accelerate the course of disease.[29] They found that standard fundus photography in young dogs, before the usual onset of photoreceptor loss in this model, caused rapid and severe degeneration restricted to the photographed areas, with a sharp boundary separating damaged from normal appearing retina. Similar results were obtained with prolonged focal light exposures comparable to indirect ophthalmoscopy, but not with a standard ERG protocol that delivered a much lower light dose.[29]

The mechanisms of photoreceptor death arising from *RHO* mutations associated with the class B1 phenotype are incompletely understood. When expressed in heterologous cells in culture, the mutant opsins are prone to misfolding and aggregation, regenerate poorly with 11-*cis*-retinal, and are inefficiently transported to the plasma membrane, unlike the wild type protein.[94–98] P23H is targeted for degradation by the ubiquitin proteasome system, but also impairs this critical pathway, and may interfere with the processing of normal opsin.[97][98] Photoreceptors may be poorly suited to degrade large amounts of misfolded, mislocalised, or aggregated opsin, because under normal circumstances, most opsin is shed with the outer segment discs and degraded by the retinal pigment epithelium (RPE).[78] Protein misfolding and aggregation have been implicated in the pathogenesis of several neurodegenerative diseases.[99]

Light could accelerate degeneration through non-specific toxicity to photoreceptors already stressed by the effects of a mutation, or through a specific interaction with mutant rhodopsin. Experiments with cultured photoreceptors have suggested that activation of mislocalised rhodopsin could kill rods by stimulating inappropriate signalling pathways.[100] Mislocalisation has been detected in mice carrying a human P23H opsin transgene[101][102] and possibly in VPP mice,[103] but not in P23H rats[72] or T4R dogs.[28] Postmortem analysis of the retina from a patient with the class B1 associated mutation, Thr17Met, did not demonstrate rhodopsin mislocalisation in rods that had not degenerated at the time of death.[90]

Alternatively, mutant rhodopsin may cause abnormalities of phototransduction. ERG analyses of VPP mice and P23H patients have suggested that the lifetime of activated rhodopsin is prolonged, although it could not be determined whether this species represented mutant rhodopsin, the normal protein, or both.[104][105] Photoexcited rhodopsin triggers the phototransduction cascade by activating transducin. When VPP mice are crossed with knockout mice lacking functional transducin, introducing a genetic block of the cascade, their degeneration in standard cyclic lighting is slowed, supporting a role for phototransduction.[106] A third hypothesis proposes that misfolded opsin destabilises outer segment discs, leading to excessive shedding in response to light, which may contribute to photoreceptor stress and eventual death.[107] Full recovery of rod sensitivity would depend on the slow process of new disc formation, which could explain the greatly prolonged late phase of dark adaptation observed in patients with class B1 RP.[88] Massive shedding of outer segment tips was observed after retinal photography in T4R dogs, consistent with this hypothesis.[29]

Whatever the mechanism by which light accelerates degeneration may be, these studies point to two general conclusions. Firstly, until more is known about the effects of light on RP patients with specific mutations, it would be prudent to minimise light exposure during office examinations, fundus photography, and ocular surgery for patients with the class B1 phenotype.[29] The use of hats and sunglasses during regular exposure to bright sunlight may also be advisable. Secondly, this would be a logical population in which to conduct further trials of light restriction.[29]

OGUCHI DISEASE AND RETINAL DEGENERATION: IMPAIRED RHODOPSIN DEACTIVATION

Following excitation by light, rhodopsin must be rapidly deactivated to restore the rod's full sensitivity. Two proteins are crucial for this process. Rhodopsin kinase (RK) phosphorylates photoactivated rhodopsin at serine and threonine residues near the carboxyl terminus.[108][109] Arrestin binds to phosphorylated rhodopsin and prevents further activation of transducin.[110]

Mutations in either RK or arrestin cause Oguchi disease, an autosomal recessive disorder characterised by prolonged insensitivity of rod vision following light exposure.[11][44][111][112] In the absence of the normal quenching pathway, photo-excited rhodopsin continues to activate transducin until deactivated by a much slower process, possibly regeneration with 11-*cis*-retinal. This persistent activity desensitises the rod, markedly slowing dark adaptation.[44][113][114] The fundus displays a golden discoloration that disappears with dark adaptation, called the Mizuo-Nakamura phenomenon. Although Oguchi disease is usually described as a form of stationary night blindness, patients with the most common arrestin mutation (1147delA) may also have degenerative features characteristic of RP.[12][114–117] Phenotypically distinct Oguchi disease and RP may be found in different members of the same family with this mutation,[117] or a single patient may have features of both diseases.[12][115][116] The same mutation has been identified in patients with autosomal recessive RP who had no relatives diagnosed with Oguchi disease.[12] A different arrestin mutation (Arg193ter) has similarly been identified in two siblings with Oguchi disease, one of whom had signs of degeneration while the other did not.[118] Therefore, each of these arrestin mutations can produce a spectrum of disease, presumably under the influence of modifying environmental or genetic factors. It remains to be determined whether RK mutations can cause retinal degeneration.[119]

Rods from knockout mice lacking either RK or arrestin exhibit prolonged photoresponses, consistent with the pathophysiology of Oguchi disease.[8][43] Photoresponses in RK knockout rods also have greater than normal amplitudes.[43] Both strains of knockout mice undergo light dependent photoreceptor degeneration. Under dim cyclic lighting, the only histological abnormality reported in the RK mutant is shortening of rod outer segments. Exposure to brighter light for 24 hours, which does not damage the wild type retina, causes degeneration in RK mutants.[43] Similarly, arrestin knockout mice exhibit gradual degeneration in cyclic light, which is greatly accelerated by a constant light regimen that causes no damage in wild type mice.[9] Mice of both genotypes have normal retinal morphology when dark reared.[9][43] The prolonged photoresponses of RK and arrestin knockout mice, and the strongly light dependent nature of their degeneration, suggest that excessive activation of the phototransduction cascade causes photoreceptor death in these mutants.[9][43][120] This conclusion is supported by analysis of double knockout mice lacking RK and transducin, or arrestin and transducin. The transducin mutation largely prevents the degeneration induced by light in the RK and arrestin single knockouts.[10]

The animal results suggest that light exposure could be an important modifier of the Oguchi disease phenotype, at least in patients with arrestin mutations. Phototransduction activity is excessive in all patients, but may remain tolerable to photoreceptors in those with moderate light exposure. Those exposed to brighter light over time may be at risk of

degeneration. There is as yet no direct evidence for this hypothesis in patients, but it is consistent with a body of evidence suggesting that constitutive phototransduction can cause either night blindness or retinal degeneration, possibly depending on the degree of transducin activation.[121 122] For example, three rhodopsin mutations (Gly90Asp, Thr94Ile, and Ala292Glu) cause autosomal dominant congenital night blindness with no reported evidence of degeneration,[123 124] or with degeneration occurring only later in life.[125] Biochemical experiments,[123 126–128] transgenic animal models,[121 129] and studies of patients[125] have shown that the mutant opsins activate transducin at low levels even in darkness and desensitise rods, as though they were exposed to a weak background light. In contrast, studies of knockout mice lacking RPE65 suggest that higher levels of constitutive phototransduction can cause degeneration. Loss of RPE65 function disrupts production of 11-*cis*-retinal.[48 130 131] Therefore, opsin lacks the chromophore and is thought to activate transducin aberrantly, causing rods to behave as if strongly light adapted[49 132–34] (although this has been disputed).[135 136] Photoreceptor degeneration in this model is rescued by a transducin null mutation, implicating constitutive phototransduction as its cause.[134] Human *RPE65* mutations cause severe, early onset retinal dystrophy phenotypes including Leber congenital amaurosis.[51] Light exposure presumably affects the level of abnormal phototransduction in patients with arrestin mutations, and might determine whether their disease manifests as night blindness or degeneration.

Of course, other environmental or genetic factors[5 50 106 137] might also modulate phototransduction activity, or the vulnerability of photoreceptors, in these patients. However, a report of a patient with Oguchi disease and degeneration preferentially involving the inferior retina,[116] similar to the class B1 phenotype of ADRP, hints at a possible role for light. As discussed earlier, this regional predilection could result from increased light exposure in the superior visual field.

STARGARDT DISEASE: TOXIC BYPRODUCTS OF VISION

Stargardt disease (STGD) is a hereditary macular dystrophy whose features often include progressive loss of central vision with onset during the first or second decade of life, macular atrophy, fundus flecks, and a dark choroid on fluorescein angiography.[138 139] Histopathological changes are most pronounced in and near the macula. These include RPE degeneration and massive accumulation in RPE cells of lipofuscin, believed to consist mainly of non-degradable material derived from ingested photoreceptor outer segments.[140–142] These findings, together with detailed analysis of fundus and psychophysical abnormalities in patients,[143] have supported the hypothesis that degeneration of photoreceptors in STGD is secondary to RPE dysfunction and loss. The disease shows autosomal recessive inheritance and is caused by mutations in *ABCA4* (also known as *ABCR*).[144] This gene encodes rim protein (RmP),[145] a transporter localised to the rims of photoreceptor outer segment discs.[146–148] *ABCA4* mutations have also been identified in fundus flavimaculatus (a variant of STGD),[149] autosomal recessive RP,[150 151] and cone-rod dystrophy.[151] A proposed link to age related macular degeneration[152 153] is less certain.[154–156] The clinical phenotype may depend on the degree of residual RmP activity.[157]

Insights into the pathogenesis of STGD and its relation to light have come from analysis of knockout mice lacking a functional *Abcr* gene, which exhibit abnormalities of the visual cycle.[45] During recovery from a photoresponse, activated rhodopsin decays to release all-*trans*-retinal inside the outer segment disc. All-*trans*-retinal reacts with a phospholipid component of the disc membrane to form *N*-retinylidene-phosphatidylethanolamine (*N*-ret-PE). RmP translocates *N*-ret-PE from the intradiscal to the outer (cytoplasmic) leaflet of the disc membrane, allowing all-*trans*-retinal to be released, reduced, transported to the RPE, and converted back to 11-*cis*-retinal.[45 158] In the absence of functional RmP, *N*-ret-PE remains trapped inside the disc, forming further intermediates. When the disc is phagocytosed by the RPE, a final set of reactions converts these to *N*-retinylidene-*N*-retinylethanolamine (A2E),[46] a component of lipofuscin with several potentially toxic effects on RPE cells.[159–165] A2E is dramatically elevated in the RPE in both *Abcr* knockout mice[45] and STGD patients.[46] The greater lipofuscin accumulation and RPE degeneration in the macula in STGD may be a consequence of the macula's high ratio of photoreceptors to RPE cells.[45]

In this model, A2E is a toxic byproduct of the visual cycle that accumulates to abnormal levels in the RPE of *Abcr* mutant mice and STGD patients as a consequence of rhodopsin activation and retention of *N*-ret-PE within outer segment discs. Therefore, A2E formation should be suppressed by preventing rhodopsin activation. Dark rearing the knockout mice prevents accumulation of A2E, suggesting that light deprivation might slow the progression of STGD and other dystrophies caused by *ABCA4* mutations.[46]

Further studies have suggested an alternative strategy for limiting A2E formation. These began with the observation that some patients taking isotretinoin, a retinoid prescribed for the treatment of severe acne, experience disturbances of night vision.[166] Isotretinoin inhibits the production of 11-*cis*-retinal, interfering with rhodopsin regeneration.[167 168] Chronic isotretinoin treatment suppresses A2E formation and lipofuscin accumulation in the RPE of *Abcr* mutant mice, presumably by reducing the availability of all-*trans*-retinal to form *N*-ret-PE in photoreceptor outer segments.[169] It remains to be determined whether this or alternative pharmacological approaches[170–172] can safely and effectively treat patients with STGD or other diseases associated with lipofuscin accumulation.

CONCLUSIONS

Our understanding of the role of light in retinal degeneration continues to evolve through the use of clinical, animal, and in vitro approaches. A growing body of evidence strongly suggests that light exposure can modify the course of at least some retinal dystrophies. This applies particularly to autosomal dominant RP with the class B1 (regional) phenotype, for which marked acceleration by fundus photography has been demonstrated in a large animal model.[29] However, carefully designed trials in patients of known genotype are required to confirm hypotheses generated by studies of animal models. Until such results become available, and in the many cases for which the underlying mutations remain unknown, it may be prudent to avoid unnecessary exposure to bright light, especially in clinical settings.

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Authors' affiliations
D M Paskowitz, Medical Scientist Training Program and Beckman Vision Center, UCSF School of Medicine, San Francisco, CA, USA
M M LaVail, J L Duncan, Beckman Vision Center, UCSF School of Medicine, San Francisco, CA, USA

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