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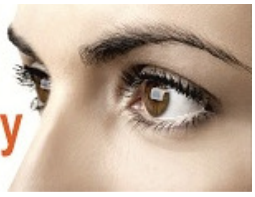

Research Article

Effects of Blue Light Filtration on Photostress-Induced Retinal Damage in Rats

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Abstract

Background: An eye with intraocular lens (IOL) implanted is easier to have retinal damage caused by blue light exposure, when the lens is removal. The aim of the present study is to evaluate retinal morphology and photoreceptor functions including rhodopsin (Rho) regeneration and Rho phosphorylation and dephosphorylation in rats subjected to photostress in the presence or absence of a yellow filter that effectively reduces blue light. Methods: We exposed rats to a 2500 or 5000 lux photostress for 24 hours in a photostress box with or without a yellow filter. After the treatment, we evaluated retinal morphology and function by electroretinogram (ERG). To examine photoreceptor function, during dark adaptation following the photostress, we employed a spectrometric assay to quantify Rho regeneration, and immunohistochemistry to evaluate in vivo Rho phosphorylation and dephosphorylation at 334Ser or 338Ser. Results: Levels of Rho bleaching upon photostress, and rates of Rho regeneration and Rho dephosphorylation during dark adaptation following the photostress were comparable with or without the yellow filter. However, retinal morphology and ERG responses were significantly preserved by the filter in both 2500 lux and 5000 lux photostresses. Conclusions: Our study reveals that although there was little impact on photostress-induced changes in photoreceptor function, reducing blue light effectively reduced photostress-induced retinal damage.

Keywords: Blue Light; Induced Retinal Damage; Intraocular Lens; Photostress; Phototransduction; Rhodopsin; Yellow Filter

Introduction: In vertebrate retinal receptors, absorption of a photon induces photoisomerization of rhodopsin (Rho), which, in turn, initiates activation of hundreds of G-proteins (Gt). These activate cyclic guanosine monophosphate (cGMP) phosphodiesterase (PDE) which metabolizes cGMP, reducing its intracellular concentration and closing cGMP-gated channels. This photoexcitation process can reset to its pre-activated baseline in advance of the next light stimulus, or its excitation level may be modulated to accommodate particular light intensity states. Phosphorylation and dephosphorylation of Rho are critical for this adaptive process [1-3]. In a rat model, we found that retinal photostress causes significant changes in Rho regeneration levels and Rho dephosphorylation rates, while also reducing retinal thickness and dampening electroretinogram (ERG) responses [4]. Now it is well accepted concept that misregulation of the Rho phototransduction cascade lead to retinal dysfunction and degeneration after photostress.

Senile cataracts are the most common cause of visual deterioration in elderly people, and intraocular lens (IOL) implantation in conjunction with cataract surgery is the most effective means of restoring visual acuity [5]. An eye with IOL implanted is easier to have retinal damage caused by short wavelength light. This so-called “blue light” may lead to age-related macular degeneration (AMD) in patients

who have undergone the surgery [6]. To minimize the impact of this photostress, our clinic has employed colored IOLs; an intervention that has proven protective against retinal damage [7-11]. Reactive oxygen species (ROS) have been implicated as possible mediators of retinal photo-toxicity during blue light exposure [12-14]. Alternatively, Grimm et al. [15] described that blue light photostress also cause Rho-mediated retinal damage. In light of our prior findings detailing the impact of photostress on Rho and retinal anatomy, it is of great interest to specifically delineate the contribution of blue light photostress to Rho regeneration, phosphorylation and dephosphorylation; [16,17] and generally to retinal morphology and function. We evaluated these parameters on rats subjected to photostress in the presence of a yellow filter, which effectively cuts out blue light.

Materials and Methods: All experimental procedures conformed with both the NIH statement for Use of Animals in Research and our own institution's guidelines. Unless otherwise stated, we performed all procedures at 4°C or on ice, using ice-cold solutions. We performed animal euthanasia by intraperitoneal injection of a large excess of pentobarbital.

Photostress Conditions and Filter Spectrophotometric Properties: We used 6 to 10 week-old Sprague-Dawley (SD) rats (Hokudo, Sapporo, Japan) reared in cyclic light conditions (650 lux, 12 hours on-off) under specific pathogen-free (SPF) conditions. We treated rats with topical cyclopentolate hydrochloride to dilate pupils, then exposed them to 2500 or 5000 lux illumination, with or without an acrylic yellow filter, in a mirrored photostress box for 24 hours (Figure 1A). Feed and Water were supplied ad libitum in the box.

Yellow filters (Shibuya Optical, Saitama, Japan) suppress transmission of wavelengths under 500 nm (blue light) (Figure 1B). Evaluation of spectral irradiance distribution of light in the photostress box under all conditions with a spectroradiometer (CL-500A; KONICA MINOLTA, Tokyo, Japan) confirmed transmission inhibition of expected wavelengths (Figure 1C). We performed ERG measurements 1 day after, and histologic assessment 7 days after light-induced stress.

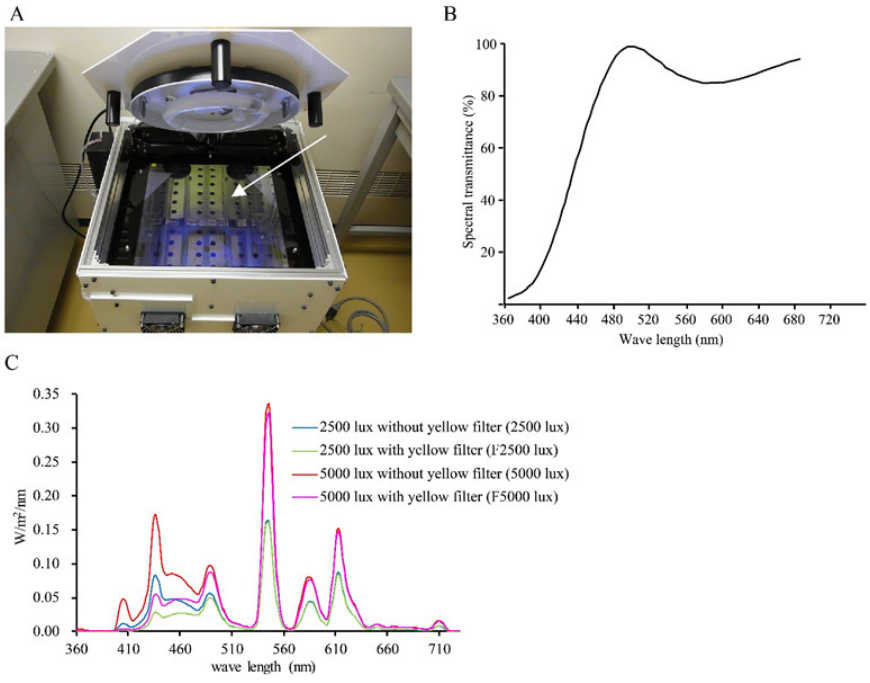

Figure 1: Photostress apparatus and spectrophotometric properties of the yellow filter

Photostress was administrated to SD rats using a photostress box. The inner walls of the box are completely lined with mirrors and white fluorescent lights attached under the top cover allow delivery of varying light intensity. Light filters can be placed as shown in panel A (with a yellow filter: white arrow). Four rats are housed in a cage divided into quadrants (not shown). The luminance levels of boxes within the cages differed by less than 3%. Spectrophotometric properties of the yellow filter are shown in panel B. Panel C shows the spectral irradiance distribution of exposed light in the stress cage by using Spectroradiometer under full condition.

ERG Measurement: Details of the preparation, recording technique, and measurements of ERG have been described elsewhere [4,18]. For ERG measurements, we kept rats in darkness for 24 hours before the procedure. In an electrically shielded room, we anesthetized rats as described above, placed animals in the lateral decubitus position, and applied surgical tape to position the head. We used 0.5 % tropicamide to dilate the pupils. We affixed the recording electrode, which is equipped with a suction apparatus (Mayo Co., Aichi, Japan), to the cornea, placed the second electrode in the mouth and attached the ground electrode to the tail. We used a Ganzfeld dome (SG-2002; Mayo Co., Aichi, Japan) and ERG-analysis software (PowerLab Scope version 3.8; AD Instruments Ltd., Castle Hill, NSW, Australia) to record and analyze responses evoked by white flashes (2.5 cd・s/m^2, 10 ms duration). The a-wave amplitude was defined from the baseline to the bottom of the a-wave, and the b-wave amplitude from the bottom of the a-wave to the top of the b-wave.

Preparation of Specific Antibodies toward Phosphorylated Rho at 334Ser or 338Ser: We prepared specific antibodies against phosphorylated Rhoat 334Ser or 338Ser as described previously [19]. Briefly, specific antisera toward phosphorylated Rho at 334Ser or 338Ser were obtained by immunization of phosphorylated authentic peptides P-Rho334 peptide (DDEApSATASK) or P-Rho338 peptide (CEASATA-pSKT) chemically conjugated with bovine thyroglobulin, and antisera were each further purified into IgG by protein G sepharose column chromatography as described before [19]. Each purified antibody (0.1 mg IgG) was then incubated with urea-washed rod outer segment of rat (20 mg) at room temperature for 2 hours, and then the mixture was ultra centrifuged at 100,000 g for 1 hour. The resultant supernatant was used as a specific antibody toward phosphorylated Rho at 334Ser or 338Ser. Antibody titers and their specificities were determined by ELISA and Western blot, respectively, as described in our previous report [19].

Light and Immunofluorescence Microscopy: We performed histologic examination 7 days after photostress, during which animals were housed in standard cyclic light conditions. After euthanasia, we enucleated eyes, fixed with superfix (Kurabo Industries Ltd, Osaka, Japan) overnight, dehydrated, and embedded in paraffin. We took 3-μm-thick, vertical retinal sections through the optic disc, mounted on subbed slides, and dried. We subjected these to hematoxylin and eosin (H-E) staining after deparaffinization with graded ethanol and xylene solutions. For evaluation of photoreceptor cell survival, we photographed sections including the full length of the retina from the optic nerve head through the ora serrata, and counted the number of cell nuclei in the photoreceptor outer nuclear layer (ONL) within horizontal 100 μm-wide areas located at 200, 400 or 600 μm away from optic nerve head (ONH).

At the same time point after photostress exposure, we performed immunohistochemistry for analysis of Rho phosphorylation and dephosphorylation as described previously [4,16,17,19]. For immunofluorescence labeling, we deparaffinized sections as described above before blocking with phosphate-buffered saline (PBS) containing 5% goat serum and 3% bovine serum albumin (BSA) for one hour, then incubating overnight with anti-P-Rho334 peptide antibody or anti-P-Rho338 peptide antibody (1:500) at 4°C. We washed sections and incubated with fluorescein-isothiocyanate (FITC)- conjugated antibodies to rabbit IgG (Cappel, Durham, NC, USA) for one hour at room temperature. Specificity controls omitted the primary antibodies. We used a fluorescence microscope (model ECLIPSE Ni; Nikon, Tokyo, Japan) for imaging.Vertical length of photoreceptor outer segment layers and that of fluorescence labeling were measured at temporal points 1.0 mm apart from optic disc and their ratios were plotted. We performed the aforementioned experiments in triplicate.

Assessment of Rho regeneration: We assessed Rho regeneration by spectrophotometric analysis, as previously described [4,17]. Briefly, we exposed rats to the different illumination intensities as described above, then subjected to dark adaptation for 4 hours. At different time points (0, 1, 2 or 4 hours), under dim red light, we euthanatized rats and collected eyes, as above, before halving into anterior and posterior segments. We homogenized posterior segments with 10 mM HEPES buffer (pH 7.5) containing 10 mM dodecyl β-maltoside and 20 mM hydroxylamine, using a glass–glass homogenizer. We centrifuged samples at 20,000 g, and recorded the spectra of the supernatants before and after complete bleaching via 5000 lux light exposure for 10 minutes. We calculated Rho concentrations based on the light-sensitive OD at 498 nm, assuming a molar extinction coefficient of 40,600 at 498 nm.

Statistical Analysis: All measured values are expressed as mean ± standard deviation (SD). Statistically significant differences between groups were assessed by using One-way ANOVA or Two-way ANOVA test, and if significance was detected

($p < 0.05$), Tukey's multiple comparison test was applied. (Prism6.0, GraphPad Software, Inc., La Jolla, CA). Differences were considered statistically significant at $p < 0.05$.

Results: As shown in (Figure 2), unbleached Rho level, measured immediately after photostress, was significantly lower in exposed vs untreated animals (all, $p < 0.05$). Levels were, however, comparable at doses of 2500 lux and 5000 lux ($p > 0.99$); and were unaffected by the presence or absence of the yellow filter (2500 lux, $p > 0.99$; 5000 lux, $p > 0.99$). Furthermore, after the subsequent dark adaptation period, there were no significant differences in levels of Rho regeneration between the 2500 lux or 5000 luxintensities or with/ without the yellow filter (all, $p > 0.05$). We next evaluated the effect of the filter on levels of Rho dephosphorylation during dark adaptation after a 5000 lux photostress.

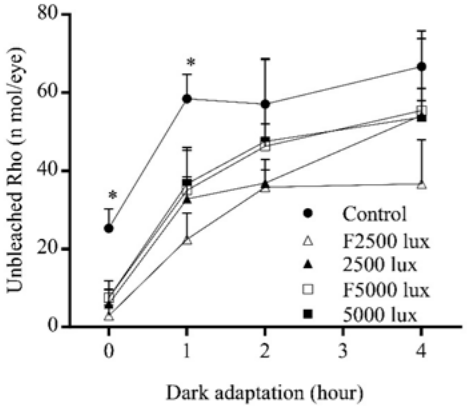

Figure 2: Rho regeneration time course after photostress with or without yellow filter

Direct concentration measurement of unbleached Rho in: SD rats treated with 2500 lux photostress (triangles) or 5000 lux photostress (squares), with (open) or without (closed) a yellow filter. Control SD rats, housed under cyclic lights are represented by (filled circles). Animals were kept in the dark for 0,1,2 and 4 hours before analysis. For each analysis, two eyes were used from one rat. n=3-4 in each experiment. Data are expressed as the mean ± SD. *p<0.05 (Two-way ANOVA and Tukey's multiple comparison test; N = 3 - 4).

As shown in (Figure 3), rates of dephosphorylation at both 334 and 338Ser sites were unaffected by the yellow filter (all, $p > 0.05$). In sum, photoreceptor function after photostress, as assayed by Rho bleaching, regeneration and dephosphorylation during post-stress dark adaptation, was not affected by light intensity of blue light reduction.

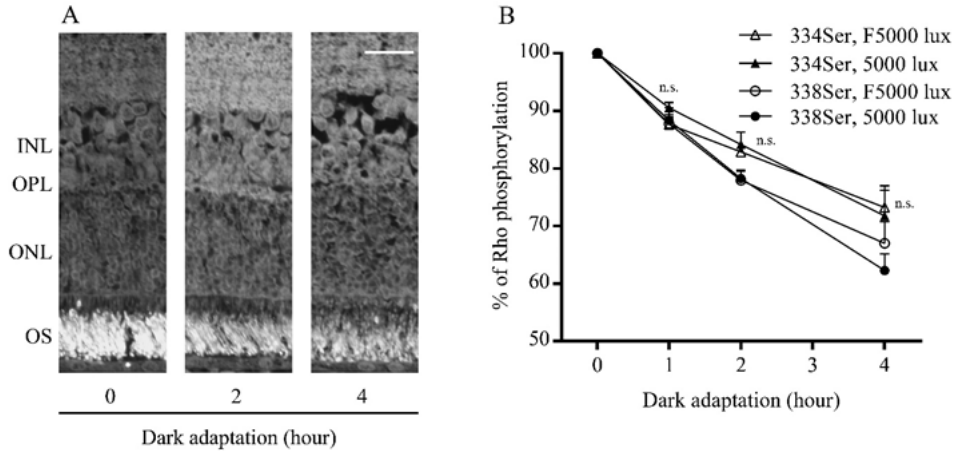

Figure 3: Dephosphorylation kinetics of Rho phosphor – 334Ser and 338Ser after photostress in the presence or absence of a yellow filter

Representative photographs of SD rat retinas under light (5000 lux) or after different intervals of dark adaptation were treated by anti-phospho-Rho 338 antibody in panel A (merged with bright field image). Immunofluorescence quantification of Rho phosphor – 334Ser (triangles) and 338Ser (circles) in SD rats exposed to 5000 lux photostress with (open) or without (closed) yellow filter. Time points indicate 0,1,2 and 4 hours after photostress. Vertical length of photoreceptor outer segment layers and that of fluorescence labeling were measured and their ratios were plotted in panel B. Each time point represents three eyes. Data are expressed as the mean ± SD. N.s., not significant, Two-Way ANOVA and Turkey's multiple comparison test; N = 3.1NL; inner nuclear layer, OPL; outer plexiform layer, ONL; outer nuclear layer, OS; outer segment. Scale bar, 12.5 µm

We observed significant diminution of ERG amplitude in animals treated with 5000 lux versus 2500 lux. This photostress-induced impact on ERG amplitudes was significantly reduced in the presence of the yellow filter (a-wave: 2500 lux, $p = 0.048$; 5000 lux, $p = 0.75$, b-wave: 2500 lux, $p < 0.0001$; 5000 lux, $p = 0.031$) (Figure 4).

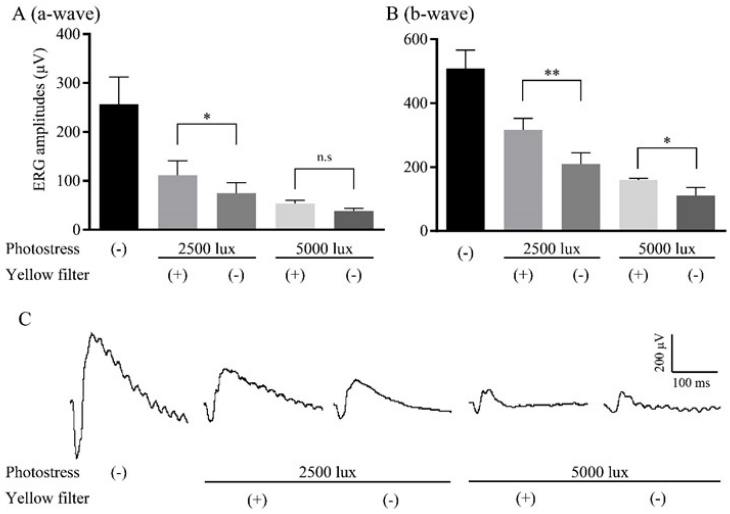

Figure 4: Effects of photostress on ERG responses in the presence or absence of a yellow filter

a-wave (Panel A), and b-wave (Panel B) ERG amplitudes, measured after 24-hour photostress (2500 or 5000 lux with or without yellow filter), followed by 24-hour dark adaptation. Black bar represents control rats housed in standard cyclic light. Mean ± SD of ERG amplitudes from 8 different eyeballs (8 rats). Panel C shows representative ERGs obtained from rats exposed to photostress with different conditions.

*p<0.05; **p<0.01; n.s., not significant, One way ANOVA and Turkey's multiple comparison test; N=8

Similarly, an intensity-dependent thinning of the ONL was recognized after light-induced stress, and the number of cell nuclei located within horizontal 100 µm-wide ONL areas 200, 400 or 600 µm away from the optic nerve head, was significantly reduced with increasing light stress intensities (Control vs 2500 lux and Control vs 5000 lux: 200, 400 and 600 µm away from ONH; $p < 0.001$). This decline was mitigated in the presence of the yellow filter (200 µm away from ONH: F2500 lux vs 2500 lux, $p = 0.019$; F5000 lux vs 5000 lux, $p = 0.066$, 400 µm away from ONH: F2500 lux vs 2500 lux, $p = 0.045$; F5000 lux vs 5000 lux, $p = 0.010$, 600 µm away from ONH: F2500 lux vs 2500 lux, $p = 0.049$; F5000 lux vs 5000 lux, $p = 0.012$) (Figure 5).

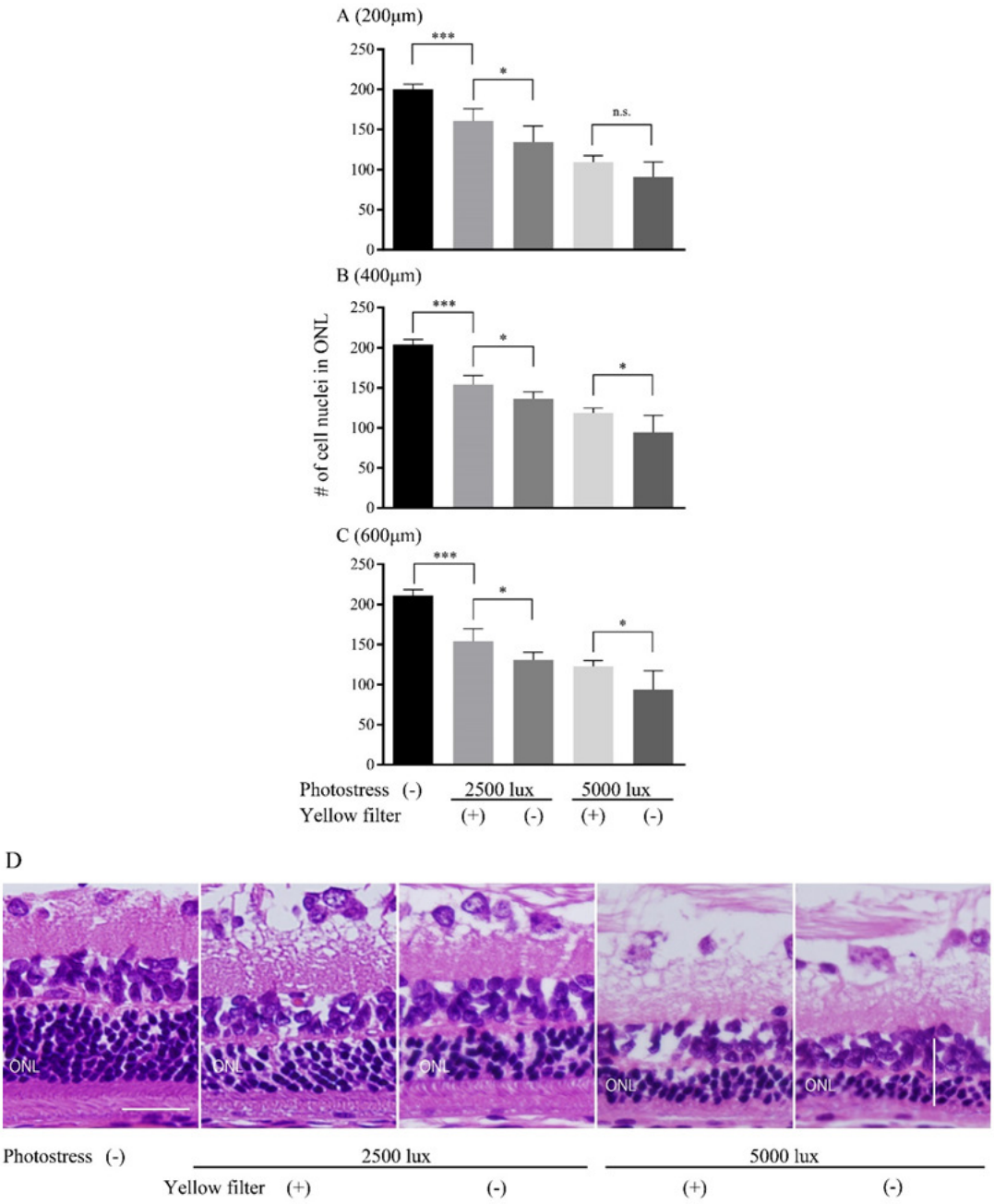

Figure 5: Effects of photostress on retinal morphology in the presence or absence of a yellow filter

Number of ONL nuclei in horizontal 100 μm-wide areas located 200 μm (panel A), 400 μm (panel B) or 600 μm (panel C) from the optic nerve head, measured after 24-hour photostress (2500 or 5000 lux with or without yellow filter), followed by 7 days in standard cyclic light. 8 eyes from 8 rats exposed to each condition. Mean ± SD of numbers of the ONL nuclei are plotted. Panel D shows representative image of SD rat retinas located at 400 μm away from optic disc with H-E staining under different conditions.

*p<0.05; ***p<0.001; n.s., not significant, One way ANOVA and Turkey's multiple comparison test; N = 8. Scale bar, 25 μm

Discussion: Many studies have detailed the ability of photostress to induce a series of intracellular processes leading to apoptotic death of retinal cells [20,21]. The severity of this effect depends on light intensity, wavelength and photostress duration [22-24], as well as degree of retinal pigmentation in the

animal model [4,25]. On the contrary, others have reported that, under certain conditions, photostress can actually protect against retinal photoreceptor apoptosis [26,27], and implicated induction of trophic factors, including fibroblast growth factor-2 (FGF2), as relevant for this process [28,29]. The molecular mechanisms underlying both the destructive and beneficial impacts of photostress have not been clarified.

To better elucidate the mechanistic basis of these phenomena, we systematically studied the effects of multiple photostress intensities on retinas of wild type and retinal degenerative Royal college of surgeons (RCS) rats. Upon photostress, intensity-dependent deterioration in retinal function, as indicated by ERG diminution, reduced ONL thickness, and prolonged Rho dephosphorylation, occurred in both rat species. Interestingly, these photostress-induced impacts on retinal morphology and function continued to progress in RCS rat retinae after photostress exposure, whereas no progression occurred in wild type rats [4]. Based upon these observations, we determined photostress-induced retinal deterioration could cause additive injury when superimposed on genetic retinal defects.

Another mysterious phenomenon in photostress-induced retinal deterioration is the ability of blue light exposure to cause photoreversal of Rho bleaching with concomitant retinal damage [15]. It was, therefore, of great interest to study the effects of blue light photostress on Rho functions, including phosphorylation/ dephosphorylation states and bleaching/ regeneration. In the present study, we found that photostress-induced deterioration of retinal morphology and function could be mitigated in the presence of a yellow filter that reduced transmission of blue light. However, levels of Rho bleaching and rates of Rho regeneration and Rho dephosphorylation during post-photostress dark adaptation unchanged in the presence or absence of the filter.

With regard to potential mechanisms of Rho-mediated, photostress-induced retinal deterioration, our previous studies [4,19] suggested that prolonged survival of phosphorylated forms of Rho could contribute to persistent dysregulation of the phototransduction processes as follows: 1) Phosphorylated Rho continuously suppresses light-dependent Gt activation causing cGMP accumulation within the cytosol. 2) cGMP-gated channels on plasma membranes remain continuously open. 3) Intracellular Ca^{2+} levels increase. 4) A Ca^{2+} dependent apoptotic pathway is activated.

Since it is known that cytosolic cGMP levels are strictly regulated by PDE and guanylate cyclase [30] for normal photoreceptor function, abnormal levels of the cytosolic cGMP may easily induce dysregulation of the phototransduction within photoreceptors. In fact, abnormal levels of retinal cytosolic cGMP have been demonstrated in RCS rats [31], photostressed rats [4] and several animal models with genetic lesions in the PDE gene [32]. A similar mechanism has been identified in the molecular pathology of cancer-associated retinopathy (CAR) [33] that, when modeled by intravitreous administration of the anti-recoverin antibody to rats, is associated with elevated Rho phosphorylation [34]. Moreover, Rho mutants within the C-terminus, in which 345Val and 347Pro are the most common sites of mutations causing autosomal dominant retinitis pigmentosa (ADRP) [35,36], were also phosphorylated at significantly higher levels compared with the wild type [37,38]. Thus, prolonged survival of phosphorylated Rho, mediated either by lower phosphatase activity or enhanced Rho kinase activity may presumably be one of the common mechanisms responsible for retinal photoreceptor degeneration.

In the present study, we found that, although Rho bleaching levels were comparable, levels of the photostress induced retinal deterioration were significantly reduced in the presence of a yellow filter that blocked blue light transmission. It can be presumed that unchanged levels of Rho bleaching and rates of Rho regeneration and Rho dephosphorylation in the presence or absence of the yellow filter were observed in that yellow filter reduced only short wavelength of photostress and the absorption wavelength of Rho differ from the one reduced by the yellow filter. It is known that the blue light photostress (at approximately 440 nm) requires 100 times less intensity to cause damage as compared to orange light photostress (at approximately 590 nm) [39]. As a possible mechanism underlying blue light photostress-induced retinal degeneration, that ROS generation may result in damage to lipids, proteins and DNAs within the retinal neurons [39]. Our present results suggest additional proof that mis-regulation of the Rho phototransduction pathway as described above is a different mechanism causing retinal deterioration by blue- light induced retinal deterioration.

In conclusion, our present study provides additional insight into the variability of photostress-induced retinal deterioration.

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