J Neurophysiol 113: 420–425, 2015.
First published October 29, 2014; doi:10.1152/jn.00702.2014.

Spontaneous oscillatory activity in rd1 mouse retina is transferred from ON pathway to OFF pathway via glycinergic synapse

Deepak Poria and Narender K. Dhingra
National Brain Research Centre, Manesar, Gurgaon, Haryana, India

Submitted 17 September 2014; accepted in final form 23 October 2014

Poria D, Dhingra NK. Spontaneous oscillatory activity in rd1 mouse retina is transferred from ON pathway to OFF pathway via glycinergic synapse. *J Neurophysiol* 113: 420–425, 2015. First published October 29, 2014; doi:10.1152/jn.00702.2014.—Retinal ganglion cells (RGCs) spike randomly in the dark and carry information about visual stimuli to the brain via specific spike patterns. However, following photoreceptor loss, both ON and OFF type of RGCs exhibit spontaneous oscillatory spike activity, which reduces the quality of information they can carry. Furthermore, it is not clear how the oscillatory activity would interact with the experimental treatment approaches designed to produce artificial vision. The oscillatory activity is considered to originate in ON-cone bipolar cells, AII amacrine cells, and/or their synaptic interactions. However, it is unknown how the oscillatory activity is generated in OFF RGCs. We tested the hypothesis that oscillatory activity is transferred from the ON pathway to the OFF pathway via the glycinergic AII amacrine cells. Using extracellular loose-patch and whole cell patch recordings, we recorded oscillatory activity in ON and OFF RGCs and studied their response to strychnine, a specific glycine receptor blocker. The cells were labeled with a fluorescent dye, and their dendritic stratification in inner plexiform layer was studied using confocal microscopy. Application of strychnine resulted in abolition of the oscillatory burst activity in OFF RGCs but not in ON RGCs, implying that oscillatory activity is generated in ON pathway and is transferred to OFF pathway, likely via the glycinergic AII amacrine cells. We found oscillatory activity in RGCs as early as *postnatal day 12* in rd1 mouse, when rod degeneration has started but cones are still intact. This suggests that the oscillatory activity in rd1 mouse retina originates in rod pathway.

spike burst; glycinergic synapse; retinal degeneration; crossover inhibition

LOSS OF PHOTORECEPTORS, as in retinal degenerative diseases such as retinitis pigmentosa and age-related macular degeneration, leads to significant remodeling in inner retina (Barhoum et al. 2008; Cuenca et al. 2005; Dagar et al. 2014; Gargini et al. 2007; Jones et al. 2003; Nagar et al. 2009; Puthussery et al. 2009; Strettoi and Pignatelli 2000). In rd1 mouse, a widely used animal model of retinal degeneration, both ON and OFF type of retinal ganglion cells (RGCs), the output neurons of the retina, exhibit spontaneous oscillatory bursts of spikes (Pu et al. 2006; Stasheff 2008; Ye and Goo 2007). This oscillatory activity is also transmitted to higher visual areas of the brain (Drager and Hubel 1978), which may explain the presence of photopsia, a condition where patients with retinal degeneration perceive spontaneous flashes of light or phosphenes (Bittner et al. 2009; Heckenlively et al. 1988; Lepore 1990; Murtha and Stasheff 2003). The aberrant oscillatory activity in RGCs has been shown to reduce the signal-to-noise ratio in their light responses and thus their ability to transmit information to the brain (Toychiev et al. 2013; Yee et al. 2012). Furthermore, this poses a unique challenge for developing prosthetic devices designed to stimulate RGCs to produce artificial vision because it is not clear how the oscillatory activity in these cells would interact with the artificial stimuli.

Several recent reports have demonstrated that the oscillatory activity in RGCs in rd1 mouse is presynaptic in origin (Borowska et al. 2011; Choi et al. 2014; Margolis et al. 2008; Menzler and Zeck 2011; Toychiev et al. 2013; Trenholm et al. 2012; Yee et al. 2012). Although the exact presynaptic locus is not fully established, these reports suggest that ON-cone bipolar cells, AII amacrine cells, and/or the gap junctions between them may be involved. However, these sources do not explain how the oscillatory activity is generated in OFF bipolar cells and OFF RGCs. A recent study showed that the oscillatory activities in ON and OFF RGCs in rd1 mouse are 180° out of phase, suggesting that they receive excitatory and inhibitory inputs, respectively, from a common source (Margolis et al. 2014). The common source could possibly be in the outer plexiform layer (OPL) where ON/OFF dichotomy itself is generated. Alternatively, it could be in the inner plexiform layer (IPL) where the AII amacrine cells carry signals from rod bipolar cells (ON cells) to OFF bipolar cells and OFF RGCs via glycinergic synapses, as suggested previously (Borowska et al. 2011; Margolis et al. 2014). We tested this by recording from ON and OFF RGCs in adult as well as in developing rd1 mouse in the presence of strychnine, a specific glycine receptor blocker. If the oscillatory activity is generated in the ON pathway and transferred to OFF bipolar cells and OFF RGCs via the glycinergic AII amacrine cells, it should persist in the ON RGCs but disappear in the OFF RGCs after application of strychnine.

MATERIALS AND METHODS

Animals and tissue preparation. The rd1 mice (*Pde6b*^{rd1}; CBA/J) were obtained from The Jackson Laboratory (Bar Harbor, ME) and bred at the animal facility of the National Brain Research Centre, India. The animals were maintained on a 12:12-h light-dark cycle. The ambient daylight was ~200 lx (measured with an IL1400 photometer; International Light Technologies, Peabody, MA). Both male and female animals from *postnatal day* (P) *8* to adult (2–3 mo) were used. All experiments were approved by the Institutional Animal Ethics Committee of the National Brain Research Centre, India.

After dark adaptation for at least 30 min, an animal was euthanized by cervical dislocation and enucleated in dim red light. The eyeballs were transferred to carbogenated (5%) Ames' Medium (Sigma-Aldrich, St. Louis, MO) containing glucose (0.8 g/l) and sodium bicarbonate (1.9 g/l; pH 7.4), given a small incision perpendicular and close to the limbus, and hemisected at the ora serrata. The retina was isolated from the posterior eyecup and flat-mounted with ganglion cells facing up on a punched filter membrane (HAWP01300; Millipore, Billerica, MA). Mounted retinas were stored in a dark chamber

Address for reprint requests and other correspondence: N. K. Dhingra, National Brain Research Centre, Nainwal Road, NH-8, Manesar, Gurgaon, Haryana 122051, India (e-mail: naren@nbrc.ac.in).

in carbogenated Ames' Medium at room temperature. After the recording, retinas were fixed with 4% paraformaldehyde for 45 min at 4°C and transferred to PBS.

Electrophysiological recording. Retina mounted on the filter paper was transferred to a recording chamber (volume = ~2 ml; model RC-27L; Warner Instruments, Hamden, CT) on an upright microscope (BX51W1; Olympus, Tokyo, Japan) and superfused at 4–5 ml/min with carbogenated Ames' Medium maintained at 34–36°C in the chamber. Extracellular loose-patch or whole cell patch-clamp recordings were made from ganglion cells under visual control using IR-DIC optics as described previously (Dhingra et al. 2003; Margolis et al. 2008). Borosilicate glass capillaries (A-M Systems) were pulled on a Flaming/Brown micropipette puller (P-97; Sutter Instrument, Novato, CA) to make electrodes with tip resistance of 4–6 MΩ. The inner limiting membrane was cleared by advancing an electrode containing Ames' Medium at a slight positive pressure followed by recording with another electrode containing Ames' Medium (for loose-patch recording) or standard internal solution (for whole cell recording). The standard internal solution contained (in mM): 120 K-gluconate, 5 NaCl, 5 KCl, 5 HEPES, 5 EGTA, 1 $MgCl_2$, 1 ATP, and 0.1 GTP (pH 7.4). All recordings were made in current-clamp mode using MultiClamp 700B Amplifier (Molecular Devices, Sunnyvale, CA). Data were sampled at 5, 10, 20, or 50 kHz (Digidata 1322A; Molecular Devices) after low-pass filtering at the Nyquist frequency. For loose-patch recordings, the data were also high-pass filtered at 10 Hz. Strychnine (1, 2, or 5 μM) was bath-applied for ~10 min. Cells recorded extracellularly were injected with 2% DiI with a sharp electrode after the recording, whereas whole cell recorded cells were filled with Alexa Fluor 488 (5 mM) present in the electrode solution. All of the chemicals were purchased from Sigma-Aldrich unless noted otherwise.

Data analysis. Spike trains were analyzed offline using pCLAMP 9 software (Molecular Devices). Spike bursts were analyzed using burst analysis. Equal-length traces of 1 or 2 min each from control (just before the drug was applied) and strychnine (just before stopping the drug application) recordings were used for burst analysis. Spike bursts were detected using the delimiting interval method. For some cells, we used two different delimiting intervals for control and strychnine recordings because application of strychnine resulted in very high spike rates in these cells. However, the delimiting intervals were defined conservatively such that in these cases the burst frequency may be slightly underestimated in control traces and slightly overestimated in strychnine traces. For some cells (7 of 24), this method of calculating burst frequency did not represent the actual frequency because some spikes were missing even though the rhythmic membrane potential oscillations were clearly visible. For these cells, the burst frequency was computed from autocorrelograms. Autocorrelograms were generated in Clampfit 9 by cross-correlation of the recording trace (30 s) with itself at each sampling point (1 lag) for 500 ms in both directions.

Microscopy and cell identification. The dye-filled cells were imaged using an inverted confocal microscope (LSM 510 META; Carl Zeiss, Göttingen, Germany). To measure IPL thickness, the nuclei in the inner nuclear layer (INL) and ganglion cell layer (GCL) were labeled by incubating the retina in propidium iodide (5 μg/ml) for 10 min at room temperature. Images of 1-μm optical thickness were obtained to include GCL, IPL, and partly INL. Three-dimensional reconstructions of the dendrites were drawn using Neuromantic software (Darren Myatt, http://www.reading.ac.uk/neuromantic/; Jain et al. 2012). The RGCs were identified as ON or OFF type based on the level of stratification of their dendrites in the IPL. The cells that stratified in the outer 40% of IPL were considered OFF cells, whereas the ones that stratified in the inner 60% of IPL were taken as ON cells (Famiglietti and Kolb 1976; Yee et al. 2012).

RESULTS

Strychnine abolished oscillatory activity in OFF RGCs but not in ON RGCs. Figure 1 shows representative ON and OFF RGCs from adult rd1 mouse retinas, which produced sponta-

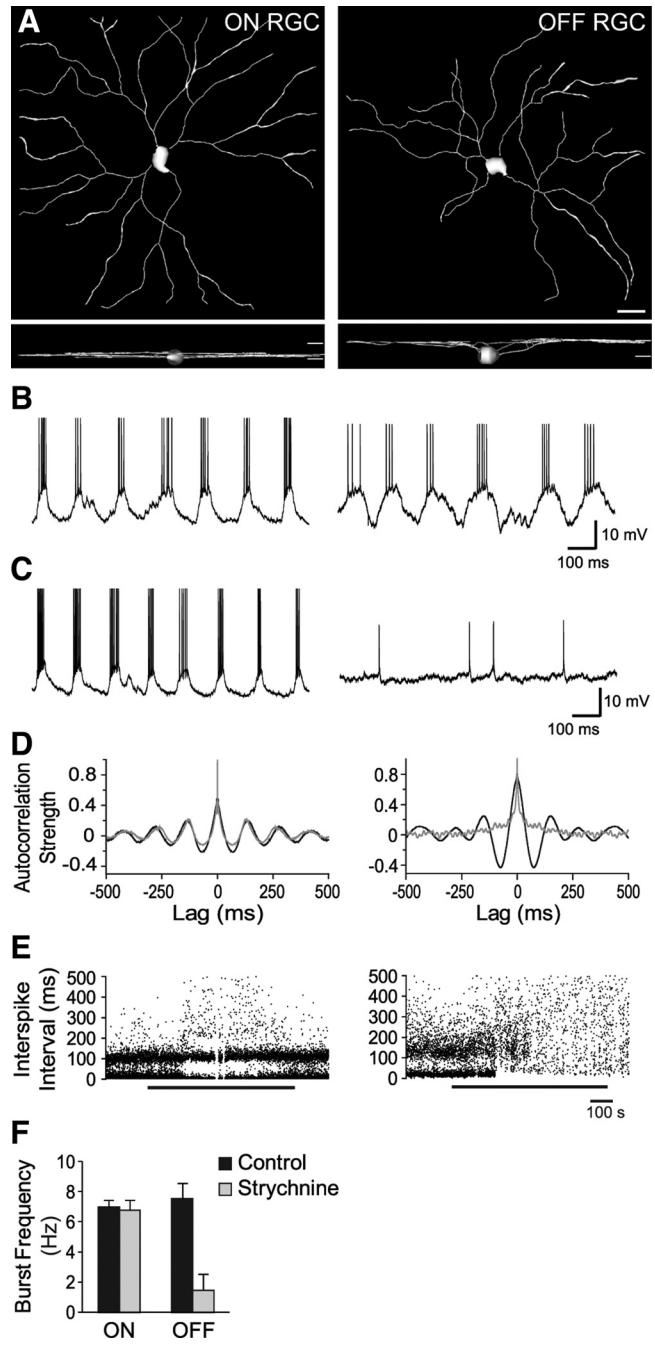

Fig. 1. Strychnine abolished oscillatory activity in OFF retinal ganglion cells (RGCs) but not in ON RGCs in adult rd1 mouse. *A*: drawings of representative ON (*left*) and OFF (*right*) RGCs that were filled with Alexa Fluor 488 showing their dendritic arbor (*top*) and stratification in inner plexiform layer (IPL; *bottom*). Scale bar: 20 μm (applies to all panels). *B*: recording traces from the ON and OFF RGC shown in *A* showing rhythmic oscillatory burst activity in control condition. *C*: recording traces from the cells shown in *A* a few minutes after application of 2 μM strychnine. *D*: autocorrelograms computed from 30-s traces from ON and OFF cells shown in *A* in control condition (black) and in strychnine (gray). *E*: interspike intervals as a function of time for the entire duration of the recordings from the cells shown in *A*. Black horizontal bar at the *bottom* denotes the duration of strychnine application. *F*: burst frequency of all ON ($n = 6$) and OFF RGCs ($n = 8$) in control and in strychnine (2 μM or 5 μM).

neous rhythmic bursts of spikes in control condition (Fig. 1, *A* and *B*). In the presence of 2 μM strychnine, the ON cell continued to produce oscillatory activity, whereas the OFF cell stopped bursting (Fig. 1*C*). This was also evident in the corresponding autocorrelograms: the ON cell showed oscillatory activity with or without strychnine, whereas there was no oscillatory activity in the OFF cell in the presence of strychnine (Fig. 1*D*). Plotting interspike interval vs. time for the entire duration of the recording showed two raster bands: the lower one originating from the spikes within bursts and the upper one for the spikes outside bursts (Fig. 1*E*). Application of strychnine did not change this pattern for the ON cell, whereas for the OFF cell the two bands merged in ~3 min, implying the disappearance of bursting.

Overall, the burst frequency of ON RGCs in control condition (6.96 ± 0.48 Hz, mean ± SE) remained unaltered in the presence of strychnine (6.75 ± 0.69 Hz, $n = 6$; Fig. 1*F*). On the other hand, the burst frequency of OFF RGCs decreased >85% from 7.52 ± 1.03 Hz in control to 1.48 ± 1.05 Hz in strychnine ($n = 8$; Fig. 1*F*). In fact, oscillatory activity disappeared almost completely in OFF RGCs except in one cell where the burst frequency decreased by ~35%. Interestingly, this outlier cell stratified near the ON/OFF border in the IPL (at 63.6% IPL depth) and might be a misidentified ON RGC. For one ON/OFF cell that bistratified at 42.8% (ON) and 77.1% (OFF), the burst frequency did not change much on strychnine application (8.1 Hz in control vs. 8.8 Hz in strychnine; illustrated in Fig. 3). We did not find any obvious difference in the responses to different strychnine concentrations (1, 2, or 5 μM) used here.

Transfer of oscillatory activity to OFF pathway occurred early during development when cones are still intact in rd1 mouse. Next, we asked when during development does the oscillatory activity appear and when is it transferred to OFF pathway? This was important because in rd1 mouse rods degenerate first, starting at around P10, and nearly all rods are lost by ~1 mo of age (Carter-Dawson et al. 1978). On the other hand, cones start to degenerate later, during around the 4th wk, and continue to degenerate slowly over several months (Carter-Dawson et al. 1978; Komeima et al. 2006; Punzo and Cepko 2007). To our knowledge, there is no report on presence of oscillatory activity in rd1 mouse during early postnatal development when most of the cones are still intact. We recorded from ON and OFF RGCs in P8–P25 rd1 mouse retinas. We found ON, OFF, as well as ON-OFF type of RGCs that showed oscillatory burst activity in these retinas (Fig. 2, *A* and *B*). The earliest stage when we found a cell with oscillatory activity was P12, and, interestingly, this was an OFF cell. This implied that the transfer of oscillatory activity from ON to OFF pathway in rd1 mouse occurs soon after the onset of rod degeneration and as early as the time of eye opening. Intriguingly, the spike bursts during development were almost always doublets, that is, each burst comprised two spikes (Fig. 2*B*).

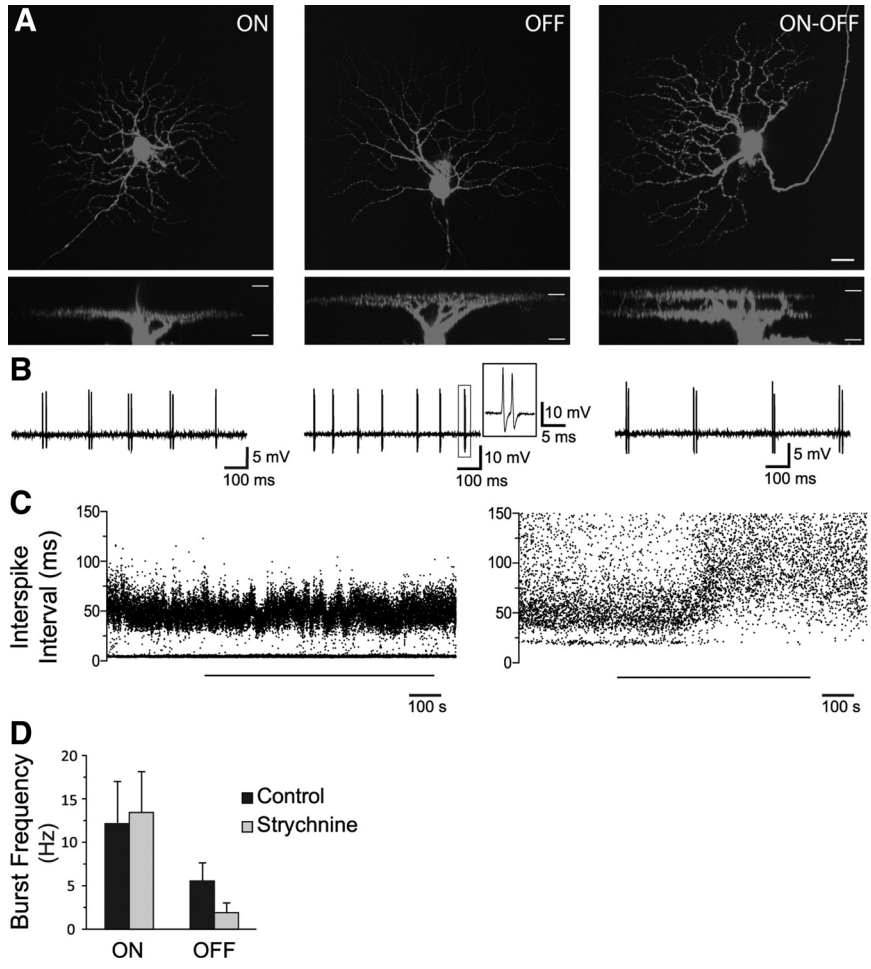

Fig. 2. Transfer of oscillatory activity from ON to OFF pathway occurs early during development. *A*: representative images of ON [*left*; *postnatal day 18* (P18)], OFF (*middle*; P19), and ON-OFF (*right*; P17) cells showing their dendritic arbor (*top*) and IPL stratification (*bottom*). Scale bar: 20 μm (applies to all panels). *B*: representative spike traces for the cells shown in *A* showing spike bursts. Spike bursts during development were typically doublets. *C*: interspike intervals as a function of time for the entire duration of the recordings for representative ON (*left*) and OFF (*right*) RGCs. Horizontal bar at the bottom represents the time when strychnine (1 μM) was applied. *D*: burst frequency of all ON ($n = 4$) and OFF ($n = 5$) cells in control and in strychnine (1 μM or 5 μM). Animal ages: P16–P25.

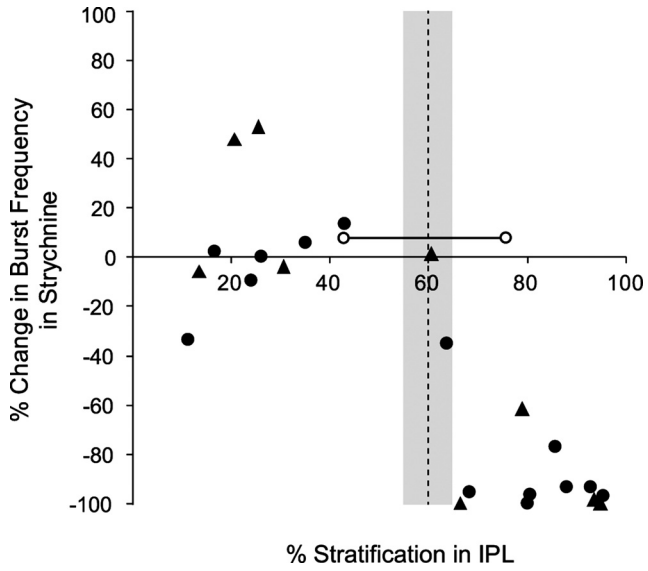

Fig. 3. Response of ON and OFF RGCs to strychnine. Percentage change in burst frequency of all recorded cells in response to strychnine (1, 2, or 5 μM) as a function of their dendritic stratification in IPL. Dotted vertical line separates ON (left) and OFF (right) cells. The shaded area covers IPL from 55 to 65%, representing the ON/OFF border. Two OFF cells included in the shaded area (at 60.6 and 63.6% IPL depths) did not show decreased burst frequency found in other OFF RGCs and might be misidentified ON RGCs. Closed circles, adult animals; triangles, developing animals (P16–P25). Open circles connected by a horizontal line represent an ON/OFF cell that stratified at approximately 43 and 77%.

For some of these cells, we also studied the effect of strychnine. Figure 2*C* shows interspike interval vs. time plots of representative ON and OFF cells where strychnine was applied. As in the case of adults, strychnine had no effect on the ON cell, whereas the oscillatory activity in the OFF cell disappeared in ~4 min after application of strychnine. Overall, the burst frequency of ON cells in control condition (12.16 ± 4.89 Hz) did not change considerably in strychnine (13.45 ± 4.69 Hz; $n = 4$; Fig. 2*D*). On the other hand, the burst frequency of OFF RGCs decreased >70% from 5.55 ± 2.1 Hz in control condition to 1.89 ± 1.16 Hz in strychnine ($n = 5$; Fig. 2*D*). In fact, even here, the burst frequency of one outlier OFF cell that stratified at the ON/OFF border in the IPL (at 60.6% IPL depth) did not show much change in strychnine (4.01 Hz, vs. 3.96 Hz in control) and might be a misidentified ON RGC.

Since the effect of strychnine on ON and OFF RGCs was qualitatively similar in adult and during development, we pooled all of the data for statistical analyses and graphical representation. The burst frequency of all RGCs that stratified in the inner 60% of IPL (ON cells; 9.04 ± 2 Hz) did not change significantly in response to strychnine application (9.43 ± 2.07 Hz; $P = 0.56$, 2-tailed, paired *t*-test; $n = 10$; Fig. 3). However, the burst frequency of the RGCs that stratified in the outer 40% of IPL (OFF cells; 6.76 ± 1.01 Hz) decreased dramatically in the presence of strychnine (1.63 ± 0.76 Hz; $P = 0.00001$; $n = 13$; Fig. 3). One ON/OFF RGC did not show a significant change on strychnine application (Fig. 3) and was not included in the statistical analysis.

DISCUSSION

Using single-cell recording, dye filling, and morphological analyses, we show here that blocking glycine receptors with strychnine results in abolition of oscillatory activity in OFF type of RGCs in rd1 mouse retina, whereas there is no change in ON RGCs. Overall, these results demonstrate that the oscillatory activity in rd1 mouse retina originates in the ON pathway and transfers to the OFF pathway via glycinergic signaling. Since the primary and most robust glycinergic input to the OFF pathway comes from AII amacrine cells making synapse with OFF bipolar cell axon terminals, it is likely that the transfer occurs at this synapse, as suggested previously (Borowska et al. 2011; Margolis et al. 2014). This is consistent with a recent report that showed that the oscillatory activity in ON and OFF RGCs are 180° out of phase (Margolis et al. 2014). This phase reversal likely originates in the fact that the AII amacrine cells make a sign-preserving electrical synapse with the ON bipolar cells and a sign-inverting inhibitory synapse with the OFF bipolar cells.

However, it is also possible that the effect of strychnine is mediated by non-AII type of glycinergic amacrine cells or AII amacrine cells making synapses directly with OFF RGCs (Menger et al. 1998; Murphy and Rieke 2008). Given the antiphase oscillations in ON and OFF RGCs in rd1 mouse (Choi et al. 2014), the contribution from non-AII glycinergic cells seems unlikely. Using voltage-clamp, Margolis et al. (2008) showed that both excitatory and inhibitory inputs to the OFF RGCs in rd1 mouse are oscillatory, both beating at the same fundamental frequency. This suggests that the transfer of oscillatory activity from AII amacrines to OFF RGCs occurs directly as well as indirectly via OFF bipolar cells. One complication here is that the oscillatory inhibitory input could also come from GABAergic amacrine cells. We performed several experiments where we blocked GABAergic inputs using picrotoxin and found that it did not block the oscillatory activity in any of the recorded RGCs ($n = 7$), although these cells were not identified as ON or OFF cells (S. Sethuramanujam and N. K. Dhingra, unpublished observations). Assuming that some of these cells were OFF RGCs, it appears that

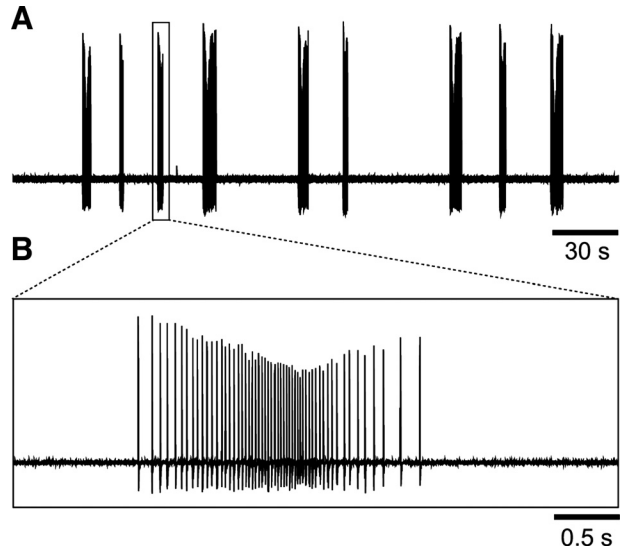

Fig. 4. rd1 Mouse retina also exhibited slow oscillatory activity during early development. *A*: a representative recording from a P10 rd1 mouse retina showing slow repetitive bursts. *B*: a part of the recording shown in *A* (rectangle) is magnified to show single spikes in a burst. Note the difference in burst frequency (*A*) and pattern (*B*) from the degeneration-induced oscillatory activity (Fig. 2*B*).

GABAergic input does not contribute to the oscillatory activity in OFF RGCs.

The earliest developmental stage where we found degeneration-induced oscillatory activity in an OFF RGC was P12. This observation has several important implications. First, the oscillatory activity in RGCs appears soon after the onset of photoreceptor degeneration (approximately P10) in rd1 mouse. Second, the transfer of the degeneration-induced oscillatory activity to the OFF pathway occurs as soon as it is generated in the ON pathway. These two observations imply that the generation of oscillatory activity in ON pathway and its transfer to OFF pathway do not require significant structural remodeling and therefore might be reversible, as suggested previously (Dagar et al. 2014). Third, and perhaps most important, the oscillatory activity in RGCs may not require loss of cones, and a partial loss of rods may be sufficient. Although the exact status of cones in rd1 mouse at P12 has not been reported, their numbers at P21 are similar to those in age-matched wild-type, suggesting that all cones are intact during the 1st 3 wk of life in rd1 mouse (Komeima et al. 2006; Punzo and Cepko 2007). The prevalent view regarding the origin of oscillatory activity in rd1 mouse is centered around ON-cone bipolar cells and the related circuitry (Borowska et al. 2011; Margolis et al. 2014; Menzler and Zeck 2011; Trenholm et al. 2012). In fact, the oscillatory activity has been observed in cone bipolar cells but not in rod bipolar cells (Borowska et al. 2011). However, our finding that the degeneration-induced oscillatory activity first appears in rd1 mouse retina in the presence of intact cones strongly suggests that the oscillatory activity originates in the rod pathway. This is consistent with a recent report showing that oscillatory activity in rd1 mouse retina originates in AII amacrine cells, the cells postsynaptic to rod bipolar cells (Choi et al. 2014).

One relevant line of questioning here is whether rd1 mouse retina exhibits the oscillatory activity of the kind present in wild-type mouse during development (Feller et al. 1996; Meister et al. 1991) and whether/how it is different from the degeneration-induced oscillatory activity. We found periodic bursts of activity in RGCs in rd1 mouse during early development (P8–P10), which resembled the oscillatory activity in developing wild-type mouse in its temporal frequency (approximately once every 1–2 min) and pattern (long bursts lasting for several seconds; Fig. 4). Although we cannot rule out the possibility that this developmental oscillatory activity eventually turns into degeneration-induced oscillations in rd1 mouse, we think it is unlikely. The reasons are manifold: *1*) we report here that degeneration-induced oscillations appear at P12 or earlier, whereas the developmental oscillations continue to be present (in wild-type) until P14 (Akrouh and Kerschensteiner 2013; Wong et al. 2000); *2*) degeneration-induced oscillations have a much higher frequency (~10 Hz) and different pattern (each burst lasting a few milliseconds; see Figs. 2*B* and 4); and *3*) the mechanisms underlying the two types of oscillations are different. Additional experiments are required to resolve this conclusively. For example, coexistence of both types of oscillations in the same cell in P12–P14 rd1 mouse retina could provide useful insight. Similarly, using specific pharmacological agents to block the two types of oscillations differentially could establish whether they are fundamentally different.

Since oscillatory activity reduces the signal-to-noise ratio of RGC light responses (Toychiev et al. 2013; Yee et al. 2012), it is likely that oscillatory activity would adversely affect the visual perception generated through prosthetic devices. Pharmacological tools have been proposed previously to abolish oscillatory bursting. For example, MFA, a gap junction blocker, has been shown to abolish oscillatory activity in animal models of retinal degeneration (Menzler and Zeck 2011; Toychiev et al. 2013; Trenholm et al. 2012). However, MFA is relatively nonspecific and blocks gap junctions throughout the retina, which may produce other undesirable physiological effects. Furthermore, the oscillatory activity has recently been shown to originate in intrinsic properties of AII amacrine cells, suggesting that MFA might be working indirectly by hyperpolarizing the AII amacrine cells and not through uncoupling of gap junctions (Margolis et al. 2014). Our study presents an additional, relatively more specific pharmacological strategy to restore the nonoscillatory, random firing in at least OFF RGCs before stimulating them with a prosthetic device.

ACKNOWLEDGMENTS

We thank Dr. Robert G. Smith, University of Pennsylvania, for valuable comments on the manuscript.

GRANTS

This work was supported by National Brain Research Centre and Grant BT/PR6410/Med/14/801/2005 to N. K. Dhingra from the Department of Biotechnology, Government of India.

DISCLOSURES

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

AUTHOR CONTRIBUTIONS

N.K.D. conception and design of research; D.P. performed experiments; D.P. and N.K.D. analyzed data; D.P. and N.K.D. interpreted results of experiments; D.P. and N.K.D. prepared figures; D.P. drafted manuscript; D.P. and N.K.D. edited and revised manuscript; D.P. and N.K.D. approved final version of manuscript.

REFERENCES

Akrouh A, Kerschensteiner D. Intersecting circuits generate precisely patterned retinal waves. *Neuron* 79: 322–334, 2013.

Barhoum R, Martínez-Navarrete G, Corrochano S, Germain F, Fernandez-Sanchez L, de la Rosa EJ, de la Villa P, Cuenca N. Functional and structural modifications during retinal degeneration in the rd10 mouse. *Neuroscience* 155: 698–713, 2008.

Bittner AK, Diener-West M, Dagnelie G. A survey of photopsias in self-reported retinitis pigmentosa: location of photopsias is related to disease severity. *Retina* 29: 1513–1521, 2009.

Borowska J, Trenholm S, Awatramani GB. An intrinsic neural oscillator in the degenerating mouse retina. *J Neurosci* 31: 5000–5012, 2011.

Carter-Dawson LD, LaVail MM, Sidman RL. Differential effect of the *rd* mutation on rods and cones in the mouse retina. *Invest Ophthalmol Vis Sci* 17: 489–498, 1978.

Choi H, Zhang L, Cembrowski MS, Sabottke CF, Markowitz AL, Butts DA, Kath WL, Singer JH, Riecke H. Intrinsic bursting of AII amacrine cells underlies oscillations in the rd1 mouse retina. *J Neurophysiol* 112: 1491–1504, 2014.

Cuenca N, Pinilla I, Sauve Y, Lund R. Early changes in synaptic connectivity following progressive photoreceptor degeneration in RCS rats. *Eur J Neurosci* 22: 1057–1072, 2005.

Dagar S, Nagar S, Goel M, Cherukuri P, Dhingra NK. Loss of photoreceptors results in upregulation of synaptic proteins in bipolar cells and amacrine cells. *PLoS One* 9: e90250, 2014.

Dhingra NK, Kao YH, Sterling P, Smith RG. Contrast threshold of a brisk-transient ganglion cell in vitro. *J Neurophysiol* 89: 2360–2369, 2003.
Drager UC, Hubel DH. Studies of visual function and its decay in mice with hereditary retinal degeneration. *J Comp Neurol* 180: 85–114, 1978.
Famiglietti EV Jr, Kolb H. Structural basis for ON- and OFF-center responses in retinal ganglion cells. *Science* 194: 193–195, 1976.
Feller MB, Wellis DP, Stellwagen D, Werblin FS, Shatz CJ. Requirement for cholinergic synaptic transmission in the propagation of spontaneous retinal waves. *Science* 272: 1182–1187, 1996.
Gargini C, Terzibasi E, Mazzoni F, Strettoi E. Retinal organization in the retinal degeneration 10 (rd10) mutant mouse: a morphological and ERG study. *J Comp Neurol* 500: 222–238, 2007.
Heckenlively JR, Yoser SL, Friedman LH, Oversier JJ. Clinical findings and common symptoms in retinitis pigmentosa. *Am J Ophthalmol* 105: 504–511, 1988.
Jain V, Ravindran E, Dhingra NK. Differential expression of Brn3 transcription factors in intrinsically photosensitive retina ganglion cells in mouse. *J Comp Neurol* 520: 742–755, 2012.
Jones BW, Watt CB, Frederick JM, Baehr W, Chen CK, Levine EM, Milam AH, Lavail MM, Marc RE. Retinal remodelling triggered by photoreceptor degenerations. *J Comp Neurol* 464: 1–16, 2003.
Komeima K, Rogers BS, Lu L, Campochiaro PA. Antioxidants reduce cone cell death in a model of retinitis pigmentosa. *Proc Natl Acad Sci USA* 103: 11300–11305, 2006.
Lepore FE. Spontaneous visual phenomena with visual loss: 104 patients with lesions of retinal and neural pathways. *Neurology* 40: 444–447, 1990.
Margolis DJ, Gartland AJ, Singer JH, Detwiler PB. Network oscillations drive correlated spiking of ON and OFF ganglion cells in the rd1 mouse model of retinal degeneration. *PLoS One* 9: e86253, 2014.
Margolis DJ, Newkirk G, Euler T, Detwiler PB. Functional stability of retinal ganglion cells after degeneration-induced changes in synaptic input. *J Neurosci* 28: 6526–6536, 2008.
Meister M, Wong RO, Baylor DA, Shatz CJ. Synchronous bursts of action potentials in ganglion cells of the developing mammalian retina. *Science* 252: 939–943, 1991.
Menger N, Pow DV, Wassle H. Glycinergic amacrine cells of the rat retina. *J Comp Neurol* 401: 34–46, 1998.
Menzler J, Zeck G. Network oscillations in rod-degenerated mouse retinas. *J Neurosci* 31: 2280–2291, 2011.
Murphy GJ, Rieke F. Signal and noise in an inhibitory interneuron diverge to control activity in nearby retinal ganglion cells. *Nat Neurosci* 11: 318–326, 2008.
Murtha T, Stasheff SF. Visual dysfunction in retinal and optic nerve disease. *Neurol Clin* 21: 445–481, 2003.
Nagar S, Krishnamoorthy V, Cherukuri P, Jain V, Dhingra NK. Early remodeling in an inducible animal model of retinal degeneration. *Neuroscience* 160: 517–529, 2009.
Pu M, Xu L, Zhang H. Visual response properties of retinal ganglion cells in the royal college of surgeons dystrophic rat. *Invest Ophthalmol Vis Sci* 47: 3579–3585, 2006.
Punzo C, Cepko C. Cellular responses to photoreceptor death in the rd1 mouse model of retinal degeneration. *Invest Ophthalmol Vis Sci* 48: 849–857, 2007.
Puthussery T, Gayet-Primo J, Pandey S, Duvoisin RM, Taylor WR. Differential loss and preservation of glutamate receptor function in bipolar cells in the rd10 mouse model of retinitis pigmentosa. *Eur J Neurosci* 29: 1533–1542, 2009.
Stasheff SF. Emergence of sustained spontaneous hyperactivity and temporary preservation of OFF responses in ganglion cells of the retinal degeneration (rd1) mouse. *J Neurophysiol* 99: 1408–1421, 2008.
Strettoi E, Pignatelli V. Modifications of retinal neurons in a mouse model of retinitis pigmentosa. *Proc Natl Acad Sci USA* 97: 11020–11025, 2000.
Toychiev AH, Yee CW, Sagdullaev BT. Correlated spontaneous activity persists in adult retina and is suppressed by inhibitory inputs. *PLoS One* 8: e77658, 2013.
Trenholm S, Borowska J, Zhang J, Hoggarth A, Johnson K, Barnes S, Lewis TJ, Awatramani GB. Intrinsic oscillatory activity arising within the electrically coupled AII amacrine-ON cone bipolar cell network is driven by voltage-gated Na^+ channels. *J Physiol* 590: 2501–2517, 2012.
Wong WT, Myhr KL, Miller ED, Wong RO. Developmental changes in the neurotransmitter regulation of correlated spontaneous retinal activity. *J Neurosci* 20: 351–360, 2000.
Ye JH, Goo YS. The slow wave component of retinal activity in *rd/rd* mice recorded with a multi-electrode array. *Physiol Meas* 28: 1079–1088, 2007.
Yee CW, Toychiev AH, Sagdullaev BT. Network deficiency exacerbates impairment in a mouse model of retinal degeneration. *Front Syst Neurosci* 6: 8, 2012.