

Development of the Electroretinographic Oscillatory Potentials in Normal and ROP Rats

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PURPOSE. To study the development of the electroretinographic (ERG) oscillatory potentials (OPs) in rats and to compare normal OPs with those in a rat model of retinopathy of prematurity (ROP).

METHODS. Following a longitudinal design, ERG responses to a greater than 5 log unit range of full-field stimuli were recorded in dark-adapted rats at postnatal day (P) 18, P31, P47, and P67. The ERG records were digitally filtered (60–235 Hz), and the trough-to-peak amplitudes and implicit times of OP2, OP3, OP4, and OP5 were measured. Additionally, rats with oxygen-induced retinopathy, a model of ROP, were studied at P31.

RESULTS. Generally, OP amplitude increased and implicit time decreased with increasing stimulus intensity. The shape of the stimulus–response functions changed with age. The amplitudes of OP2, OP3, and OP4 were largest at P31. OP5 was largest at P47. All OPs were significantly affected in ROP rats; OP5 was least affected by ROP.

CONCLUSIONS. A prolonged normal course of OP development, which featured waxing and waning of amplitudes, was observed and might have been consequent to maturation and then to final refinements of inner retinal circuitry. In ROP rats, marked attenuation of early OPs was consistent with persistent dysfunction of photoreceptors, and significant attenuation of the late OP5 was evidence of compromised function of inner retinal circuitry. (*Invest Ophthalmol Vis Sci.* 2006;47:5447–5452) DOI:10.1167/iovs.06-0702

The development of rat electroretinographic (ERG) a-waves and b-waves, representing the activity of photoreceptors and postreceptor retinal neurons, has been documented.^{1,2} These studies investigated the activation of phototransduction (a-waves) and activity in postreceptor retinal neurons (b-waves) using brief flashes over a range of intensities. Such stimuli have not been used to study the development of the rat ERG oscillatory potentials (OPs).^{3–7}

OPs appear as high-frequency periodic wavelets superimposed on the leading edge of the b-wave. The OPs signal retinal activity distinct from that represented in the a- and b-waves^{8–12} and show particular susceptibility to altered levels of retinal neurotransmitters.^{13–16} Although the specific cellular origins of

the OPs have yet to be established, early OPs have been associated with the activity of photoreceptors and bipolar cells in the outer retina, whereas later OPs are attributed to activity in amacrine and ganglion cells in the inner retina.^{11,15–21} The interplexiform cell (IPC), which links the inner and outer plexiform layers and contacts many retinal cell classes, may also be involved in the generation of the OPs.^{8,15}

Rat OPs first appear at postnatal days (P) 12 to 15. At this age, synaptic structures in the inner plexiform layer (IPL) begin to form.^{3,22,23} Developmental organization of the IPL advances rapidly from eye opening at P12 to P13 through P25 to P30. For instance, the terminals of cone bipolar cells in the IPL develop mature characteristics after P25,²⁴ and dopaminergic neurons in the IPL are not fully light responsive until P25.²⁵ Spontaneous activity in differentiated retinal ganglion cells surges at P22 to P27 and tapers thereafter.^{26,27} In the outer nuclear layer, normal developmental loss of cells begins at P10 and proceeds until approximately P27.²⁸ Thus, developmental changes in the OPs are forecast to occur at least through the first month after birth.

Abnormalities in OPs are markers for retinal diseases, including diabetic retinopathy,²⁹ glaucoma,^{30–32} vascular occlusion,^{33,34} macular degeneration,³⁵ and the developmental disorder retinopathy of prematurity (ROP).³⁶ Rat models of all these diseases have been reported.^{2,10,37–43}

Herein, we studied normal rats from infancy into adulthood (P67). We have analyzed OP responses to a range of stimulus intensities, including those used in studies of the activation of phototransduction.^{1,2} In addition, we have compared the OPs in normal rats with those in rats with oxygen-induced retinopathy, a model of ROP.⁴⁴

METHODS

Subjects

Following a longitudinal design, each of 12 Sprague–Dawley albino rats (Charles River Laboratories, Inc., Worcester, MA) was tested at four postnatal ages designated by the median: P18 (16–19 days), P31 (29–33 days), P47 (45–48 days), and P67 (62–67 days). Additionally, 11 rats with oxygen-induced retinopathy, which we refer to as ROP rats,² were studied at P31. All animals were maintained in alternating 12-hour dark and 12-hour light (75 lux). The a- and b-wave responses at P18 and P31 in the normal control rats and in the ROP rats have been previously described. At P18, the b-waves of the ROP rats were markedly attenuated and the retinal vasculature was highly tortuous.² All procedures in this study were approved by the Animal Care and Use Committee at Children's Hospital in Boston and were carried out in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Procedures

After dark adaptation overnight, each rat was prepared for electroretinography.² Under dim red illumination, the rat was anesthetized with an intraperitoneal injection of 75 to 100 mg/kg ketamine and 10 mg/kg xylazine. After one drop each of 0.5% proparacaine hydrochloride, 2.5% phenylephrine hydrochloride, and 1% cyclopentolate hydrochloride

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ride, a Burian-Allen bipolar electrode (Hansen Laboratories, Coralville, IA) was placed on the cornea. The ground electrode was placed on the tail.

As previously described,^{1,2,38,45} ERG responses to brief (< 1 ms) white flashes were recorded over a > 5 log unit range. Stimuli were delivered at a rate that did not attenuate subsequent response amplitudes. The unattenuated flash, measured at the position of the rat's eye using an integrating radiometer (S350; United Detector Technology, Orlando, FL), produced approximately $4.6 \log \mu\text{W}/\text{cm}^2$ and was calculated to elicit approximately 135,000 photoisomerizations of rhodopsin per rod (R^*) in the adult rat.^{1,2} The latter value was used throughout this study. Stimuli (Novatron, Dallas, TX) were delivered through an integrating sphere and were controlled in intensity by calibrated neutral-density filters (Wratten filters; Eastman-Kodak, Rochester, NY). Responses were amplified ($\times 1000$; 1–1000 Hz), digitized (2 kHz), and stored for off-line analysis (UTAS-E 2000; LKC Inc., Gaithersburg, MD).

To demonstrate the OPs, ERG records were digitally filtered with a two-pole Butterworth filter (Matlab; MathWorks, Natick, MA) with bandpass from 60 to 235 Hz and similar to those used in previous studies of OP development.^{10,46,47} In agreement with previous reports,^{47–50} we found that OP1 was contaminated by the a-wave; therefore, OP1 was not analyzed. For each other OP wavelet (OP2, OP3, OP4, OP5), the trough-to-peak amplitude and the implicit time from stimulus onset to the peak were measured (Fig. 1). To estimate the noise in these records, traces were recorded in the absence of a stimulus. The SD of the digitized, filtered records was $2.5 \mu\text{V}$. Therefore, only wavelets greater than $5 \mu\text{V}$ (2 SD) were analyzed. Preliminary analysis indicated OPs were markedly attenuated in P18 ROP rats, as were their b-waves,² and therefore were not analyzed further. On the other hand, OPs were detectable in every P31 ROP rat.

Statistical Analyses

Amplitude and implicit time of the OP wavelets were examined as a function of flash intensity at all ages. Responses to two intensities were selected for further statistical analyses. The more intense flash produced approximately $17,000 R^*$, a stimulus sufficient to saturate the rod dominated a-wave and to evoke a b-wave driven by rod and cone activity.⁵¹ The less intense flash produced approximately $65 R^*$, suffi-

cient to saturate the rod-driven b-wave but too dim to evoke a cone-driven b-wave.⁵¹

For normal rats, OP amplitude and implicit time were each evaluated by repeated-measures analysis of variance (ANOVA); the factors were OP number (OP2, OP3, OP4, OP5), age (P18, P31, P47, P67), and flash intensity ($17,000 R^*$, $65 R^*$). OP interpeak interval was evaluated by an additional repeated-measures ANOVA with factors interpeak interval (OP2–3, OP3–4, OP4–5), age, and flash intensity. OP amplitudes of the P31 group of ROP rats were compared with those of the P31 normal rats using a three-factor (group, OP number, flash intensity) ANOVA. A complete data set is required to perform repeated-measures ANOVA. In 24 of 384 instances, an OP wavelet was not detectable; to fill these cells, a random amplitude value within the range for that condition was entered, and the implicit time was interpolated or extrapolated by linear fit to that animal's observed OPs. The significance level for all tests was $P < 0.01$.

RESULTS

As shown in the sample records (Fig. 1), amplitudes were larger and implicit times were shorter for OP responses to the $17,000 R^*$ stimulus than to the $65 R^*$ stimulus. At both intensities, the OP amplitudes were larger in the normal rat than in the ROP rat.

In Figure 2, mean OP amplitude and implicit time in normal rats are shown as a function of stimulus intensity at the four ages. In general, as stimulus intensity increased, OP amplitude increased and implicit time decreased. However, at the youngest age (P18), the amplitudes of OP3, OP4, and OP5 did not continue to increase at the highest stimulus intensities. At all ages, the smallest mean amplitude was OP2 and the largest OP amplitude observed was OP4. Except at P31, mean OP5 was larger than mean OP3. Implicit time curves (lower panels) were nearly parallel; there was no significant interaction of interpeak interval with flash intensity ($F(1,11) = 0.01$; $P = 0.93$). However, the interpeak interval decreased significantly with increasing age ($F(3,33) = 13.47$; $P < 0.001$). The OP4-to-OP5 interpeak interval was significantly longer than any earlier

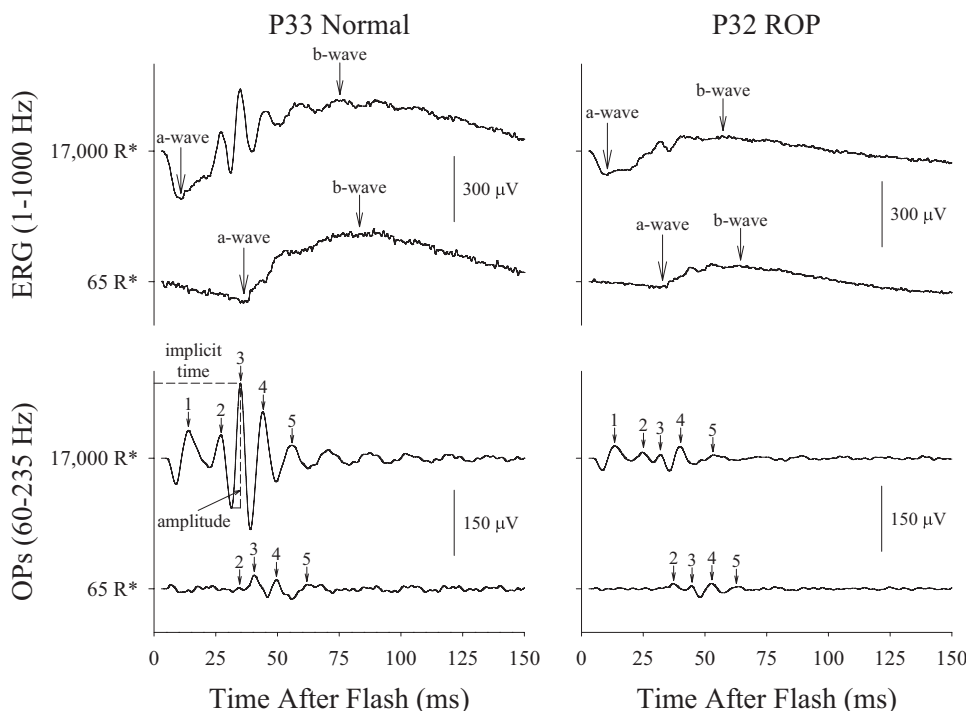


FIGURE 1. Sample ERG (*upper*) and OP (*lower*) responses to $17,000 R^*$ and $65 R^*$ stimuli for a P33 normal rat (*left*) and a P32 ROP rat (*right*). Amplitude and implicit time were measured as indicated for OP3 (*lower left*). Note that the OPs are shown at twice the gain. The first 2 ms were not plotted because they contained an artifact from the amplifier.

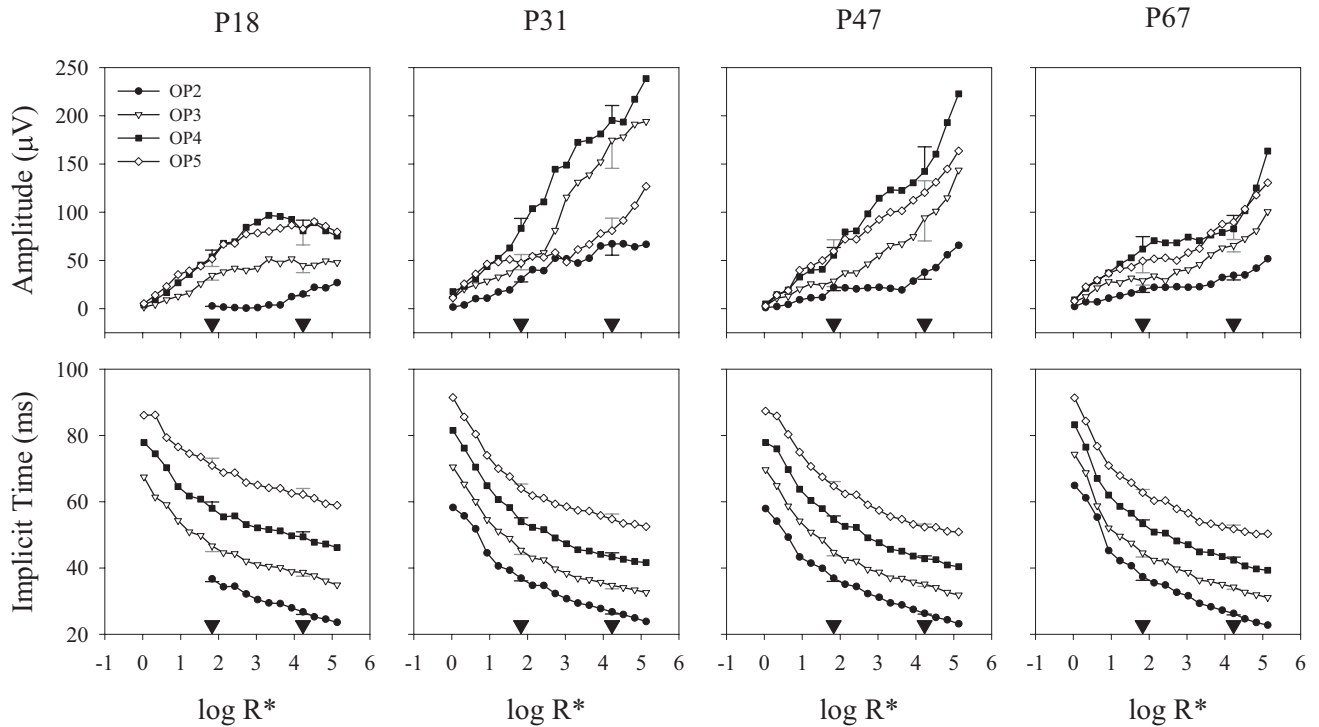


FIGURE 2. Mean OP2, OP3, OP4, and OP5 amplitude (*upper*) and implicit time (*lower*) in normal rats as a function of stimulus intensity at the four ages. The 17,000 R* (4.2 log R*) and 65 R* (1.8 log R*) stimuli are indicated by *triangles* on the abscissa. SEM is plotted at these two intensities. Variability was a similar proportion of the mean at other intensities. For clarity, the error bar is shown in only one direction.

interval (Student's *t* test, corrected for the Bonferroni inequality).

Amplitude and implicit time of the OP responses to the 17,000 R* and 65 R* stimuli are shown as a function of age in Figure 3. Amplitudes of the OP responses to the more intense

flash were significantly larger ($F(1,11) = 24.4; P < 0.001$) and varied significantly with age ($F(3,33) = 15.7; P < 0.001$) and OP number ($F(3,33) = 39.9; P < 0.001$). At both intensities, the amplitudes of OP2, OP3, and OP4 peaked at P31, whereas OP5 was maximum at P47. OP implicit times were significantly

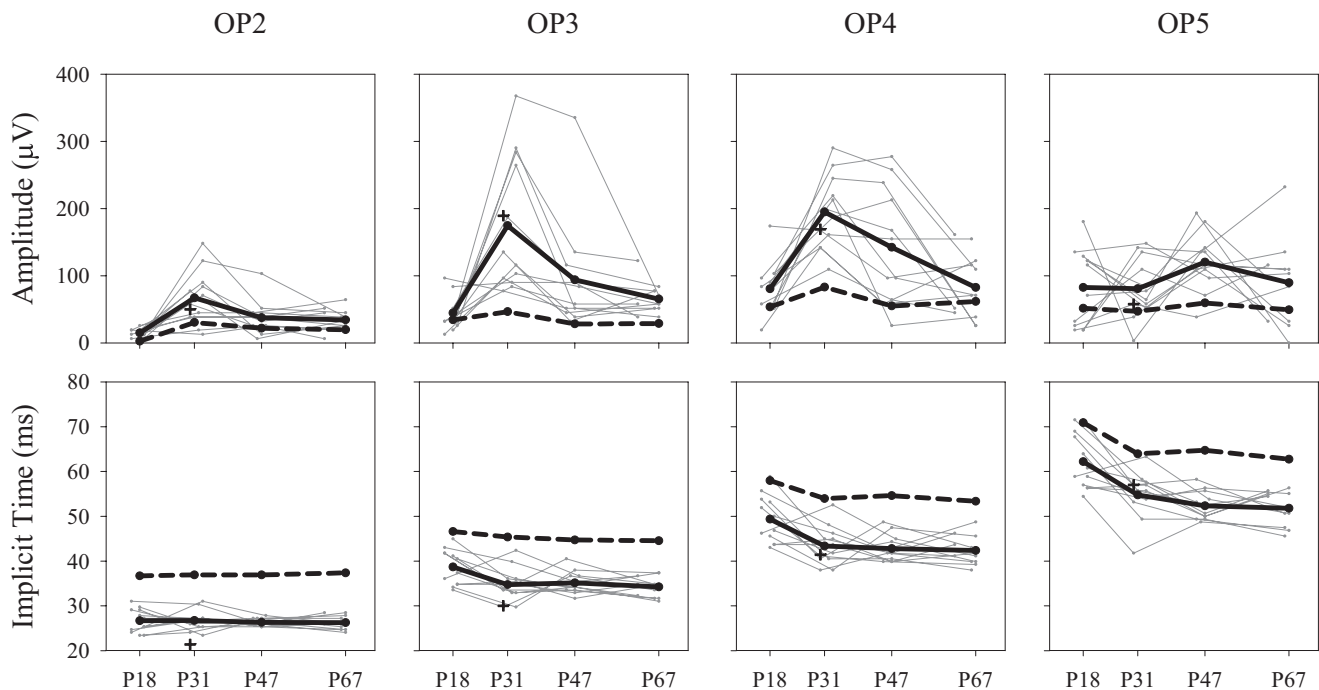


FIGURE 3. Amplitude (*upper*) and implicit time (*lower*) of OP2, OP3, OP4, and OP5 in normal rats as a function of age. *Solid lines*: Mean response to the 17,000 R* stimulus. *Dashed lines*: Mean response to the 65 R* stimulus. Each *gray line* indicates an individual's responses to the 17,000 R* stimulus. *Crosses (+)* replot the data from normal controls reported in Dembinska et al.¹⁰

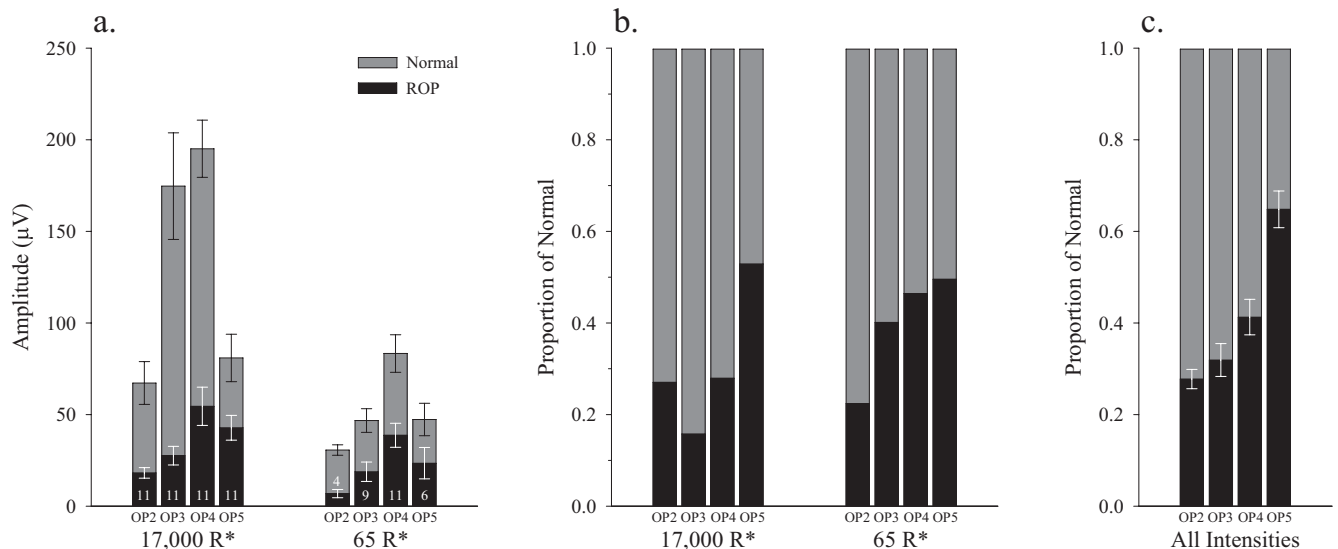


FIGURE 4. OP responses in P31 normal and ROP rats. (a) Mean (\pm SEM) amplitude of the OP responses to the 17,000 R* and the 65 R* stimuli. Of the 11 ROP rats, the number with measurable responses is indicated on each bar. In all normal rats, every OP was measurable at both intensities. (b) Mean amplitude of each OP in ROP rats shown as a proportion of normal for the 17,000 R* and 65 R* stimuli. (c) Mean amplitude of OPs in ROP rats as proportion of normal, averaged across all flash intensities (4–135,000 R*).

shorter in response to the brighter flash ($F(1,11) = 350$; $P < 0.001$) and became shorter with age ($F(3,33) = 5.63$; $P = 0.003$). The P31 data are in reasonable agreement with those reported by Dembinska et al.¹⁰ Although the amplitudes of the OPs and the a- and b-waves^{1,2} increased over similar ages, no OP (OP2, OP3, OP4, OP5) at either intensity (17,000 R*, 65 R*) was correlated with a- or b-wave amplitude at any age (P18, P31, P47, P67).

OP amplitude for normal and ROP rats at P31 is plotted for the 17,000 R* and 65 R* stimuli in Figure 4a. At both intensities, mean amplitude of all OP wavelets in ROP rats was significantly smaller than in normal rats ($F(1,21) = 60.5$; $P < 0.001$). To assess the effect of ROP on each OP wavelet, each ROP rat's OP amplitudes were expressed as a proportion of normal at every stimulus intensity. Figure 4b shows mean amplitude of the OPs in ROP rats as a proportion of normal for the 17,000 R* and 65 R* stimuli. Figure 4c shows the normalized amplitudes averaged across all flash intensities (4–135,000 R*); later OPs were systematically less affected by ROP than earlier OPs ($F(3,45) = 29.4$, $P < 0.001$). The amplitude of OP5 was less affected by ROP than were the amplitudes of the earlier OPs (Student *t* test, corrected for the Bonferroni inequality). For the ROP rats, the retinal blood vessel parameter reported by Liu et al.²—tortuosity index—was not significantly correlated with the amplitude of any OP for responses to either the 65R* or the 17,000R* stimulus.

DISCUSSION

In this longitudinal study of the OPs in rats from shortly after eye opening (P18), through intermediate ages, to adulthood (P67), the shape of the stimulus–response functions changed with age (Fig. 2). After P18, the amplitude of the OPs waxed and then waned by P67, whereas OP implicit time became progressively shorter. The course of maturation of OP5 was relatively delayed (Fig. 3), and OP5 was relatively unscathed by ROP (Fig. 4). Developing retinal circuitry^{22–28} must underpin the maturation of the OPs (Figs. 2, 3).

The circuitry in the mature retina that has been associated with OPs includes ON, OFF, and feedback pathways.^{8,11,42,52} Radial current flow must be the basis for the transretinal po-

tentials recorded as the ERG components.⁵³ Many retinal cells have demonstrable effects on characteristics of the OPs.^{11,15} It is possible that a neuron that spans the retinal layers can generate a radial current, register activity of many classes of cells from outer to inner retina, and provide feedback. The interplexiform cell is such a neuron.^{54–56}

The developmental courses of the OPs (Fig. 3) are remarkably similar to those of the spontaneous excitatory postsynaptic currents (EPSCs) and inhibitory postsynaptic currents (IPSCs) in retinal ganglion cells. The activity of ganglion cells is influenced by input from more distal retinal cells. EPSCs and IPSCs peak at approximately P25, and IPSCs show a secondary peak at P40 to P59,²⁶ the age at which the amplitude of OP5 is greatest (Fig. 3). Visual performance also undergoes developmental changes. Specifically, grating acuity and contrast sensitivity improve rapidly between P15 and P30 in mouse.⁵⁷ In rat, gradual refinements in brightness discrimination and grating acuity continue until at least 3 months of age.⁵⁸ Mouse and rat retina have many developmental features in common.^{59–62} Indeed, visual experience appears to refine late maturing inner retinal processes²⁷ and thus may influence later OP development by refining feedback circuits.

The deficits in OPs (Fig. 4) indicate a persistent effect of ROP on retinal function, even though the retinal vascular abnormalities have resolved spontaneously in ROP rats by P31,² the age at which the OPs have been assessed. Retinal vascular abnormalities are considered the hallmark of ROP. The retinal vasculature and ERG responses are markedly abnormal in young (P18) ROP rats.² It is the earlier developing and earlier occurring OPs that are most vulnerable to ROP (Fig. 4c). Photoreceptor activity, which remains abnormal at P31 in ROP rats, is associated with the early occurring OPs.¹¹ The relative sparing of OP5 (Fig. 4c) suggests that some inner retinal processes are little affected by ROP disease. Interestingly, as was the case for the a-wave and b-wave response parameters,² the OP amplitudes were not correlated with the retinal vasculature parameter tortuosity index. Thus, in ROP there may be no simple interdependence of developing retinal function and vasculature. Study of the growth factors that share the control of neural and vascular development⁶³ and further investigations of the structure and function of the immature retina and

its vasculature are forecast to demonstrate important determinants of normal retinal development and the abnormalities caused by the ROP disease process.

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