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Visual Functional Effects of Constant Blue Light in a Retinal Degenerate Rat Model

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ABSTRACT

Retinal degenerative conditions increase susceptibility to light damage, but rapid retinal degeneration (RD) models show less susceptibility to cyclic dim light. We investigated whether constant blue light (BL) exposure can eliminate the residual visual responses in a comparatively rapid RD rat model. Pigmented rhodopsin mutant S334ter line-3 rat pups (21 days old) were exposed for 5–6 consecutive days to constant BL. Visual behavior was evaluated with an optokinetic head tracking apparatus. Electrophysiological recordings were made from the superior colliculus (SC). S-antigen, red-green opsin and rhodopsin immunoreactive residual photoreceptors were counted. Following BL exposure, head tracking was significantly reduced at 0.25 cycles degree^{-1} in 38-day-old line 3 rats. With a 0.125 cycles degree^{-1} stimulus, the head tracking performance of 80-day-old BL rats were similar to that of 220-day-old no–BL-treated line-3 rats. SC recordings also revealed a significant decrease in the residual photoreceptor activity. Histological evaluation showed reduction of the rod population in the central area of the light-damaged retina. Exposure to constant BL considerably reduces the residual visual responses in a rapid degenerating RD rat model.

INTRODUCTION

Although photon capture is a critical component of normal photoreceptor function, excessive absorption of the photons by the visual pigment rhodopsin triggers damage to the photoreceptors (1–3). There is a dose-response relationship in light-induced retinal damage. A higher intensity of light or an exposure of longer duration results in greater retinal damage (4,5). The spectral sensitivity of the photoreceptors can also influence the extent of light damage. Anderson *et al.* (6) observed that most severe photoreceptor damage is caused by blue light (BL).

In the case of human retinal degenerative (RD) conditions such as age-related macular degeneration and retinitis pigmentosa, environmental lighting conditions have a deleterious effect on the progression of the disease (7,8). It has been reported that the influence of light exposure on the progression of the disease varies between different RD models (9,10). Vaughan *et al.* (11) reported less susceptibility to light damage in rapid retinal degeneration rat models compared with slow degeneration models. Later investigations suggested that presence of a retinoic acid component in the retina is the factor responsible for the increased light susceptibility in slower degeneration models such as transgenic P23H rats (12). In Royal College of Surgeons (RCS) rat retina, exposure to bright light elicits a protective response that enhances photoreceptor survival (13). This protective response to light stress is ascribed to the increased basic fibroblast growth factor (bFGF) expression that was measured in the light-treated RCS rat retinas.

In most of the RD rat models, a certain level of residual visual activity persists for an extended period of time (14–20), which appears to be due to the presence of a few photoreceptors that may survive until the very late stages of degeneration. It has been reported that in normal nondegenerative rats, light damage is an effective method to selectively eliminate those residual photoreceptors leaving the remainder of the retina relatively intact (21–23). In normal albino rats, constant light exposure for 80 days from birth apparently eliminates all the photoreceptors. Visual activity, however, persists in the brain and has been inferred to be due to the presence of certain photoreceptor cells (rods and/or cones), which could not be detected during standard histological evaluation (24). According to LaVail *et al.*, the visual function, which persists in very old retinal degenerate RCS rats, after the loss of all the normal photoreceptors, could be mediated by nonphotoreceptor sources present in the retina (14).

The visual functional effects of constant light exposure in an RD rat model has not been well studied. The persistent residual visual activity present in RD rat models (14,17,20) has interfered with the functional evaluations following treatment strategies aimed at visual restoration. Although the use of more rapid model of retinal degeneration such as the rd1 mouse would appear to be a ready solution, the inner retinal morphology in these rodent models may be less suitable for studying restorative mechanisms. The present investigation is

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designed to evaluate the residual visual activity following constant BL exposure in a comparatively rapid RD model, the S334ter-line-3 rat. Residual visual activity in these rats persists for several months after most of the photoreceptors are degenerated (17,19). Following BL exposure, visual function was evaluated by behavioral and electrophysiological means. For behavioral analysis, an optokinetic head tracking apparatus that can measure the visual function of each eye independently was used (17). To allow spatial comparison of morphological and functional data, the visual responses were recorded from a higher visual center, the superior colliculus (SC) which is known to retain a topographic retinal map (25).

MATERIALS AND METHODS

Animals. Animals were maintained in accordance with the NIH statement for the use of animals in research, and the research was approved by the Animal Care and Use Committee of the University of Southern California. S334ter-line-3 retinal degenerate rats (35–205 days old) expressing a mutated human rhodopsin protein were used in this study. The rats were produced by Xenogen Biosciences (formerly Chrysalis DNX Transgenic Sciences, Princeton, NJ) and developed and supplied with the support of the National Eye Institute by Dr. Matthew LaVail, University of California San Francisco (http://www.ucsfeye.net/mlavailRDratmodels.shtml). Because a pigmented background was required for measuring the optokinetic response, all the S334ter-line-3 rats used in this study were pigmented heterozygous, the F1 generation of a cross between homozygous albino line 3 and pigmented Copenhagen rats (Harlan, Indianapolis, IN).

BL exposure. Blue light exposure was conducted according to a previously described method (23). Briefly, after weaning, at the age of 22–25 days, S33ter- line-3 rat pups ($n = 7$) were exposed for 5–6 days to BL in an acrylic plastic/wire cage. The cage was surrounded by 48 inch daylight fluorescent light bulbs (Sylvania, F40/DX) covered with a blue plastic filter (Lee filter No 197, transmission peak at 420 nm, band pass width between 320 and 500 nm). The acrylic plastic of the cage blocks all wave lengths below 385 nm. The light intensity was 678 lux at bottom of the cage and 1291 lux at top of the cage (63–120 foot-candles[ft-c]) measured with a 371 R Optical Power Meter (Graseby Optronics, Orlando, FL). After completion of the exposure period, the rats were returned to normally lit cages in the animal facilities (12 h light on/off, light intensity 8–320 lux, 0.5 to 30 ft-c). Nonlight damaged heterozygous pigmented S334ter-line-3 transgenic rats ($n = 16$) and Normal wild type pigmented Copenhagen rats ($n = 3$), served as the controls. Rats of both sexes were used.

Optokinetic behavioral testing. A modified optokinetic head tracking apparatus (17) was used to measure vision in each eye separately. The device consisted of a rotating drum with stripes of differing spatial frequencies. Approximately 170° of the rotating drum were evenly illuminated with three flood lights (250 cd m^{-2} at the level of the rat's eye) from the outside. The remaining 190° of the drum moved behind a stationary black wall opposite from the light path so that only one eye was exposed to the rotating stripes. The rat was placed inside a plastic tube attached to the top of a 9- inch-high holder. The holding tube could easily be turned 180°, for subsequent exposure of the fellow eye to the optokinetic stimulus. A video camera recorded the rat's head movements for subsequent analysis and scoring. For each rat, the drum was rotated (at a constant rate of 12° s^{-1}) for 120 s per eye, 60 s clockwise and 60 s counterclockwise. The head tracking score was defined as the number of seconds the animal spends moving its head to track the stimulus during the 2 min stimulus period. All rats were tested three times with an interval of at least 2 weeks between two consecutive tests.

Electrophysiology. Electrophysiological assessment of visual responses in the SC was performed according to previously described methods (20). Rats were dark-adapted overnight and anesthetized by intraperitoneal injection of ketamine/xylazine (37.5 mg kg^{-1} ketamine and 5 mg kg^{-1} xylazine) followed by a gas inhalant anesthetic (1.0–2.0% halothane in 40% O_2/60% N_2O) administered *via* an anesthetic mask (Stoelting Company, Wood Dale, IL). Multiunit visual responses were recorded extracellularly from the superficial laminae of the exposed SC using nail polish–coated tungsten microelectrodes. To prevent bleaching of the photoreceptors, the eyes were covered and protected from the light source during surgery. Recording sites (20–40 locations, 200–400 μm apart) covered the full extent of the SC with the exception of its medial area, which was located just under the superior sagittal sinus. At each recording location, 16 presentations of a full-field strobe flash (1300 cd m^{-2}, Grass model PS 33 Photic stimulator, W. Warwick, RI), positioned 30 cm in front of the rat's eye, was delivered to the contralateral eye. An interstimulus interval of at least 5 s was used. All electrical activity was recorded using a digital data acquisition system (Powerlab; ADI Instruments, Mountain View, CA). All responses at each site were averaged. Blank trials, in which the illumination of the eye was blocked with an opaque filter, were also recorded at each site. At the end of each recording session, stereotactic coordinates of the electrode penetrations were plotted on a graph paper and superimposed on the diagrammatic sketch of the SC to display the area sampled by the electrode.

The following characteristics of the visual responses were analyzed: (1) percentage of visually responsive sites—defined as the total number of SC sites that had visual responses divided by the total number of sites from where recordings were performed, (2) response onset latency—defined as the point at which a clear, prolonged (> 20 ms) increase (at least two-fold) in the light-evoked activity above background could be measured (background activity was determined using the 100 ms of activity preceding the light flash) and (3) peak response amplitude—the largest excursion peak to peak in the averaged response.

Histology. For histological evaluation, rats from both the BL-exposed group ($n = 2$ for each time point) and the no-BL group ($n = 2$ for each time point) were killed at both 35–36 days and 50 days of age. Eyes were immersed in 4% *p*-formaldehyde in 0.1 *M* sodium phosphate buffer, pH 7.2, in ice for several hours, washed with phosphate buffer, infiltrated with 30% sucrose in phosphate buffer overnight and frozen in optical coherence tomography (OCT) compound. Transverse sections of the retina were cut along the dorsoventral axis, mounted on slides and stained with hematoxylin–eosin.

Sections containing the optic nerve were analyzed by immunohistochemistry for S-antigen and red-green opsin to identify residual photoreceptors in the retina. Briefly, frozen sections were washed with phosphate-buffered saline and incubated for 30 min in 20% horse serum. The sections were incubated with a mouse monoclonal antibody against S-antigen or rod arrestin (clone A9C6) (26) at a dilution of 1:20 000 or with a rabbit antibody against red-green opsin (Chemicon, Temecula, CA, dilution 1:7500) overnight at 4°C, and the binding of the primary antibody was detected using the Vector Elite ABC kit for mouse or rabbit antibodies (Vector Laboratories, Burlingame, CA), respectively. Rod arrestin/S-antigen is found both in rods and cones and is reported to specifically stain photoreceptors in the retina and cells in the pineal gland and nothing else in the body (26–29). A series of sections (average four) through the full extent of the retina were evaluated at the light microscopic level. As no rhodopsin immunoreactivity was found in 50-day-old retinas (data not shown), photoreceptors were only counted on sections of 35-day-old retinas. The residual S-antigen immunoreactive photoreceptor population (number of cells/100 μm) was measured from the central retina (between 100 and 500 microns superior and inferior to the optic nerve) and peripheral areas of the retina, both in the dorsal (superior) and ventral (inferior) retina. For each rat, at least 12 different representative sites (including a minimum of six sites from the central area and six sites representing the peripheral area) were selected and photographed using a SPOT RT digital camera on a Nikon FXA microscope. Cells were counted by two independent evaluators masked as to the experimental condition.

In addition, adjacent sections were double stained by rabbit anti–red-green opsin (RGopsin) (dilution 1:2000; Chemicon, Temecula, CA) and either mouse anti–S-antigen (clone A9C6 (26), 1:2000) or mouse anti-rhodopsin (clone rho1D4, a gift of R. Molday (30), 1:100 dilution). Sections were first blocked with 20% goat serum for at least 30 min at room temperature. Incubation in primary antibodies was overnight at 4°C, followed by three washes with phosphate-buffered saline and a 1 h incubation in AF488 goat anti rabbit IgG and RhodX goat anti mouse IgG (Molecular Probes,

Eugene, OR), diluted 1:200 in blocking serum. Sections were mounted with Vectashield mounting medium (Vector Laboratories). Images were taken from dorsal and ventral periphery and center (as described above) using a 40× objective in a Zeiss LSM 510 confocal microscope. Rhodopsin- and S-antigen immunoreactive cells were counted on the confocal images; the numbers were then recalculated as cells/100 μm.

Statistical analysis. Statistical comparisons were made using the Fisher exact probability test, Student's *t*-test, paired "*t*" test and one-way analysis of variance (ANOVA) with subsequent *post hoc* tests, using a statistics package of Graphpad Software, Inc., San Diego, CA.

RESULTS

Effect of BL exposure on optokinetic behavior

After BL exposure, the head tracking responses in 38-day-old line-3 rats were significantly reduced when compared with the control no-BL line-3 rats (Fig. 1a). At 80 days of age, only weak head tracking responses could be observed in both BL and no-BL groups when the narrow 1 cm stripe (0.25 cycles per degree) was used (Fig. 1a). The effect of BL exposure on head tracking responses was further evaluated using a larger 2 cm stripe (0.125 cycles per degree) which can produce larger optokinetic responses. When the larger stripe was used, the head tracking response in 80-day-old BL-treated rats was found to be reduced to the level of 220-day-old no–BL-treated transgenic rats (Fig. 1b).

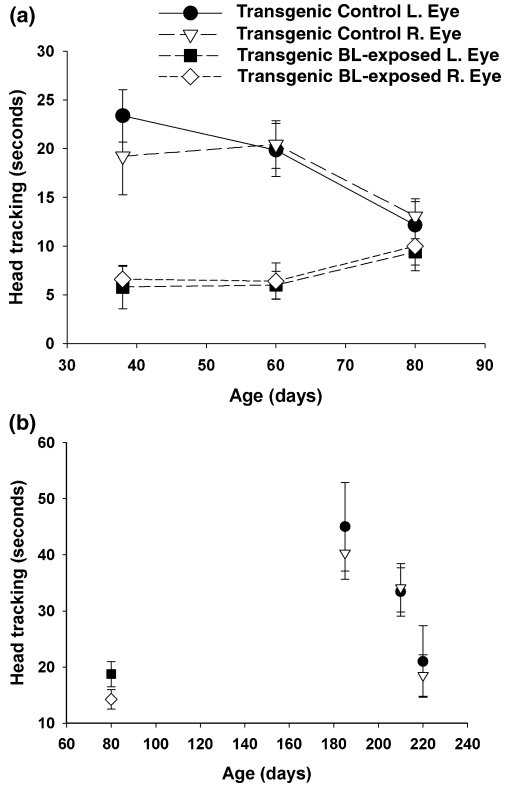

Figure 1. (a) Optokinetic head tracking response in S334ter- line-3 transgenic rats at various time points following blue light (BL) exposure. The responses were measured using the narrow 1 cm stripe (spatial frequency of 0.25 cycles degree^{-1}). The head tracking response between BL-exposed (n = 5) and no-BL transgenic rats (n = 14) was found to be statistically significant when tested at the age of 38 days (P < 0.05, BL *vs* no-BL, left eye, Bonferoni multiple comparison test). (b) Head tracking responses in S334ter-line-3 transgenic rats when measured using a lower spatial frequency (0.125 cycles degree^{-1}, 2 cm stripe). Using the lower spatial frequency, robust optokinetic responses could be recorded from no–BL-treated transgenic rats (n = 7) up to an age of 180 days. After BL exposure (n = 5), the head tracking responses of the transgenic rats were reduced. The responses in 80-day-old BL-treated transgenic rats were reduced almost to the level of 220-day-old control transgenic rats (without BL).

Effect of BL exposure on SC response

Electrophysiological recording revealed a decrease in the visual activity recorded from the SC of BL-treated line-3 rats. In

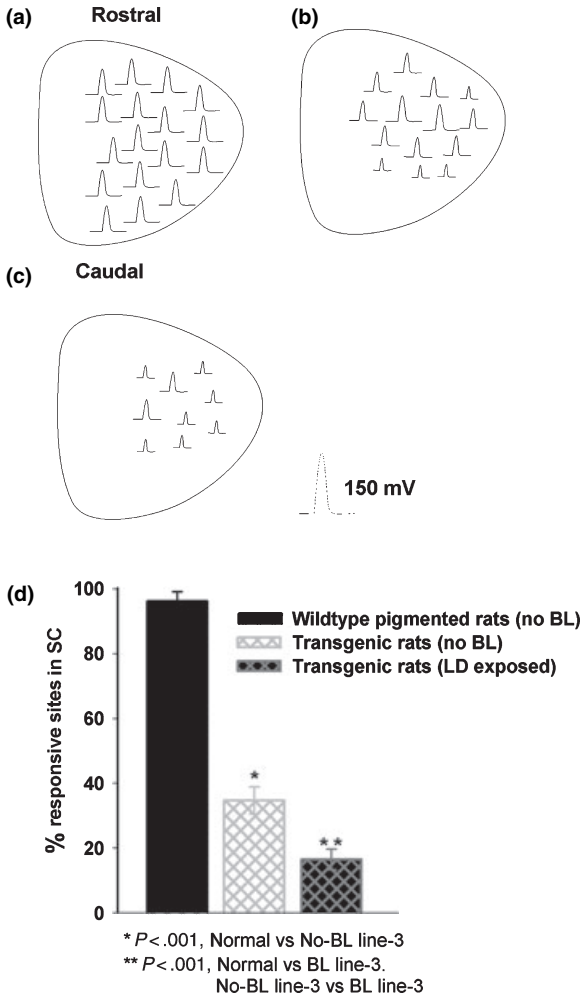

Figure 2. Schematic representation of the visually responsive sites in the superior colliculus (SC) of (a) wild type pigmented rats, (b) nonblue light (BL)-exposed S334ter-line-3 transgenic rats and (c) BL-exposed S334ter-line-3 transgenic rats. In transgenic rats without light damage (b), residual visual activity could only be recorded from the central SC area. After BL exposure (c), a smaller number of visually responsive sites were observed in the central area of the SC of the transgenic rats and the amplitudes of the responses were significantly reduced. (d) Percentage of visually responsive sites in the SC of wild-type pigmented normal rats (Copenhagen, n = 3, 97–145 days), nonlight-damaged transgenic S334ter- line-3 rats (n = 8, 80–105 days) and light-damaged line-3 rats (n = 5, 81–100 days). Compared with normal wild-type rats, the number of visually responsive sites in the SC was significantly reduced in all the transgenic rats (including BL and no-BL groups). Compared with the nonlight-damaged line-3 transgenic rats, the SC evoked responses were significantly reduced in the light-damaged group, demonstrating deteriorated visual acuity caused by BL exposure (P < 0.001, Fisher exact probability test).

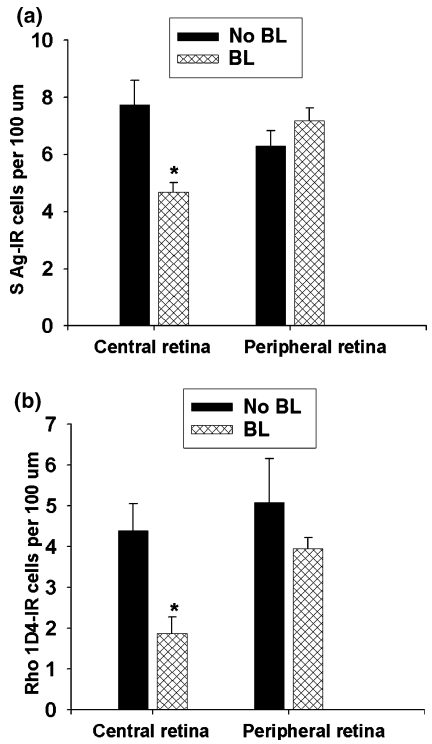

Figure 3. (a) Residual S-antigen (A9C6) immunoreactive cells, (b) rhodopsin (rho1D4) immunoreactive cells (per 100 μm) in the central and peripheral retinal areas in blue light (BL)-treated (35-day-old, $n = 2$) and nontreated control S334ter-line-3 transgenic rats (36-day-old, $n = 2$). After BL exposure, both cell populations were significantly reduced in the central retina. $^*P < 0.05$ (BL transgenic *vs* no-BL transgenic). A statistical evaluation (paired "*t*" test) was performed using the data computed from several (7–19) images representing each retinal area.

no–BL-treated 80-day-old rats, visual responses could be recorded from many areas of the SC and robust responses could be recorded from an area of the SC, extending from the center into the rostral and lateral borders. After BL exposure, significant reduction was observed in the peak response amplitude (no–BL-treated rats 105.53 ± 5.46 mV and BL-treated rats 68.80 ± 3.96 mV, $P < 0.0001$, Student's *t*-test) and in the number and percentage of visually responsive sites in the SC ($P < 0.001$, Fisher exact probability test, Fig. 2a–d).

Effect of BL exposure on residual photoreceptor population

Histological evaluation revealed that the population of surviving S-antigen immunoreactive photoreceptors was considerably reduced ($P < 0.05$, paired "*t*" test) in the central region of the BL-treated retina (Fig. 3a). No difference was found in the number of red-green cones (data not shown). However, the number of remaining rods in the central retina was also significantly reduced ($P < 0.05$, paired "*t*" test , Figs. 3b and 4).

DISCUSSION

A functional evaluation of the visual responses in S334ter-line-3 rats with and without light damage was performed by behavioral testing as well as by electrophysiology. The head tracking response level at a spatial frequency of 0.25 cycles degree^{-1} (narrow stripes) in the line-3 transgenic rats at the age of 38 days (Fig. 1a) was similar to the head tracking response level reported for normal (nontransgenic) no–BL-treated rats (17), although the thickness of the photoreceptor layer was considerably reduced. Following BL exposure, the head tracking response in line-3 rats was almost abolished at this spatial frequency of 0.25 cycles degree^{-1}, suggesting a considerable decrease in the activity of the residual photoreceptors. The almost complete elimination of the head tracking response following BL exposure at an early age is an important observation, as many studies of cell replacement therapies are commenced during this period (30–40 days of age).

The deleterious effect of light damage on the optokinetic head tracking response was also apparent when larger gratings (0.125 cycles per degree) were used. At the age of 80 days, a good preservation of the visual response was observed in no–BL-treated line-3 controls, but the response was nearly absent in the BL-treated line-3 rats. Indeed, the level of residual behavioral head tracking response in the BL-treated group at this 80-day age was comparable with the head tracking response expected in a 220-day-old no–BL-treated line-3 rat. This observation suggests that in line-3 rats subjected to light damage, the functional assessment of therapeutic interventions could be initiated at an earlier age.

The visual activity evaluated by SC-based electrophysiology in no–BL-treated S334ter-line-3 rats demonstrated that responses could be recorded from most areas of the SC up to 80 days of age and comparatively robust responses could be recorded from the SC area extending from the central to the lateral and rostral areas. The spatial pattern of visual sensitivity loss in the line-3 rats was also noted to be similar to the pattern of loss described in a much slower degeneration model, the S334ter-line-5 rats (20). Previously, it was reported that loss of visual sensitivity in S334ter-line-3 rats is initiated with a central scotoma in the SC at the age of 44 days postnatal, after which only long latency responses are recordable from the lateral and rostral areas of the SC (19). This discrepancy between the former and present studies may be related to further refinements in the testing procedures, the light exposure of the animals or some unknown changes in the animal model over successive breeding.

Histological evaluation revealed that the population of surviving S-antigen and rhodopsin immunoreactive photoreceptors was considerably reduced in the central area of the retina after BL exposure. Specifically, S-antigen and rhodopsin immunoreactivity was more reduced in the dorsal (superior) central area than in the ventral (inferior) central area. This indicates that BL exposure has a more deleterious effect in this retinal area. Because the preservation of retinal pigment epithelium (RPE) is necessary for any therapeutic intervention, it is noteworthy that the acceleration of photoreceptor loss after BL exposure is achieved without apparent changes occurring to the RPE, at least as evidenced by light microscopy.

The significant loss of head tracking responses observed in BL exposed rats suggests that the photoreceptors preserved in the central retina are the major contributors to the head tracking response in RD line-3 rats. This hypothesis is also supported by the electrophysiological data demonstrating loss of visual sensitivity in the BL exposed rats mostly from an area of the SC corresponding to the central retina (Fig. 2b,c).

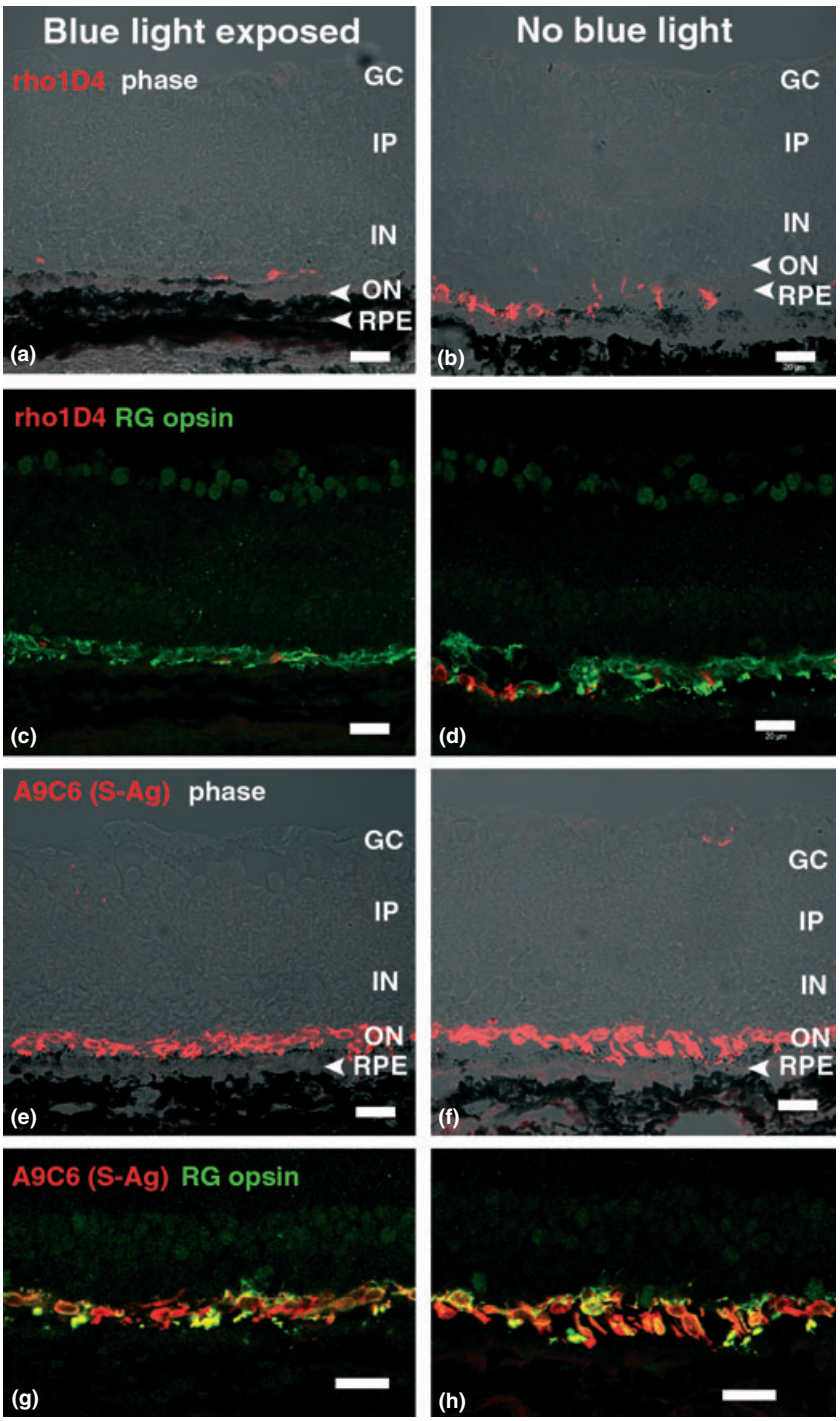

Figure 4. Representative examples of rhodopsin (red) (a–d), S-antigen (red) (e–h) immunoreactivity and double staining with red-green opsin (green) (c, d, g and h). Sections through the dorsal central area of the blue light (BL)-exposed (a, c, e and g) and no-BL (b, d, f and h) S334ter-line-3 rat retinae. Note the difference in rhodopsin-immunoreactive cells between (a) and (b). The difference in the number of S-antigen-immunoreactive cells (e and f) was considerably more subtle. (g and h) More cells are stained for S-antigen (red) than for red-green opsin (green). Fewer apparent remnants of inner and outer segments of cone cells were observed in the light-damaged rats. Scale bar = 20 μm.

Although the number of visually responsive sites was significantly reduced in BL-treated rats and no visual sensitivity could be detected from the rostral and lateral areas of the SC, some weak visual responses could be recorded from an area representing the central to superior-temporal retina (the rostral lateral SC) that produced robust residual visual activity in the no–BL-treated control rats. Such an area of better visual preservation was also noticed in a slow retinal degeneration model, the S334ter-line-5 rat (20). This suggests that some light-sensitive cells remain in the retina even after most of the photoreceptors are degenerated. In RCS rats, a few photoreceptors have been reported to survive up to 2 years of age (31) and still have functional capability (14). In a retinal ganglion cell degeneration model, light sensitive melanopsin expressing retinal ganglion cells are reported to be more resistant to degeneration (32). Light damage experiments performed in normal albino rats demonstrated that visual activity in the brain could persist even after the apparent elimination of all the photoreceptors (24). The above finding indicates that in various types of retinal degeneration rat models (natural, transgenic or induced), certain light-sensitive cells capable of surviving severe degenerative conditions are present in the retina.

Previous reports indicate that BL exposure in normal albino rats results in comparatively more photoreceptor loss in the central superior area of the retina (21–23,33). If one presumes that the central retinal area is more susceptible to BL exposure in normal rats, it is surprising to find that even after BL exposure, the corresponding region in the SC exhibited relatively better visual preservation in a retinal degenerate animal. LaVail *et al*. (14) suggested that the residual visual activity in retinal degenerate rats may originate from nontraditional sources such as the RPE. According to Parnavelas (24), the residual visual activity recorded from the visual center of a light damage model (normal albino rats after long-term light exposure, apparently devoid of any photoreceptors) could be attributed to photoreceptor cells that could not be detected during histological evaluation. It may be possible that certain light-sensitive cells more resistant to BL may also be present in the retina of S334ter-line-3 rats, in an area corresponding to the responsive sites in the SC. More detailed investigation into the physiological basis of this localized residual visual activity may reveal the mechanism underlying the restorative effect of treatment strategies reported among RD rat models.

It may be concluded that the S334ter-line-3 RD model is susceptible to constant illumination damage as evidenced by increased photoreceptor loss and severe visual functional deficits. Weak visual activity recorded after BL exposure may be comparable with the residual visual activity reported to persist in nondegenerate rats, even after long-term exposure to light. The present investigation demonstrates that BL exposure in an RD rat model is a feasible technique to remove most of the residual visual activities, which might have otherwise persisted until a very late stage of degeneration.

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