Effects of Punctate Foveal Damage on Foveal ERG Spectral Sensitivity

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In this study we have demonstrated that a single foveal lesion can produce suppression of central cone function and increased sensitivity of parafoveal receptor systems that might be adjacent cones, partially functional long wavelength cones, or normally suppressed rods. Passive and active movement of receptors during the repair process and damage to the neural retina represent additional sources of spectral sensitivity modulation that may explain some of the complexities of change observed in the postexposure measurement period. These retinal sensitivity changes may provide a retinal basis for earlier behavioral investigations of punctate foveal damage where enhancement effects were observed.
In this study, we have demonstrated that a single foveal lesion can produce suppression of central cone function and increased sensitivity of parafoveal receptor systems that might be adjacent cones, partially functional long wavelength cones, or normally suppressed rods. Passive and active movement of receptors during the repair process and damage to the neural retinal represent additional sources of spectral sensitivity modulation that may explain some of the complexities of change observed in the postexposure measurement period. These retinal sensitivity changes may provide a retinal basis for earlier behavioral investigations of punctate foveal damage where enhancement effects were observed.
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INTRODUCTION

The effects of minimal spot retinal exposure on the central retinal area, the fovea, is a key laser safety issue. Unfocused collimated laser light produces a retinal spot of about 50 microns on the retina. A foveal lesion produced by such a spot size may compromise fine visual acuity and spatial contrast vision for transient and possibly permanent periods of time (1).

Functional assessment of acute small spot threshold foveal damage has been difficult to document in human accident investigations (1) and early animal investigations of intense light effects on foveal visual function (1). Initial animal investigations utilizing nonhuman primates trained on visual acuity tasks used anesthesia for placing large spot exposures (> 500 microns) foveal lesions under funduscopic control preventing immediate measurements of acuity for up to 48 hours postexposure (1). Such investigations were thus unable to detect and measure early changes in retinal tissue induced by laser retinal injury. Long-term changes in visual acuity generally lasted from 3 to 6 months before preexposure acuity levels were reestablished. On the other hand, behavioral measurements of long-term foveal spectral sensitivity appeared more permanent reflecting possible mechanical reorganization of the foveal parafoveal retinal receptor mosaic (2).

In more recent animal investigations, behavioral techniques for measuring the immediate and permanent effects of foveal laser exposure have been developed (3). The importance of foveal retinal spot size has been demonstrated in such experiments. The threshold for permanent functional change was found to be lower than that for damage threshold for large foveal spot sizes that can be considered as extended sources (4). For small spot sizes at or near minimal spot size, the transition from temporary to permanent functional acuity loss is very near or at the level required for threshold retinal damage (5). Permanent functional effects from small spot Q-switch exposure are more elusive. While punctate foveal lesions from such exposure can produce transient change lasting 10 to 15 minutes, permanent effects are not easily detected with visual acuity or contrast
sensitivity measures (6). When such effects are obtained, they are associated with repetitive exposure that has produced cumulative foveal damage over much of the fovea. Under such conditions, visual acuity has been permanently altered (7,8).

In this paper, we have utilized focal electroretinography to assess long-term changes in foveal macular spectral sensitivity. We have employed a focal synchronous ERG (Electro-retinogram) measure of foveal spectral sensitivity to evaluate the long-term effects of minimal spot foveal retinal damage. In large spot acute effects, spectral sensitivity measurements have demonstrated their sensitivity over achromatic measurements. We expect that ERG spectral sensitivity will better measure alterations in retinal neural processing than achromatic contrast sensitivity and possibly reflect alterations in specific retinal receptor systems induced by small spot foveal retinal damage.

METHODS

In this experiment, ERG spectral sensitivity was measured using a synchronous detection technique (9). A fundus camera was employed to view the fundus for placement of test beam on the central region of the macular. An automated goniometer positioned the test spot on the anesthetized animal's macular. The test spot was 3 degrees. A Princeton Applied Research dual phase lock-in amplifier (Model 129A) was used to process the repetitive ERG via a Burian Allen bipolar contact lens electrode. This signal was referenced to the chopping frequency of our light chopper to obtain a low voltage signal at the output of the lockin-amplifier. A servo loop maintained a constant voltage offset of 0.5 uv rms by changing direction of the motor driven 4-log unit circular optical density wedge. When the signal was below the criterion voltage of 0.5 uv, the motorized wedge decreased the optical density. When above this criterion, it increased the optical density. In this manner a continuous on-line measure of sensitivity was derived for different interference filters. Spectral sensitivity functions were derived by normalizing the spectral energy of the test light source to the energy measured at the 600 nm interference filter and plotting the relative reciprocal test light energy at each wavelength versus wavelength (10,11). Threshold measurements at each wavelength were measured for 2 minutes. Spectral sensitivity functions were measured at chopping frequencies of 25 Hz and 40 Hz.
Laser wavelengths were provided from a Q-switched dye laser pumped source at 580 and 680 nm at energy levels of 30 uJ and 60 uJ, respectively. A foveal lesion was produced in both cases. ERG postexposure measurements were begun 4 to 8 days postlaser exposure and were made periodically over a 2-year period.

RESULTS

In Figures 1 and 2 spectral sensitivity functions for the two animals at 40 Hz before and at various times up to 24 months are presented. Both animals showed an initial global increase in spectral sensitivity that tended to produce a flatter function over the mid wavelength region from 500 - 600 nm. Over time both animals showed a return to baseline with a small loss in overall sensitivity. At 24-months postexposure, both animals showed a deficit in the short and intermediate spectrum. The loss was much more severe for 8892 than for 084x.
Figure 1. ERG spectral sensitivity functions for #8892 measured at 40 Hz are presented. The 4-day (4d) functions show as much as a 0.6 log unit increase in sensitivity across the visible spectrum. At 24 months (24m) a significant decrease in spectral sensitivity for the short to intermediate visible spectrum (460-600 nm) developed. Slight deviations from the average function are evident at 62 days (62d) and 9 months (9m) post exposure.
Figure 2. ERG spectral sensitivity functions for 084x measured at 40 Hz are presented. The 8-day (8d) function shows almost a 1.0 log unit increase in sensitivity over most of the visible spectrum. The postexposure function at 24 months (24m) peaks at 580 nm. It is more sensitive than the average function from 540 to 600 nm but slightly less sensitive below 520 nm. At 6 months (6m) post exposure, spectral sensitivity appears more similar to the average than the 24m function.
A more selective spectral increase was found at 25 Hz for both animals (Figures 3 and 4). In both animals, a long wavelength increase in sensitivity occurred and is maximal from 580 to 700 nm. It is more obvious in the 62-day and 24-month functions of 8892 (Figure 3); more variability but persistence of this effect was measured over the full 24-month period for Ø84x (Figure 4).

Figure 3. ERG spectral sensitivity functions measured at 25 Hz for 8892 are presented. The 4-day (4d) function shows an increase in sensitivity above 540 nm with a small deficit below this wavelength. At 62 days (62d), the function shows a significant increase from 520 to 700 nm with a maximum difference from the average of more than 1.0 log unit at 640 nm. At 24 months (24m), a much more restricted long wavelength increase above 600 nm is observed. From 580 to 460 nm, deficits in sensitivity relative to the average curve range up to 1.0 log unit at 500 nm.
Figure 4. ERG spectral sensitivity functions measured at 25 Hz for 084x are presented. An increase in long wavelength sensitivity is observed for the 8-day (8d) function above 520 nm. At 5 months (5m) a function close to the average function is obtained. At 24 months (24m) a broad increase in sensitivity occurs with peaks at 500-520 nm and 640 nm. Sensitivity increases of 1.0 log units relative to the average function are evident.

Functions for both animals during this time, including the 5-month function of 084x, could be fitted to the long wavelength nomogram 575 cone pigment nomogram. In Figure 5, the 9-month, postexposure data wavelength (575) and the intermediate (520) nm cone photopigment nomograms (12). These fits were fairly consistent over the 9-month period of measurement suggesting the emergence of the long wavelength cone system following foveal laser damage. Similar but more
variable modeling of the long wavelength photopigment nomograms was possible for 084x through the 5-month function. In Figure 6 a comparable fit of the 520 and 575 nm photopigment nomograms is presented for 084x at 24 months post exposure.

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\text{Figure 5. We have compared the average 25 Hz spectral sensitivity function and the post 62-day spectral sensitivity function of 8892 with photopigment nomograms for 520 and 575 nm. While both the average and post 62-day functions are easily matched with the 520 nm pigment nomogram, the post 62-day functions require the 575 nm nomogram for their long wavelength data points. This type of match was possible in this animal over at least a 12-month, postexposure period. It was no longer possible at 24 months.}
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Figure 6. We have compared the average 25 Hz and the post 24-month (24m) spectral sensitivity function of 084x with photopigment nomograms at 500 and 575 nm. Results are similar to those presented in Figure 5 for 8892 measured at 62 days. In both animals, matching the spectral sensitivity function with photopigment nomograms requires the use of both an intermediate and long wavelength photopigment nomogram.
DISCUSSION

In these animals, we initially observed enhancement of spectral sensitivity over a broad spectral region at 40 Hz, a chopping frequency that normally samples cone function (Padmos and Von Norren). As we measured for a 3-degree central area in the macula including an area of foveal damage, it is likely that the enhanced activity resulted from undamaged receptor cells located within or slightly outside of this 3-degree area. Cones that were damaged would have a weakened response output disabling their normal ability to inhibit parafoveal receptors. Because of the broadness of this function it is probable that such parafoveal receptors included cones as well as rods. However, rod activity would presumably result from a weakened inhibitory capacity of the central damaged receptors on rods, as rod activity is excluded from the normal spectral sensitivity function measured at 40 Hz.

At 25 Hz more selective enhancement toward the long wavelength region was observed in both animals. Such selective enhancement may suggest the emergence of either the long wavelength cone system or normally suppressed rod system as retinal repair processes proceed. Long wavelength cones may emerge as either the result of an ability to still function or as the result of long wavelength cones that have escaped damage. Rods may emerge because long wavelength cones have been damaged, disinhibiting the normal neural lateral suppression of such cones on the rod system. Increased long wavelength sensitivity may reflect rod enhancement because the absolute difference in spectral sensitivities between the rod and cone systems beyond 600 nm is minimal. An overall increase in rod spectral sensitivity function would, therefore, result in an increase in rod versus cone long wavelength sensitivity.

While the above explanations can account for some of the observed ERG spectral sensitivity changes, modulation of such spectral sensitivity may result from receptor movement induced by the damage process. Passive movement processes have been demonstrated in the reorganization of the foveal receptor mosaic after photic macular injury (13). Such movement processes have significant effects on spectral sensitivity functions (16). More active alignment processes involved in small but significant adjustments of the receptors with regard to the plane of the pupil may also be involved in final optimization of sensitivity (14,15). Anatomical and psychophysical studies suggest the presence of
such mechanical alignment processes in normal and altered retinal states (11,17,18).

Although laser wavelengths were not equated for effect or energy in this investigation, such factors have demonstrated their importance in previous work. While both animals received suprathreshold foveal lesions, equivalent changes in spectral sensitivity were not induced. Both showed an increase in long wavelength sensitivity and long-term change in the intermediate to short wavelength exposure. The most severe effect on short wavelength sensitivity was obtained with the longer wavelength exposure at 680 nm. In previous work, long wavelength exposure has been demonstrated to have significant effects in the short as well as the long wavelength spectral regions. Neural connections between short and long wavelength cones have been postulated for such effects. Damage to these neural connections could have mediated alterations in the short and long wavelength regions of the functions displayed for 8892 (10,16,17).

The site of long-term retinal damage remains for histological evaluation. However, based on our observation of retinal sensitivity enhancement, we speculate that alteration to the inner retina will represent the significant damage site. Long-term evaluation of similar lesion sites reveals relatively normal receptors populating the site months after exposure (13). Originally such receptors may have occupied positions adjacent to those in the field of exposure. Subsequently, as damaged receptors were cleared during the metabolic repair process, the adjacent receptors may have "migrated in" to fill the void (13). Long-term retinal pigment epithelial cell damage might be reflected as funduscopically observable residual alteration in the retina.

CONCLUSION

In this study, we have demonstrated that a single foveal lesion can produce suppression of central cone function and increased sensitivity of parafoveal receptor systems that might be adjacent cones, partially functional long wavelength cones, or normally suppressed rods. Passive and active movement of receptors during the repair process and damage to the neural retina represent additional sources of spectral sensitivity modulation that may explain some of the complexities of change observed in the postexposure measurement period. These retinal sensitivity changes may provide
a retinal basis for earlier behavioral investigations of punctate foveal damage where enhancement effects were observed (7,8). While we cannot assess differences in effect with regard to laser wavelength because of nonequal dose levels, the exposure wavelengths of 580 and 680 nm correspond to the two significant dips for threshold retinal damage dose reported by Lund et al. (19). Further study of these latter questions as well as the development of this ERG methodology as a viable human assessment tool in laser exposure represent our present course of investigation.
REFERENCES


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