Visual Response Properties of Y Cells in the Detached Feline Retina

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PURPOSE. To evaluate early changes in the visual response properties of Y cells in the detached feline retina.

METHODS. The retinas of young adult cats were detached by injection, with a glass micropipette, of a solution of 0.004% sodium hyaluronate in a balanced salt solution between the neural retina and the retinal pigment epithelium. At 1, 3, and 7 days after detachment, the eyes were removed. The eyecup was prepared as a flat mount in a recording chamber and superfused with medium. Extracellular single-unit responses from Y cells in the retinas were recorded.

RESULTS. One, 3, and 7 days after retinal detachment surgery, Y cells showed clear signs of functional deterioration. At each time point, more ON center cells than OFF cells were encountered. Y cells in the detached retinas showed a statistically significant elevation in the average threshold irradiance after 1-, 3-, and 7-day detachment, respectively. The average contrast threshold recorded from cells in the normal retina was 3.6%, but it increased to 14.5%, 21.8%, and 47.5% after 1-, 3-, and 7-day detachment, respectively. Furthermore, at each time point, the capability of Y cells to process contrast information decreased significantly more because of detachment than because of luminance task performance.

CONCLUSIONS. Retinal detachment induced rapid functional remodeling that resulted in degenerated Y-cell function, including an elevated luminance threshold and a deteriorated contrast threshold. Detachment had a greater impact on the latter. These physiological changes after retinal detachment could be used as objective indicators of early deterioration of visual function in future studies of retinal remodeling. (Invest Ophthalmol Vis Sci. 2010;51:1208–1215) DOI:10.1167/iovs.09-4179

Retinal detachment (RD) is characterized by separation of the photoreceptor cell layer from the retinal pigment epithelium. Numerous studies demonstrate that RD triggers a cascade of molecular and cellular events, including death of photoreceptor cells, proliferation or hypertrophy of Müller cells,1–3 apparent growth of neurites from second- and third-order neurons,4 and increased expression of growth-associated protein GAP43 and neurofilament protein in retinal horizontal and retinal ganglion cells (RGCs)5 However, prompt repositioning of the retina and retinal pigment epithelial layers can result in restoration of vision, implying that some of these abnormal changes can be arrested or even reversed by reattachment.6 This is partly attributed to the intrinsic nature of photoreceptor cells, in that outer segments are able to regenerate after reattachment and that most of them achieve near-normal morphologies. Nevertheless, visual deficits are common after successful reattachment surgery.7–9

Regardless of the initial insult, stressed photoreceptors can remodel their synaptic terminals and their relationship to second-order neurons. These changes are proposed to progress through three phases: photoreceptor stress, photoreceptor death, and complex neural remodeling.10 Although the cells are in detachment, neural remodeling occurs early—with a few days—and, therefore, before massive photoreceptor cell death. Substantial evidence suggests that diagnosis and intervention at the early stages of retinal remodeling, especially during the stress phase, when there is significant photoreceptor terminal modifications, are critical for the successful rescue of injured cells and the restoration of visual function. Over the years, molecular and morphologic changes during this stage have been explicitly addressed in experimental retinal detachment,5 whereas objective neurophysiological observations correlating these early structural changes have been reported only in data from electroretinography.11

Electroretinographic (ERG) testing provides one objective measurement of the electrical activity of detached and reattached retinas.12–16 However, current ERG technology is not sensitive enough to detect alterations at the single-cell level. RGCs play the crucial role in collecting appropriate input from second-order neurons and transmitting visual information to higher visual centers, but little is known about the functional consequence of these neurons after RD and subsequent reattachment. Y cells have been studied for more than 40 years,17 and morphologic and physiological properties of these cells have been studied extensively.17,18 Recent evidence suggests that Y cells are more susceptible to RD injury based on their increased GAP43 and neurofilament protein expression.5 Here we have measured the physiological properties of Y cells recorded from detached feline retinas during early stages of retinal remodeling. Our study demonstrates the first evidence of the rapid physiological impact of RD on the function of RGCs, including compromised luminance threshold and reduced contrast sensitivity. These results offer physiological evidence for the importance of understanding neuromechanisms underlying the early stages of retinal remodeling after photoreceptor injury.
Materials and Methods

Animals

Thirty young adult domestic cats (Felis catus) of either sex, ranging from 2 to 3 years of age and weighing between 2.5 and 3 kg, were used in this experiment. Animals purchased from a local research animal provider were housed in a 12-hour light/12-hour dark cycle, and food and water were provided ad libitum. All experiments were performed in accordance with Peking University guidelines for animal research and the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Retinal Detachment Surgery

RD surgery has been described in detail elsewhere.20 In brief, after anesthesia by an intramuscular injection of 50 mg/kg ketamine (Ketalar; Parke-Davis, Morris Plains, NJ) and 25 mg/kg pentobarbital (Nembutal; Abbott Laboratories, North Chicago, IL), a glass micropipette with a tip diameter of 100 μm was advanced through a scleral incision near the limbus until it entered the subretinal space. Some vitreous was gently massaged out of the incision site to reduce intraocular pressure before the injection. The entire operation was completed using an ophthalmic microscope. A continuous digital syringe infusion pump (model 360; McGaw Inc., Irvine, CA) was then used to infuse a solution of 0.004% sodium hyaluronate (Healon; Pharmacia, Piscataway, NJ) in balanced salt solution (BSS; Alcon, Fort Worth, TX) into the subretinal space. When the retina was detached to a size of approximately 4 to 6 mm in diameter, the pipette was removed and the scleral incision closed with a 8-0 nylon suture. The center of the detached area was approximately 7 mm from the area centralis. In later experiments, a subretinal injection device (Retinaject; SurModics Inc., Eden Prairie, MN) was used to create the detachment. This procedure only required a small incision of <1 mm in the sclera, and no suture was needed after detachment surgery.

In Vitro Preparation

The retinal preparation has been described previously.20,21 Briefly, the animal was dark adapted for 45 minutes before enucleation. Under dim red light, the lens and vitreous were carefully removed with a pair of fine-tip forceps. The eyecup was flat mounted, sclera side down, on the bottom of a recording chamber and superfused by medium (Ames; Sigma-Aldrich, St. Louis, MO) at a fixed rate (5 ml/min) at room temperature between 22°C to 24°C. Cells recorded at this temperature showed similar response profiles to those recorded in vivo.17,22

Visual Stimulation

Computer-generated visual stimulation paradigms have been described previously.20,21 Briefly, visual stimuli were generated by programming a graphics card (Millennium 3000; Matrox, Dorval, Quebec, Canada), displayed on a 5-inch monochromatic CRT monitor (P4 phosphor, 600 × 800 pixels, 60 Hz; VGA; Kristel Corp., St. Charles, IL) and imaged with a first-surface mirror and lens (Edmond Scientific, Barrington, NJ) on the film plane of the microscope’s camera port. This method ensured that when the electrode tip was in focus in the eyepieces, the stimulus was also sharply focused. Luminance level of the CRT was measured by a first-surface mirror and lens (Edmond Scientific, Barrington, NJ) on the film plane of the microscope’s camera port. This method ensured that the intensity of the testing spot was attenuated by a series of neutral-density filters (Oriel Corp., Stratford, CT). Incremental threshold luminance sensitivity tests were conducted according to previously published methods.20,25 In general, a criterion response for threshold irradiance was obtained by gradually increasing the intensity levels of the testing stimuli; a firing rate of two spikes per second above the baseline rate was set as a threshold response. If none of the test stimuli produced exactly two spikes per second, the threshold was determined by linear interpolation. This difference also matched our subjective auditory criteria. For contrast sensitivity testing, the contrasts of drifting sinusoidal gratings were defined by percentage Michelson contrast: 100 × (1 − \text{I}_{\text{min}}/\text{I}_{\text{max}}), where \text{I}_{\text{max}} and \text{I}_{\text{min}} were the peak and trough intensities (range, 0%-100%). We applied conventional Fourier analysis techniques to plot poststimulus time histograms and to determine the amplitude of response components at the frequency of stimulation (fundamental) and at the second harmonic. The amplitude was used to estimate Y-cell responsiveness. The histograms were based on unit responses to a minimum of eight stimulus cycles. To determine a cell’s contrast sensitivity, we plotted response magnitude (spk/s) against contrast curves for each spatial frequency (eight spatial frequencies ranged from 0.08 to 1.66 cyc/deg). From these curves we obtained the contrast values required to evoke a threshold response, and reciprocals of these values were taken as contrast sensitivity. Threshold response was defined as a firing rate of 2 spk/s above the baseline rate. If none of the test stimuli produced exactly 2 spk/s, the threshold was determined by linear interpolation. A linearity test was performed to distinguish between Y and X cells. Stimuli were temporally counterphase-modulated sinusoidal gratings of various spatial frequencies. Spatial frequency was 0.08, 0.1, or 0.11 cyc/deg. Temporal frequency was 2 Hz. The spatial phase of the grating was advanced from 0° to 360° across the receptive field in 45° increments. X cells exhibited linear spatial summation. At some positions of the grating the cell exhibited little or no modulation in firing frequency (null point). In contrast, for Y cells with nonlinear spatial summation, this modulation would occur mainly at twice the temporal modulation frequency (frequency doubling).17,22

The acquired data were further analyzed offline (pCLAMP9 software; Axon Corp., San Mateo, CA). Additional data analysis, including fast Fourier analysis, was performed (Excel; Microsoft Corp., Redmond, WA).

Intracellular Staining and Immunohistochemistry

Once physiological recording was completed, the recording electrode was withdrawn and replaced with an injection microelectrode con-
taining 4% Lucifer yellow (Sigma Chemical, St. Louis, MA) and 3% neurobiotin (Vector Laboratory, Burlingame, CA.). A small amount of current (1–2 nA for 1–2 minutes) was applied to the electrode until the soma and process terminals were completely stained. Lucifer Yellow allowed the monitoring of the filling quality, and neurobiotin stained the fine end of the processes. The combination of the two allowed for better visualization of the recorded cells. Details of the immunohistochemical staining techniques have been described elsewhere.24 Briefly, the retinas were fixed with 4% paraformaldehyde for 45 minutes. After rinsing in Tris-buffered saline (TBS) for 30 minutes, the retinas were placed in 2% Triton-X-100 and 0.5% dimethyl sulfoxide TBS solution for 24 hours at 4°C before incubation in primary antibodies: anti–Lucifer yellow polyclonal antibody (1:800; Invitrogen, Eugene, OR) and for 72 hours at 4°C. The retinas were then placed in secondary antibodies, including biotinylated antibody (1:1000; Vector Laboratory) and Cy3-conjugated streptavidin (1:1000; Jackson ImmunoResearch, West Grove, PA), overnight at 4°C. All retinas were rinsed and coverslipped with the ganglion cell side up in an aqueous mounting medium (Dako Corp., Carpinteria, CA). Images of recorded cells were taken using a digital camera (700D; Nikon, Tokyo, Japan).

RESULTS

Recent evidence suggests that the α-cell population is more susceptible to RD injury.5 However, little is known about the physiological response patterns of these cells. The goal of this experiment was to characterize the Y-cell visual response patterns in the detached retina. We recorded 52 Y cells from 19 detached retinas and 25 Y cells from 11 controls with normal vision. Figure 1A is a microphotograph of a recorded ON-center Y cell from a retina that was detached for 1 day. This cell was located at the superior nasal retina (eccentricity, 7.1 mm). Arrow: axon of the cell. (B) Receptive field map of the cell in A. (+) ON response was evoked. (C) Boundary of the receptive field where no response was recorded. Scale bar, 100 μm.

Receptive Field Polarity

RD causes photoreceptor degeneration and initiates retinal neurocircuitry remodeling. Recently, in dystrophic RCS rats,

FIGURE 1. Receptive field map and dendritic field of a recorded Y cell in a detached retina. (A) Micrograph of a recorded ON-center Y cell from a retina that was detached for 1 day. This cell was located at the superior nasal retina (eccentricity, 7.1 mm). Arrow: axon of the cell. (B) Receptive field map of the cell in A. (+) ON response was evoked. (C) Boundary of the receptive field where no response was recorded. Scale bar, 100 μm.

FIGURE 2. Discharge patterns of two OFF-center Y cells recorded from both normal and detached retinas. These cells responded to a light spot centered on the RF, presented for the interval indicated by the stimulus marker at the bottom. (A) Visual response pattern of a Y cell (0905-2) recorded from a normal retina. The cell was located at the superior nasal retina (eccentricity, 5.6 mm). (B) Discharge pattern of another Y cell (1118-3) that was recorded from a retina that had been detached for 7 days. The RGC recorded from the detached retina did not deliver a consistent response to the light spot centered on the receptive field. The cell was located at the superior nasal retina (eccentricity, 5.8 mm).
we reported that ON and OFF pathways exhibit different levels of tolerance to retinal degeneration. Thus, we examined the consequence of RD on the ON- and OFF-channels. To carry out this task, we recorded extracellular discharges from Y cells in the detached retina. The receptive field polarity of randomly recorded ON- and OFF-center Y cells was determined by turning a 0.2° spot on and off in various locations within the field. In retinas detached for 1, 3, and 7 days, we encountered more ON (control, 19; 1 day, 15; 3 days, 16; 7 days, 13) than OFF cells (control, 6; 1 day, 2; 3 days, 2; 7 days, 6) (Fig. 3A). As shown in Figure 3A, similar numbers of ON and OFF cells were encountered at the first two time points; however, 13 ON and 6 OFF cells were recorded from retinas after 7-day RD. Therefore, to make a quantitative comparison, we calculated the frequency of encountering OFF cells after RD. Figure 3B shows the frequency of encountering OFF cells reduced to 12% and 11% across the first 2 time points (day 1 and day 3), respectively. However, as shown in Figure 3B, the frequency of recording from OFF cells went up to 32% at the last time point.

Luminance Threshold
For any given Y cell, we selected the optimal spot size that evoked the maximum discharge by running an area–threshold visual stimulation program. This stimulus was used in conjunctiion with various neutral-density filters in the optic path to measure threshold irradiance. After 40 minutes of dark adaptation, cells recorded from detached retinas showed elevated threshold irradiance; their discharge frequencies were also attenuated. Figure 4 reveals visual responses of two ON-center Y cells, one from a normal retina (1021-1) and the other from a detached retina (1125-8) for 3 days. They had different response patterns at two retinal irradiance levels, 3.18 and 2.41 log photons/μm²/s, respectively. The latter irradiance level was chosen because most of the cells recorded from normal retinas still had reliable response characteristics; however, for cells recorded from detached retinas, it was close to their
Error bars, SEM.

day 7 (***)

used as a control. Average irradiance threshold and number of cells threshold irradiance of Y cells recorded from the normal retina was density filters ranged from 0.1 to 4 log ND (neutral density). The photons response to the testing spot at a retinal irradiance of 3.18 log photons pattern, but it delivered only weakly modulated discharges in the detached retina that did not have a typical transient firing in Figure 4A. Figure 4B depicts a Y cell (1125-8) recorded from a typical transient discharges at both irradiance levels is shown threshold irradiance. A normal retinal cell (1021-1) that had a similar receptive field size. Figure 6A illustrates a tent responses (2.41 log photons · μm²/s). Figure 4C reveals response profiles of the two cells. It is evident that the cell from the detached retina exhibited a substantially reduced response magnitude at all tested irradiance levels. For instance, at a retinal irradiance level of 3.18 log photons · μm²/s, the cell from the normal retina delivered an average of 7 spikes/s. It continued to respond as the stimulus irradiance was reduced to 2.41 log photons · μm²/s. In contrast, the cell from the detached retina had an average of <1 spike/s at 2.41 log photons · μm²/s. Therefore, the normal cell could be driven by a wide range of visual stimulus intensity, whereas the cell from detached retina responded to only high-intensity visual stimuli. This response pattern was confirmed in most recorded cells in later experiments. As shown in Figure 5, compared with normal control cells (n = 13), we observed a statistically significant elevation in threshold irradiance from cells recorded from 1-day (Student's t test; P < 0.0001, SEM = 0.08, n = 10), 3-day (P < 0.003, SEM = 0.15, n = 10), and 7-day (P < 0.0001, SEM = 0.14, n = 12) retinas, respectively. In fact, the range of average threshold irradiance was elevated from 1.87 to 2.28 log photons · μm²/s after RD. On the other hand, there were no statistically significant changes in threshold irradiance among the three time points after detachment (1 day vs. 3 day, P = 0.39; 1 day vs. 7 day, P = 0.16; 3 day vs. 7 day, P = 0.07). Together, the present data suggest that RD could have substantial impact on the luminance threshold of Y cells.

Contrast Threshold

It is reported that the longer the duration of macular detachment, the lower the contrast sensitivity score.25 However, at the single-cell level, little physiological data are available on how ganglion cells respond to RD. Therefore, we went on to investigate the contrast threshold of Y cells in normal and detached retinas. For each cell, the discharge profile of the cell to drifting, sinusoidally modulated contrast gratings at eight different spatial frequencies (from 0.08 to 1.66 cyc/deg) was recorded. Figure 6 shows recordings made from two Y cells that had a similar receptive field size. Figure 6A illustrates a

FIGURE 5. Comparison of the average threshold of retinal irradiance between normal and detached retinas. Each point of the data represents averaged threshold irradiance for each RD group. The testing spot was adjusted to match the center size of the RF. Ganglion cells were dark adapted for 40 minutes before entering the threshold test. The unattenuated retinal irradiance levels ranged from 2.47 to 3.40 log photons · μm²/s. This irradiance level was reduced by a set of neutral-density filters ranged from 0.1 to 4 log ND (neutral density). The threshold irradiance of Y cells recorded from the normal retina was used as a control. Average irradiance threshold and number of cells tested in each group: control (1.21 log photons · μm²/s, SEM = 0.13, n = 13); day 1 (2.02 log photons · μm²/s, SEM = 0.08, n = 10); day 3 (1.87 log photons · μm²/s, SEM = 0.15, n = 10); day 7 (2.28 log photons · μm²/s, SEM = 0.14, n = 12). Threshold irradiance was significantly elevated at day 1 (***P < 0.0001), day 3 (***P < 0.003), and day 7 (***P < 0.0001). Student's t test was applied in the statistical analysis. Error bars, SEM.

threshold irradiance. A normal retinal cell (1021-1) that had typical transient discharges at both irradiance levels is shown in Figure 4A. Figure 4B depicts a Y cell (1125-8) recorded from the detached retina that did not have a typical transient firing pattern, but it delivered only weakly modulated discharges in response to the testing spot at a retinal irradiance of 3.18 log photons · μm²/s, whereas a weaker stimulus evoked inconsis-

FIGURE 6. Contrast response of two Y cells recorded from normal and detached retinas. Both cells responded to 0.26 cyc/deg sinusoidal drifting gratings at two different contrasts, 100% and 20%, respectively. (A) Discharge pattern of cell (1021-1) recorded from normal retina, ON-center receptive field, located at the superior nasal retina (eccentricity, 6.8 mm). (B) Discharge pattern of cell (1112-1) recorded from the detached retina, ON-center receptive field, located at the superior nasal retina (eccentricity, 6.5 mm). (C) Comparison of the contrast sensitivity response of the two cells. The abscissa is spatial frequency in cyc/deg. Vertical coordinate shows the contrast sensitivity.
normal Y-cell discharge in response to 0.26 cyc/deg drifting sinusoidal gratings at two contrast levels, 100% and 20%, respectively. As expected, this cell responded well at both contrast levels with an increase in response amplitude at 100% contrast. On the other hand, as shown in Figure 6B, although the cell from the 1-day retina responded well at 100%, contrast-modulated activity was substantially reduced at 20% contrast. In fact, the cell scarcely responded to testing gratings at this contrast level. Figure 6C shows contrast-sensitivity response profiles of the two cells. We plotted response magnitude (spk/s) versus contrast curves for each spatial frequency. Then, from these curves, the contrast values required to evoke a threshold response were obtained; the reciprocals of these values are plotted in Figure 6C. The contrast sensitivity curve of the Y cell, which was recorded from a retina detached for 1 day, shifted downward, suggesting the overall contrast response capacity was eradiacted. In Figure 7, compared with normal Y cells (mean, 3.6%; SEM, 0.004; n = 11), day 1 (14.5%; SEM, 0.02; P < 0.0002; n = 10), day 3 (21.8%; SEM, 0.04; n = 12), and day 7 (47.5%; SEM, 0.05; P < 0.0001; n = 10), there were statistically significant differences between day 1 and day 7 (***P < 0.0002), day 3 (***P < 0.0003), and day 7 (***P < 0.0001). In addition, there were statistically significant differences between day 1 and day 7 (***P < 0.0001) and between day 3 and day 7 (**P < 0.0006) retinas. Conventions are as for Figure 5.

FIGURE 7. Comparison of average contrast threshold in normal and detached retinas. Response magnitudes of recorded cells versus contrast curves for each spatial frequency were plotted first. From these curves the contrast values required to evoke a threshold response were obtained. Contrast threshold of Y cells recorded from the normal retina was used as a control. Contrast threshold and number of cells in each post-RD group: control (3.6%, SEM = 0.004, n = 11); day 1 (14.5%, SEM = 0.02, n = 10); day 3 (21.8%, SEM = 0.04, n = 12); day 7 (47.5%, SEM = 0.05, n = 10). In comparison with the control group, the threshold was significantly elevated at day 1 (**P < 0.0002), day 3 (***P < 0.0003), and day 7 (***P < 0.0001). In addition, there were statistically significant differences between day 1 and day 7 (***P < 0.0001) and between day 3 and day 7 (**P < 0.0006) retinas. Conventions are as for Figure 5.

DISCUSSION

The present investigation demonstrates that Y-cell single unit and population characteristics deteriorate quickly after RD, with a significant decrease in the luminance threshold and contrast response detected on the first day of detachment. Visual function declines progressed after 3 days and 7 days of detachment. Taken together, our data suggest that rapid early-stage retinal neurocircuitry remodeling, induced by RD can be objectively demonstrated and quantitatively investigated at the single-cell level.

RD Impact on Y Cells

One essential question is whether RD affects a specific population of ganglion cells. Alpha cells, for example, were found to be more susceptible to RD injury based on their increased GAP43 and neurofilament protein expression. Our study offers, for the first time, physiological evidence that Y cells absorbed RD impact that was reflected in its physiological response properties.

There were different degrees of functional impact at ON and OFF responses, luminance sensitivity, and contrast sensitivity. First, we encountered more ON-center Y cells than OFF-center cells in the controls and all RD retinas during this experiment, though it could not be excluded that our recording method had a sampling bias. However, using the same recording setup and approach, we demonstrated in the congenic and dystrophic RCS rats that the sampling bias had only a limited impact. For example, our results show that most of the encountered cells had ON-center receptive fields in the congenic RCS rats, whereas a similar number of ON and OFF cells were recorded in the dystrophic rats younger than 1 month of age. Therefore, if the sampling bias was not playing a major role in our RD experiment, the present data appear to suggest that the OFF cells absorbed more impact than the ON cells because of the physical separation of the photoreceptor outer segments from the retinal pigment epithelium at the early stages of the detachment. Physically moving the retina away from its choroidal blood supply would create hypoxia. It is possible that the retina becomes hypoxic because of the large energy requirement of rods when in the dark-adapted state. This energy consumption could further diminish the already low oxygen tension of the inner plexiform layer (IPL), which is one of the highest O2 consumption regions in the retina. Moreover, evidence shows a higher oxygen demand of the processes in the deeper regions of IPL involved in the OFF pathway. Thus, the OFF cells could be more vulnerable to hypoxic attack than the ON cells. Indeed, as illustrated in Figure 3B, some OFF cells may start to recover from hypoxia 7 days after detachment surgery. In fact, the frequency of encountering OFF cells was 12% and 11% for 1-day and 3-day retinas, respectively, but by day 7, it was 52%, which was even slightly higher than that of the control group (24%). Although our data are suggestive, additional work must be done to determine conclusively whether RD affects the ON and OFF retinal pathways differently.

Second, our result reveals that both low and high retinal irradiance levels of visual stimuli were impaired by the detachment, suggesting both rods and cones were injured. The intensity of low irradiance stimuli fell well into the scotopic range; there is a quick depression in the ganglion cell luminance sensitivity. This quick decline in luminance sensitivity could be attributed to factors such as hypoxia, gradual photoreceptor apoptosis, and reattachment. Hypoxia is created by physically separating the retina from its choroidal blood supply, causing fluid accumulation between the retinal pigment epithelium and the detached retina. Excess fluid under the retina
does not impose a barrier to diffusion, but it does increase the distance of the retinal pigment epithelium from the outer segments. In addition, our result suggests that RD had substantial impact on the contrast sensitivity. An earlier ERG study shows that the functional abnormalities persist in the retached retina, even after brief RD. Additional clinical evidence also shows that there is a clear correlation between the duration of the detachment and contrast sensitivity. Our data are consistent with these observations. The deterioration of the contrast sensitivity is faster and more severe than the luminance threshold. As shown in Figure 4, compared with data are consistent with these observations. The deterioration of phase 1 remodeling consists of three phases: phase 1, photoreceptor stress; phase 2, photoreceptor death; and phase 3, neuronal remodeling. Successful rescue must begin during phase 1. However, the links among molecular expression, cellular architecture, physiological properties, and recovery of normal visual function during phase 1 are largely unknown. The absence of physiological response properties of neurons in the detached retina could be one of the reasons. Our study demonstrates that in vitro whole mount recording could be an alternative and effective way of investigating ganglion cell response profiles during phase 1 remodeling. For instance, the quick reduction in ganglion cell luminance and contrast responses reported here may be linked to injured photoreceptors and perhaps the reactivity of Müller cells. Müller cells react to detachment very quickly in several ways. One of the most important is the downregulation of glutamine synthetase, which results in a subsequent disturbance of the glutamate balance in the detached retina. Another is that, by day 7, the percentage of encountered OFF cells increased to 32%. This result implies that some OFF cells started to recover, although this type of quick functional loss and recovery was probably not a result of the massive cellular remodeling that occurs relatively late in many inherited retinal degeneration diseases but rather of more subtle changes in the retinal circuitry that may result from events such as slow recovery from hypoxia, neurite sprouting, and changes at the level of individual synaptic connections. Thus, additional in vitro physiological experiments should be designed to address these issues. This study can be the basis for a model to test new treatments for retinal detachment and other retinal degenerative diseases.

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