Developmental time course distinguishes changes in spontaneous and light-evoked retinal ganglion cell activity in rd1 and rd10 mice

Steven F. Stasheff,1,2 Malini Shankar,1 and Michael P. Andrews1

Departments of 1Pediatrics (Neurology) and 2Ophthalmology and Visual Sciences, The University of Iowa and The Carver College of Medicine, Iowa City, Iowa

Submitted 10 August 2010; accepted in final form 8 March 2011

Stasheff SF, Shankar M, Andrews MP. Developmental time course distinguishes changes in spontaneous and light-evoked retinal ganglion cell activity in rd1 and rd10 mice. J Neurophysiol 105: 3002–3009, 2011. First published March 9, 2011; doi:10.1152/jn.00704.2010.—In a subset of hereditary retinal diseases, early photoreceptor degeneration causes rapidly progressive blindness in children. To better understand how retinal development may interact with degenerative processes, we compared spontaneous and light-evoked activity among retinal ganglion cells in rd1 and rd10 mice, strains with closely related retinal disease. In each, a mutation in the Pde6b gene causes photoreceptor dysfunction and death, but in rd10 mice degeneration starts after a peak in developmental plasticity of retinal circuitry and thereafter progresses more slowly. In vitro multielectrode action potential recordings revealed that spontaneous waves of correlated ganglion cell activity comparable to those in wild-type mice were present in rd1 and rd10 retinas before eye opening [postnatal day (P) 7 to P8]. In both strains, spontaneous firing rates increased by P14–P15 and were many times higher by 4–6 wk of age. Among rd1 ganglion cells, all responses to light had disappeared by ~P28, yet in rd10 retinas vigorous ON and OFF responses were maintained well beyond this age and were not completely lost until after P60. This difference in developmental time course separates mechanisms underlying the hyperactivity from those that alter light-driven responses in rd10 retinas. Moreover, several broad physiological groups of cells remained identifiable according to response polarity and time course as late as P60. This raises hope that visual function might be preserved or restored despite ganglion cell hyperactivity seen in inherited retinal degenerations, particularly if treatment or manipulation of early developmental plasticity were to be timed appropriately.

retinal degeneration; maturation; plasticity; hyperactivity; multielectrode recording

RETNAL DEGENERATIONS represent the most common monogenic inherited cause of blindness and remain incurable (Birch 1999; Chang et al. 1994; Hansen et al. 2008). Among these, some of the most devastating are those causing rapid blindness from birth or early childhood (Ahmed and Loewenstein 2008; Chung and Traboulsi 2009; den Hollander et al. 2008; Drack et al. 2009; Fulton et al. 1996; Heher et al. 1992). However, in recent clinical trials, young children undergoing gene therapy had greater recovery of visual function than adults (Maguire et al. 2009). This finding highlights the importance of understanding how physiological processes uniquely active during retinal maturation interact with early onset retinal degenerative diseases to produce changes in retinal circuits and their downstream targets in the central visual system. Improved understanding of such developmental mechanisms may facilitate improvements in treatment.

Mutations in the gene encoding rod phosphodiesterase (PDE6b) are the most frequent cause of autosomal recessive retinitis pigmentosa in humans (Wang et al. 2001). A mutation in this gene causes early onset, rapidly progressing photoreceptor degeneration in rd1 mice. The vast majority of photoreceptors are lost over a brief early developmental period during which inner retinal circuits for visual processing are formed and consolidated (Coombs et al. 2007; Diao et al. 2004; Kim et al. 2010; Morgan et al. 2008; Myhr et al. 2001; Sernagor et al. 2001; Tian 2004, 2008; Wang et al. 1997; Wong 1999). Recent work has refined our understanding of how corresponding physiological behavior matures: for example, the role of synaptic transmission in establishing ON/OFF segregation of ganglion cell dendrites, alterations in spontaneous activity and action potential threshold that differ between ON and OFF cells, in the relative strength of ON and OFF synaptic inputs and timing of postsynaptic potentials driving ON and OFF cells’ outputs (spike trains), and the formation of receptive fields (Bisti et al. 1998; Blankenship and Feller 2010; He et al. 2011; Kerschensteiner et al. 2009; Kerschensteiner and Wong 2008; Myhr et al. 2001; Tian 2004, 2008; Tian and Copenhagen 2003; Xu and Tian 2004).

In rd1 mice, we previously demonstrated two striking alterations of retinal ganglion cell signaling to the brain. First, ganglion cells exhibit hyperactivity, firing spontaneously at rates many times greater than normal. Second, for a brief period before responses to stimulation with light disappear, OFF responses are preferentially preserved compared with ON responses. Importantly, ganglion cell activity is normal before an active period of synaptogenesis and circuit refinement that begins near the time of eye opening (Stasheff 2008). Together, these findings suggest that significant reorganization of inner retinal circuitry occurs during a critical period between approximately postnatal days 12 and 30 (~P12–P30).

To determine whether ganglion cell physiology is affected by the interaction of retinal disease and early developmental plasticity, we studied changes in retinal physiology in rd10 mice. The rd10 mouse carries a mutation in the same rod Pde6b gene as rd1, yet measurable photoreceptor loss does not begin until ~P18. By this time the most active period in developmental plasticity is drawing to a close (Wang et al. 1997; Wong 1999).

In this report we delineate the time course of changes in spontaneous and light-driven activity of rd10 ganglion cells, comparing these with our previous findings (Stasheff 2008) as well as additional data on wild-type (wt) and rd1 ganglion cell...
activity, all on a C57 genetic background. We demonstrate for the first time that in rd10 retinas, spontaneous hyperactivity emerges in a manner similar to that in rd1, yet normal developmental processes form and maintain light-evoked activity for an extended period. This includes maintaining recognizable response classes of individual ganglion cells. We emphasize how the time course of these activity changes compared with that of normal maturation of the retinal circuits that process visual information. Thus we deduce that developmental mechanisms active during the critical period between eye opening and −P30 contribute little to the emergence of hyperactivity in these models and that the mechanisms underlying spontaneous hyperactivity are separable from those that alter light-driven responses. We discuss the implications of these findings for our understanding of interactions between visual system development and degenerative diseases, at the level of both the retina and the central nervous system, as well as for treatments aimed at preserving or restoring normal visual function in patients with inherited retinal degenerations.

MATERIALS AND METHODS

Tissue preparation. Wild-type (wt; C57BL/6J strain), rd1 (B6.C3-Pde6brd1<sup>+/−</sup>Hps4<sup>−/−</sup> or C3H/HeJ), and rd10 mice (B6.CXB1-Pde6brd1<sup>+/−</sup>H11022) were generated locally from purchased breeding pairs (Jackson Laboratories, Bar Harbor, ME). Animals were cared for in accordance with institutional guidelines of the University of Iowa under an approved Institutional Animal Care and Use Committee protocol and in accordance with the Institute for Laboratory Animal Research Guide for the Care and Use of Laboratory Animals. Animals were dark-adapted for ≥30 min before being anesthetized with intraperitoneal or intramuscular injection of xylazine (50–200 mg/kg) and ketamine (50–200 mg/kg) sufficient to extinguish tail pinch and corneal reflexes. Under infrared illumination to minimize exposure to visible light, with the use of a dissecting microscope (Leica Microsystems, Bannockburn, IL) with infrared image intensifiers (Bionetics, Bannockburn, IL) and perfused with warm (36–37°C), oxygenated Ringer medium at a rate of 2.5–4 ml/min (Meister et al. 1994; Tian and Copenhagen 2001). Ringer medium included (in mM) 124 NaCl, 2.5 KCl, 2 CaCl<sub>2</sub>, 2 MgCl<sub>2</sub>, 1.25 NaH<sub>2</sub>PO<sub>4</sub>, 26 NaHCO<sub>3</sub>, and 22 glucose. Data presented are from a total of >900 wt cells from 27 retinas, >2,300 rd1 cells from 42 retinas, and >1,500 rd10 cells from 20 retinas.

Multielectrode recording. A 60-channel amplifier (Multichannel Systems, Reutlingen, Germany) interfaced with digital sampling hardware and software (Bionic Technologies, Salt Lake City, UT) for recording and analyzing spike trains from each of the electrodes in the array. Digitized data were streamed onto the computer’s hard drive and further analyzed off-line. After transfer of the retina to the recording chamber, recordings were allowed to stabilize for at least 1 h (Stasheff 2008). Data presented are from the first 1–3 h of recording, unless otherwise specified.

Visual stimulation. In experiments with light stimulation, a miniature computer monitor (Lucidiv; MicroBrightField, Colchester, VT) projected visual stimuli through a ×5 objective, focusing them onto the photoreceptor layer of the retina via standard microscope optics (Zeiss Axiosplan). Luminance was calibrated via commercial software (VisionWorks; Vision Research Graphics, Durham, NH) with the use of a radiometer (PR-670; Photo Research, Chatsworth, CA) and photodiode (S1133-11; Hamamatsu, Hamamatsu City, Japan) placed in the tissue plane. Full-field flash stimuli (illuminance 0–355 cd/m<sup>2</sup>, retinal irradiance 0–34 μW/cm<sup>2</sup>, 500 or 1,000 ms, P43 phosphor with peak emission at 545 nm) were displayed at 5-s intervals, and responses were averaged over 10–20 trials.

Spike waveform analysis. Action potential (spike) waveforms accepted for further analysis were ≥60 mV in amplitude and ≥1.85 times the root mean square (RMS) of the background signal. To distinguish responses from different cells that might appear on the same electrode, we used a component of the data acquisition software (Bionic Technologies) or similar freeware (PowerNAP, Neuroshare, http://neuroshare.sourceforge.net/index.shtml) for supervised automated sorting of action potential profiles according to a principle components analysis paradigm (Wheeler 1999). In cases where an optimal solution was not immediately distinguished on this basis, the data initially were segregated into a greater number of clusters than seemed the likely final solution. Interspike intervals (ISIs) and cross-correlation functions for the corresponding spike trains were analyzed to confirm appropriate assignment of individual waveforms to the same or distinct cells. Accepted data demonstrated a refractory period of >1 ms (typically 2–5 ms) and did not display recognizable noise patterns [60 Hz, very high-frequency (>10 kHz) transients, or sinusoidal oscillations] (Segev et al. 2004). These procedures typically resulted in one to three cells being isolated from each electrode.

Spike train analysis. The spontaneous mean firing rate for each recorded cell was computed as the total number of spikes divided by the length of the recording period. Cross-correlation functions were computed for pairs of spike trains by measuring all intervals between each spike in one train and all spikes in the other train, binning at 5 ms. Parameters of spontaneous developmental waves of ganglion cell activity were computed in accord with previous investigators (Torborg et al. 2004, 2005; Wong et al. 1993) from recording segments of 20–30 min: mean firing rate (total number of spikes divided by the length of the recording period), instantaneous firing rate (inverse of ISI within bursts), burst duration and frequency (as interburst interval), and percentage of the entire recording period spent firing at >1 Hz or ≥10 Hz. A burst was defined as a group of at least three spikes in which all ISIs were <1 s. In addition, the correlation coefficient (CI) was computed as described by Wong et al. (1993):

\[ CI = N_{AB}(-\text{intcorr} + \text{intcorr}) \cdot T \]

where \( N_{AN} \) is the number of instances in which a spike from neuron \( A \) occurs within the interval \( \text{intcorr} \) (we chose 100 ms) of a spike from neuron \( B \), \( T \) is the total length of the recording, and \( N_A \) and \( N_B \) are the numbers of spikes in each neuron’s spike train over the total recording period.

Light-evoked responses were quantified as the total number of action potentials occurring within 1 s following a light transition (ON or OFF), after subtracting the background spontaneous firing rate over the 1 s preceding the stimulus. These responses were averaged over 10 or 20 trials, and amplitude was expressed as a net mean firing rate (spikes/s). For such calculations, ganglion cells were included if the net response to the maximum stimulus (34 μW/cm<sup>2</sup> retinal irradiance) was at least 1 spikes/s.

Statistical analysis. Data from our previous study on rd1 ganglion cells (Stasheff 2008) were pooled with those from an additional 492 cells in 7 wt retinas and 320 cells in 3 rd1 retinas (on the C57 background), and statistical analysis was repeated on the combined sample. None of the rd10 data presented have been published previously. Means ± SE are presented for most of the parameters above. Given their nonnormal distribution, however, central values for many of these parameters were also expressed as medians and were compared using the Wilcoxon-Mann-Whitney U-test.

RESULTS

Normal developmental retinal waves in rd10 ganglion cells.

A well-recognized developmental pattern of retinal ganglion...
cell activity is the correlated burst firing that migrates across multiple ganglion cells in waves during the early postnatal period before eye opening (in mouse, up to ~P12) (Feller et al. 1997; Firth et al. 2005; Stafford et al. 2009; Wong 1999). We confirmed the existence of such periodic bursts of action potentials at P7–P8 in rd10 mice as well (Fig. 1) and found that a number of spatiotemporal parameters used to quantify this activity differed minimally from those of wt (C57BL/6J) or rd1 waves (Stafford et al. 2009; Stasheff 2008; Torborg and Feller 2005; Torborg et al. 2004; Wong 1993). These parameters were average firing rate, burst duration, interburst interval, intraburst firing rate, and percentage of time spent firing >1 Hz or > 10 Hz. Figure 1B displays the distributions of these parameters for 231 ganglion cells from 3 rd10 retinas and for 226 cells from 6 wt retinas. We also found very similar values for the correlation index (CI) as a function of distance between cell pairs (although these were statistically distinguishable at short distances) (Fig. 1C). Despite small statistically significant differences (P < 0.05, Mann-Whitney U-test; see Supplemental Material, Supplemental Table S1) in some of these parameters, the similarity of all these parameters indicates that rd10 ganglion cells, like rd1 cells (Stasheff 2008), exhibit normal spontaneous, periodic wavelike inner retinal activity before eye opening.

At least three phases of retinal wave activity have been recognized during early postnatal development of the retina (Firth et al. 2005). To determine whether these waves retain normal spatiotemporal features during a later phase of their existence, we also recorded from wt, rd1, and rd10 ganglion cells at P10–P11 (see Supplemental Table S2 and Fig. S1). Although the primary neurotransmitter drive for retinal waves (glutamate) is different at this age than at P7–P8 (acetylcholine), the pattern of waves among the strains was highly similar. Until after the eyes opened, there was no sign of spontaneous hyperactivity such as described in the following section.

Spontaneous hyperactivity in maturing rd10 ganglion cells. To determine whether hyperactivity similar to that seen in rd1 mice (Stasheff 2008) emerges in rd10 ganglion cells and with a similar time course, we examined the spontaneous activity of 2,175 cells in 21 retinas from P14 (just after eye opening) to P120. Figure 2 shows that spontaneous firing was more rapid in rd10 than wt retinas at the earliest age examined (P14). Thereafter, spontaneous discharge rates increased still further, peaking by P28 at rates higher than seen in rd1 ganglion cells (Stasheff 2008) and remaining elevated well beyond that of wt cells through P120. This may be seen in the sample raster plots of Fig. 2A and in the comparison of mean firing rates (±SE) for wt, rd10, and rd1 ganglion cells across age groups in Fig. 2B. Closer inspection reveals a shift in the distribution of firing rates within the ganglion cell population, favoring a greater proportion of cells with higher frequency firing (Fig. 3). Note that spontaneous activity was greater among rd10 than rd1 ganglion cells even at stages where photoreceptor degeneration was less advanced both histologically (Barhoum et al. 2008; Gargini et al. 2007; Strettoi et al. 2005) and as judged by the strength of light-evoked activity (see the following two sections and Fig. 5).

1 Supplemental Material for this article is available online at the Journal of Neurophysiology website.
Recognizable response groups among rd10 ganglion cells. We examined the responses of rd10 ganglion cells to full-field illumination (1-s flashes, 34 μW/cm²) at P28 and compared these with those of age-matched wt cells and of rd1 cells at an equivalent stage of photoreceptor degeneration (P14) (Barhoum et al. 2008; Chang et al. 2002; Gargini et al. 2007). We were able to recognize several broad physiological groups of cells in each of the strains we studied, according to response polarity and time course (Fig. 4). The majority of cells displayed rapid responses typical of those driven by classic photoreceptors, although we also occasionally recorded responses with the slower dynamics characteristic of intrinsically photosensitive retinal ganglion cells (Schmidt and Kofuji 2009; Wong et al. 2007).

One particular aspect of these responses was of special interest based on our previously reported findings in rd1 ganglion cells; namely, at intermediate stages of degeneration, ON responses were disproportionately diminished and OFF responses relatively preserved (most prominently in mice with the original C3H genetic background) (Stasheff 2008). In contrast, among rd10 ganglion cells, we found that at several stages of degeneration, ON and OFF responses were affected to a similar degree.

Delayed decay of rd10 light-evoked responses. Although spontaneous hyperactivity begins to emerge in rd10 ganglion cells shortly after eye opening, the responses of these cells to full-field flash illumination do not begin to decay (relative to those of wt cells) until several weeks later. This deterioration is thus of later onset, and also proceeds more slowly, than in rd1 mice (Fig. 5) (Stasheff 2008). In fact, although by P60 the vast majority of ganglion cells did not exhibit any discrete response to the maximal intensity light flash used, we did notice a small proportion of cells that remained vigorously responsive to light at this age (compared with wt at P60 and at P114–P120). This
contrasts with an earlier disappearance of full-field electroretinogram (ERG) responses in this strain (Chang et al. 2007; Gargini et al. 2007). These cells may have been located more peripherally in the retina, although more detailed analysis and a larger sample size are needed to confirm this. We also noticed that at P14, despite less efficient phototransduction by rods with mutant Pde6<sup>−/−</sup>, rd10 ganglion cell responses were of greater magnitude than those of the wt, and also more sustained. This could be explained by increased signal amplification from rods and ON cone bipolar cells and/or reduced activation of GABA- or glycinergic amacrine cells that in turn disinhibit ganglion cell responses. Quantitative analysis of this feature awaits a larger sample size, and intracellular recording will be needed to test the underlying mechanisms rigorously.

DISCUSSION

Pediatric recipients of gene therapy for retinal degeneration have had greater recovery of vision than adults (Maguire et al. 2009). Our previous findings suggested that the normal maturation of retinal circuits for visual processing might substantially influence the natural history of these diseases and the outcome of attempts to treat them (Stasheff 2008). The goal of the current study was to distinguish among changes in retinal function that can be attributed primarily to degeneration of photoreceptors, secondary mechanisms involving the development of retinal circuits, or interactions between the two. Our strategy was to compare two mouse models of retinal degeneration, both caused by mutations in Pde6<sup>b</sup>, but differing in their age of onset and speed of progression: rd1 and rd10.
By comparing these two models, we gained insights of broad significance. (See Supplementary Materials for more extensive discussion.) First, developmental spontaneous retinal waves in the inner retina appear normal, indicating retinal circuit function similar to wt before eye opening. Second, rd10 ganglion cells display increased spontaneous firing, suggesting that such hyperactivity may be a feature common to retinal degenerations (Dräger and Hubel 1978; Marc et al. 2003; Margolis et al. 2008; Sauvé et al. 2001; Sekirnjak et al. 2009; Stasheff 2008; Ye and Goo 2007b).

Third, excessive spontaneous activity in both rd1 and rd10 retinal ganglion cells emerges near the time of eye opening, when the first reliable communication between the outer and inner retina is established. Finally, hyperactivity emerges before light-evoked responses deteriorate in rd10, implying separate mechanisms underlying these two types of activity.

**Normal retinal waves in immature rd10 retinas.** We find that the genetic defect in phototransduction in rd10 mice does not substantially affect the early development of spontaneous waves of correlated firing in the inner retina; rd1 and rd10 waves have spatiotemporal dynamics highly similar to those of wt. This is true when the primary drive for the waves is either cholinergic (P7–P8) or glutamatergic neurotransmission (P10–P11) (Blankenship et al. 2009; Butts et al. 2007; Syed et al. 2004; Zhou and Zhao 2000). This might be expected given that at these ages, synapses between abnormal photoreceptors, bipolar cells, and their targets, the amacrine and ganglion cells that mediate the waves, have not yet matured (Morrow et al. 2008; Wong 1999). This contrasts with the effects of a selective deficit in photoreceptor-to-ON bipolar cell neurotransmission, which leads to persistent abnormal retinal waves and aberrant projections to the central nervous system (Demas et al. 2006; Maddox et al. 2008; McCall and Gregg 2008). The presence of normal spontaneous activity in rd1 and rd10 before eye opening indicates relatively intact function of retinal circuits, so if treatment could be applied at this early stage, visual outcomes might be greatly improved.

**Temporal dissociation between hyperactivity and loss of light responsiveness.** The parallel acceleration of spontaneous activity and diminution of light-evoked responses in rd10 had suggested that these two changes are related mechanistically (Stasheff 2008). In contrast, our rd10 findings show temporal segregation between the emergence of hyperactivity and the loss of light-evoked responses. This implies that spontaneous and light-driven activity develop from different underlying physiological mechanisms, as in wt ganglion and amacrine cells (He et al. 2011).

The fact that in both rd1 and rd10, spontaneous activity is normal shortly before eye opening, then supranormal just after it, suggests that developmental events may initiate hyperactivity within outer retinal circuits (photoreceptors, horizontal or bipolar cells) before a critical period of neural plasticity in the inner retina. Excessive signals would then be transmitted to the inner retina only after synapses form between bipolar, amacrine, and ganglion cells.

**Preservation of light-evoked responses and role of developmental plasticity.** After simple full-field stimulation with light, we recorded a number of readily recognizable broad categories of rd10 ganglion cell response types. We do not propose these response groups as a classification scheme (cf. Blankenship and Feller 2010; Carcieri et al. 2003; Farrow and Masland 2011; Kerschensteiner et al. 2009; Sernagor et al. 2001; Stone and Pinto 1993; Tian 2008; Xu and Tian 2004), particularly since response properties depend on the form of stimuli (Sagdullaev and McCall 2005) and complex cross-pathway interactions within the intricate circuitry of the inner retina (Liang and Freed 2010; Molnar et al. 2009; Werblin 2010). However, the relative preservation of simple physiological properties in at least a subset of ganglion cells, similar to other models of retinal degeneration (Margolis et al. 2008; Sekirnjak et al. 2006; Ye and Goo 2007a) and early stage rd1 degeneration (Stasheff 2008), argues that several distinct physiological cell classes ["labeled lines" of the neural code the retina uses to communicate with the brain (Farrow and Masland 2011; Roska et al. 2006)] persist for a time. More detailed characterization of ganglion cell responses with more complex stimuli and response analysis is ongoing in our laboratory.

Comparison of rd1 and rd10 did reveal two clear differences between the strains. First, substantial responses are preserved for several more weeks in rd10 ganglion cells, even longer than full-field ERG responses (Chang et al. 2007; Gargini et al. 2007). Second, in contrast to the disproportionate loss of ON responses seen in rd1 mice (Stasheff 2008), ON and OFF responses were affected similarly in rd10 mice (Fig. 5). In contrast to rd1, the diminution of ON and OFF responses in rd10 mice begins only after a period of heightened neural plasticity from ~P12–P30 critical for normal ON-OFF segregation in visual processing pathways. Therefore, it seems likely that in rd1 mice, early distortion of signal transmission during synaptic maturation leads to a functional dysregulation of ON and OFF pathway physiology. Although some evidence suggests that a disproportion of ON and OFF pathway signaling might be related to spontaneous hyperactivity (Demas et al. 2006; Maddox et al. 2008; McCall and Gregg 2008; Myhr et al. 2001), we found a more proportionate loss of ON and OFF responses in rd10 than in rd1, yet a similar degree of hyperactivity at the same age in both strains.

**Implications for treatment of retinal degenerations.** The finding that retinal output to the brain is initially normal in photoreceptor degeneration encourages the development of treatments to sustain such normal activity. The rapid appearance of markedly aberrant spontaneous activity shortly thereafter also suggests that to be maximally effective, treatments may need to be introduced at an early age; normal retinal waves instruct targeting of retinal projections to downstream central visual system targets, but certain aberrant patterns of spontaneous activity lead to abnormal projections (Blankenship and Feller 2010; Cang et al. 2005; Demas et al. 2006; Firth et al. 2005; Grubb et al. 2003; Hooks and Chen 2006; Maddox et al. 2008; McCall and Gregg 2008; Muir-Robinson et al. 2002; Sernagor et al. 2001; Stafford et al. 2009; Wong 1999).

At the same time, the rd10 model demonstrates that characteristic responses to light ("labeled lines" in the neural code of vision) may persist beyond the emergence of spontaneous hyperactivity.

Although this study does not address in detail the mechanisms or timing of changes in retinal circuits that lead to abnormal ganglion cell activity, three of our rd10 findings taken together imply that spontaneous hyperactivity need not prevent recognizable encoding of visual signals by the inner retina: 1) these circuits mediate normal retinal waves before eye opening; 2) the emergence of hyperactivity and loss of light-evoked responses are temporally segregated; and 3) dis-
tinct response classes remain recognizable well after hyperac-

activity has emerged.

The implied degree of preservation of inner retinal process-

ing in the face of such hyperactivity provides encouragement that treatments such as gene replacement, stem cell transplanta-
tion, or electrical stimulation could restore effective commu-
nication between the retina and brain (Alexander and Haus-

wirth 2008; Das et al. 2005; Delyfer et al. 2004; Loewenstein et al. 2004; Simonelli et al. 2009). Indeed, recently gene therapy for rdl and rd10 has led to partial restoration of visual function in both the retina and central nervous system (Busskamp et al. 2010; Jing Pang et al. 2010). Thus the window of opportunity for successful treatment may extend beyond the developmental period studied presently. Finally, because spontaneous hyperactivity can precede photoreceptor loss, if it can be identified clinically, it might allow early detection and treatment of retinal degenerations.

Although these concepts are speculative at this point, they do suggest directions for future studies and indicate that the role of developmental neural plasticity in other neurodegenerative diseases is worth exploring. Clearly, we need to understand in much greater detail the interaction between developmental plasticity and degenerative mechanisms in these blinding diseases before we can translate such knowledge into real advances toward effective treatment.

ACKNOWLEDGMENTS

We thank Erik Nylen for assistance in data analysis.

GRANTS

This work was supported by the Lewis Rhodes Charitable Trust, the Child Neurology Foundation, and Care For Kids-Iowa Department of Public Health.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES


