Documenta Ophthalmologica **91:** 87–100, 1996.

Electroretinogram responses and refractive errors in patients with a history of retinopathy of prematurity

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Accepted 20 November 1995

Key words: Electroretinography, Infants and children, Myopia, Photoreceptors, Retinopathy of prematurity (ROP)

Abstract. Ametropias, particularly myopia, and mild retinal dysfunction are found in eyes with a history of retinopathy of prematurity. The retina is an important controller of refractive development. The aims of this study were to find out whether altered measures of retinal function and ametropias are associated and to consider mechanisms by which the retina might control refractive development. Nine infants and children with a history of stage 1, 2 or 3 retinopathy of prematurity and known courses of refractive development were studied. Spherical equivalents at the time of the electroretinogram ranged from +5.50 to −9.00 diopters. Rod photoresponse characteristics were derived from the a-wave, and postreceptoral components were also analyzed with calculation of the sensitivity and saturated amplitude of the b-wave, the sensitivity of oscillatory wavelet OP_2, and average amplitudes of OP_3 and OP_4. In hyperopic and myopic patients alike, the saturated amplitude and gain of the rod cell response were attenuated. In all patients, b-wave sensitivity was low, but in most there was little effect on saturated b-wave amplitude. In patients with courses toward myopia, the amplitude of OP_4, an 'OFF' signal, is relatively more attenuated than that of OP_3, an 'ON' signal. OP_4 is relatively larger in patients with courses toward hyperopia. The OP results suggest that an imbalance of 'ON' and 'OFF' activity in the retina is associated with development of ametropias in retinopathy of prematurity.

Abbreviation: ROP – retinopathy of prematurity.

Introduction

Rod photoreceptor function and scotopic b-wave sensitivity are attenuated in infants and children with a history of retinopathy of prematurity (ROP), even if the ROP is mild and completely resolved at the time of electroretinographic (ERG) testing [1, 2]. Specifically, both the saturated amplitude and gain of rod photoreceptor responses, as assessed with the ERG a-wave, and scotopic b-wave sensitivity are significantly lower than normal for age [2]. These alterations in retinal function are similar to those observed in a rat model of ROP [3].

Ametropias are frequent in ROP [4], and abnormal courses of refractive development have been demonstrated in patients with a history of mild ROP

Table 1. Clinical features of the patients

	Gestational age at birth (wk)	Birth weight (g)	ROP stage, zone, plus disease	Age post term	Fundus appearance hours	Refractive error (diopters spherical equivalent)
1	24	780	1, 2, 12	10 wk	Normal	+4.00
2	26	499	3, 2, 12; plus disease	6 mo	Laser burns, 360°; laser therapy scars, 360°	−0.50
3	27	1334	1, 2, 3	8 mo	Normal	+1.00
4	25	800	3, 2, 12; plus disease	8 mo	Laser therapy scars, 360°	−4.50
5	24	710	3, 2, 12	8 mo	Dragged macula; extra macular retina normal	−4.00
6	26	900	2, 2, 12; plus disease	7 y	Mild pigmentary changes	+5.50
7	31	1300	2, 2, 3	9 y	Normal	−9.00
8	28	1100	3, 2, 12; plus disease	9 y	Cryotherapy scars, 360°	−0.50
9	25	801	2, 2, 5	10 y	Normal	−9.00

[5]. In experimental animals the retina is known to be an important controller of eye growth and refractive development [6, 7], and photoreceptor involvement has been demonstrated in experimental ametropias [8–10]. The mechanisms by which the retina controls eye growth remain to be specified [11]. Human ametropias are also associated with retinal dysfunction. Among patients with heritable retinal disorders, ametropias, both myopic and hyperopic, are also frequent [12–16].

We studied retinal responses in infants and children with a history of ROP and a broad range of refractive errors. The aims were to examine retinal response variables for associations with refractive error, and to consider possible mechanisms by which the retina controls refractive development in ROP.

Patients and methods

Patients

The clinical features of the nine patients are summarized in Table 1. The ERG responses of patients 1, 3, 5, 7 and 9, who had complete resolution of stage 1 or 2 ROP, have been previously reported [1, 2]. The additional four patients had more severe ROP (stage 2 with plus disease or stage 3). Three patients 2, 3 and 8) received laser therapy or cryotherapy at preterm ages. One (patient 5) had a dragged macula (which represented only about 5% of the total retinal area) but no cicatricial changes in the extramacular retina. None had active ROP at the time of ERG testing.

Table 1 indicates the most severe ROP that was ever observed in the eye from which the ERG was recorded. The designation of intensity (stage), position (zone), and extent (hours of the clock) of the ROP follows that outlined in the International Classification for Retinopathy of Prematurity [17].

Each child's ophthalmic condition had been monitored since infancy by ophthalmologists in this department. Thus, the courses of refractive development of each patient were known. For normal subjects, the 99% prediction interval for spherical equivalent at term is +3.75 to −1.24 diopters, and during the first decade spherical equivalent changes −0.011 (SD, 0.029) diopters per month [5].

The spherical equivalents at the time of ERG testing ranged from +5.50 diopters to −9.00 diopters (Table 1). Although two infants (patients 1 and 3) were hyperopic at the time of the ERG, they had courses of decreasing hyperopia that exceeded the normal rate of emmetropization by 45 and 10 times. Although myopic at the time of the ERG, patient 2 had a course toward lessening myopia, and patient 6 had a course with hyperopia increasing at +0.140 diopter per month. Patients 4, 5, 7, 8 and 9 had been myopic since infancy, with courses of rapidly increasing myopia as previously described [5].

The Children's Hospital Committee on Clinical Investigation approved this study. Informed consent was obtained from the parents. Assent was obtained from the children when possible.

Electroretinography

The pupils were dilated with cyclopentolate, 1%, and the child was dark adapted in the company of a parent for 30 min. Then, in dim red light, after instillation of a drop of proparacaine, a bipolar Burian-Allen electrode was placed on one eye. The ground electrode was placed over the ipsilateral mastoid. A xenon strobe (Novatron Model 600 VR, series 2100, Dallas, TX;

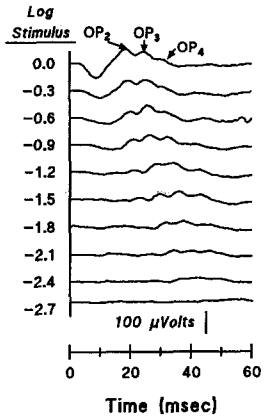

Figure 1. Sample records showing OPs from patient 9, digitally filtered (30 to 1000 Hz; two pole Butterworth filter).

<1-ms duration) and 41-cm-diameter integrating sphere produced the 'full-field' stimuli.

Responses were recorded with a Nicolet Compact 4 (Nicolet Biomedical, Madison, WI), differentially amplified (band pass, 1-1000; gain 1000), displayed on an oscilloscope, digitized, and stored on disc for later analysis. An adjustable voltage window was used to reject records contaminated by artifacts. Two to 16 responses were averaged in each stimulus condition. The interstimulus interval ranged from 2 seconds to 2 min.

The flashes were controlled in intensity by calibrated neutral-density filters and in color by blue (Wratten 47B) or red (Wratten 29) gelatin filters. Stimulus intensities were increased in 0.3-log unit steps starting with a dim flash that evoked a small (<15-μV) b-wave. Amplitudes of a- and b-wave (trough to peak) responses were measured and examined as a function of log relative stimulus energy. The responses to photopically matched red flashes [18] were subtracted digitally from the responses to the blue flashes to isolate the rod responses. Cone intrusion became apparent at about +0.9 log scotopic troland seconds and did not differ significantly between infants and adults [19].

The patients' records (Figure 1) were digitally filtered (30 to 1000 Hz; two- pole Butterworth filter) to demonstrate the oscillatory potentials (OPs). Previously obtained [19] records from normal adults (n=7) and full-term 10-week-olds (n=7) were also filtered 30 to 1000 Hz. The trough to peak amplitudes and implicit times of the OP wavelets were measured and examined as a function of log relative stimulus energy. The mean noise level of the traces was 2.2 μV (SE, 0.20 μV; n=180) with the upper limit of the 95% confidence interval at 4.9 μV. Thus, an averaged response amplitude had to exceed 4.9 μV to be detected.

Differences between infant and adult ocular media, dilated pupil diameter and eye size as well as attenuation of normal retinal sensitivity by the blue and red filters were taken into account for calculation of retinal illuminance [19, 20]. The maximum-intensity white light in the apparatus was calculated to produce approximately 4.8 log scotopic troland seconds for both infants and adults. On the assumption that 1 scotopic troland second produces 8.6 isomerizations per rod [21], the maximum light in the system produced 5.73 log isomerizations per rod.

Rod photoreceptor response analysis

The rod photoresponse characteristics were calculated by means of a formulation similar to that of Hood and Birch [22] which is summarized as follows:

$$\mathrm{P3}(i,t) = \{1 - \exp[-0.5 \cdot i \cdot S \cdot (t - t_d)^2]\} \cdot Rmp_3 \text{ for } t > \mathrm{t}_d \qquad (1)$$

This equation has similarities to the quantitative model of the processes involved in the activation of phototransduction proposed by Lamb and Pugh [23] and has previously been applied to a-wave analyses [3, 22, 24–26]. In equation 1, i is the number of photoisomerizations caused by the stimulus, and t is the time after flash onset. S is the gain [23] or sensitivity parameter in units isoms^{-1} sec^{-2}, Rmp_3 is the estimated saturated rod response amplitude and t_d is a brief delay [22].

To fit equation 1, a least-squares minimization (fmins) procedure based on the simplex algorithm in the Matlab package (The Math Works, Natick, MA) was used to estimate Rmp_3, S and t_d. Fitting of equation 1 was restricted to the leading edge of the a-wave response before obvious intrusion of the b-wave, or to a maximum of 20 ms after stimulus onset. All three parameters were free to vary. For each subject the best-fit parameters for the whole family of a-waves (five to nine; median, eight per subject) were determined; this was termed the ensemble fit [25]. Representative fits of equation 1 to a-waves are shown in Figure 2.

B-wave analysis

The stimulus/response function

$$V \,/\, Vmax = i^n \,/\, (i^n + \sigma^n) \qquad (2)$$

was fitted to the rod isolated b-wave amplitudes of each subject with an iterative procedure that minimized the mean square deviation of the data from the equation [27]. Each parameter was free to vary. In this equation, V is the b-wave amplitude, $Vmax$ the saturated amplitude, i the stimulus in scotopic troland seconds and σ the stimulus that evoked a half-maximum

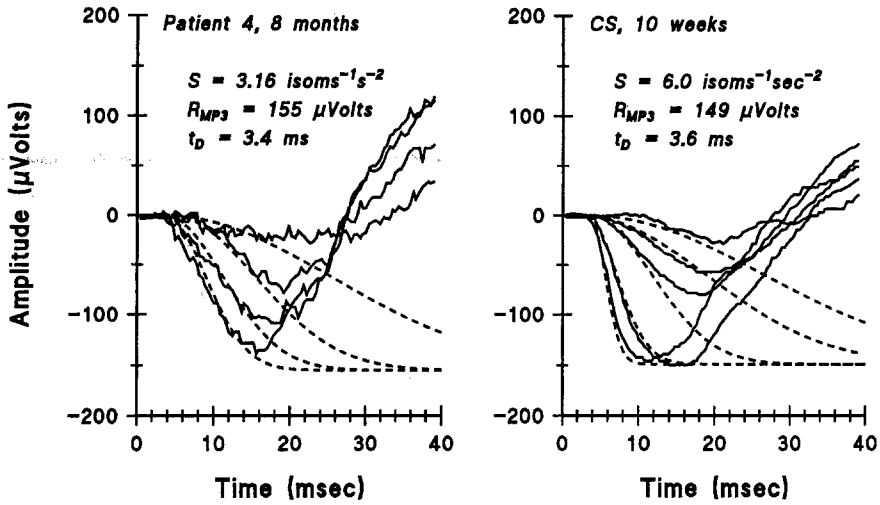

Figure 2. Model fits to the rod isolated a-waves of the ERG from patient 4 (left) and a normal subject (right). Dashed lines show the fit of equation 1. The parameters calculated by the fit of equation 1 are shown in each panel. Note that the value of S for patient 4 is smaller than that of the normal subject and also smaller than the average (4.23 $isoms^{-1}$ sec^{-2}) for normal 10-week-olds (Table 2).

b-wave amplitude. Thus, $1/\sigma$ is a measure of sensitivity. The exponent, n, indicates the slope of the function at σ.

Results

The patients' rod response parameters, S and Rmp_3, and also $log\ \sigma$ and $Vmax$ for the b-wave stimulus/response functions, are listed in Table 2. For the patients, S in equation 1 ranges from 3.04 to 5.54 $isoms^{-1}$ sec^{-2}. The mean value ($\pm$ SD) for normal adults is 9.51 $\pm$ 1.4 $isoms^{-1}$ sec^{-2} and that for normal, full-term 10-week-olds is 45% of the adult mean, or 4.23 $\pm$ 1.4 $isoms^{-1}$ sec^{-2}. The values of S for individual normal 10-week-olds ranged from 38% to 64% of the normal adult mean.

In the patients the saturated rod response amplitude, Rmp_3 in equation 1, ranged from 76 to 287 μV. The mean value of Rmp_3 for normal adults is 379 $\pm$ 88 μV, and for normal, full-term 10-week-olds is 37% of the adult mean, or 141 $\pm$ 30 μV. The values of Rmp_3 for individual normal 10-week-olds ranged from 28% to 46% of the normal adult mean.

The values of S and Rmp_3 in each patient are shown relative to the adults' means in Figure 3. The mean values of S and Rmp_3 in normal, full-term 10-week-olds are also plotted. The smooth curve (Figure 3) shows the normal developmental increase in human rhodopsin [28]. In rats the normal devel-

Table 2. Photoreceptor and b-wave response parameters

Group	Photoreceptor			B-wave	
	S (isoms^{-1} sec^{-2})	Rmp_3 (μV)	t_d (ms)	σ (log scot Td s)	$Vmax$ (μV)
Patients					
1	4.94	85	4.4	+0.41	225
2	3.99	84	2.9	+0.44	120
3	3.04	126	3.3	+0.30	355
4	3.16	155	3.4	−0.36	259
5	4.45	150	3.3	+0.88	251
6	4.78	88	3.0	−0.08	126
7	4.26	136	6.3	−0.24	320
8	5.54	76	3.4	+0.34	188
9	4.79	287	2.3	−0.63	315
Controls (mean ± SD)					
Normal adults[1] (n=7)	9.51 ± 1.4	379 ± 88	3.1 ± 0.5	−0.88 ± 0.14	378 ± 76
Normal full-term 10-week-olds (n=7)	4.23 ± 1.4	141 ± 30	3.4 ± 1.3	−0.29 ± 0.27	165 ± 57
Myopic adults[2] (n=5)	- - -	- - -	- - -	−0.83 ± 0.25	388 ± 80
Hyperopic adults[2]	- - -	- - -	- - -	−0.86 ± 0.40	491 ± 110

[1]From Fulton and Hansen [19].
[2] From Chen et al. [30] Myopic subjects were aged 18 to 32 years with spherical equivalents of −7.37 to −9.50 doopters; hyperopic subjects were aged 15 to 24 years with spherical equivalents of +4.25 to +7.75 diopters.

opmental increases in both S and Rmp_3 follow the rhodopsin growth curve [24]. Assuming, as previously reported [28], that the development of normal, dark-adapted human rod function also follows rhodopsin, all values of S and Rmp_3 were too small for age with the exception of S in the 10-week-old patient. In the others, S and Rmp_3 were too small whether the patient was hyperopic or myopic and also whether or not laser or cryotherapy had been done. On average, S in patients was 57% (range, 40% to 60%) and Rmp_3 was 42% (range, 33% to 76%) of the expected normal values for age.

The b-wave parameters, σ, the flash producing a half-maximum response and $Vmax$, the saturated amplitude, are plotted in Figure 4 along with the normal developmental courses [29] of σ and $Vmax$. The values of σ were below the 95% prediction interval for normal in all but two patients, and these two were below the normal mean. The majority of $Vmax$ values were within the 95% prediction interval for normal. All patients with myopia did have $Vmax$ below the normal mean value, but a hyperopic patient also had a

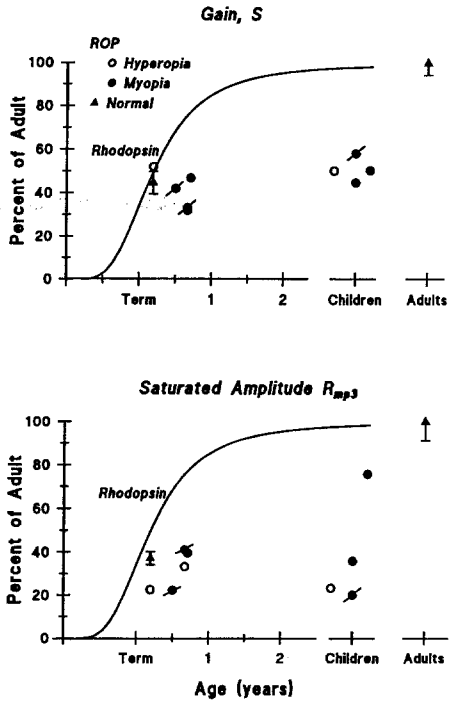

Figure 3. Rod photoreceptor response parameters of the patients as a function of age. All points are relative to the mean adult value. Each circle represents a patient (Table 1). Open circles indicate hyperopia at the time of ERG; closed circles, myopia at the time of ERG; and slashed circles, as history of laser or cryotherapy. The mean (± SEM) gain (*S* in equation 1) and saturated amplitude (Rmp_3 in equation 1) in normal 10-week-old and adult control subjects are also shown (triangles). In both panels the normal developmental increase in human rhodopsin [28] is represented by the smooth curve.

low *Vmax* value. Also shown in Figure 4 are the mean σ and *Vmax* values for previously studied adolescents and young adults with hyperopia (+4.25 to +7.75 diopters) and myopia (−7.43 to −9.5 diopters), but no history of prematurity or ROP [30].

Eight patients had detectable OPs. For these patients, the amplitude of OP_2 increased with log stimulus energy, as it does in adults (Figure 5, top left). Although the maximum amplitude of OP_2 was smaller in the patients than in adults, the mean OP_2 thresholds (50 μV criterion) in patients and adult controls did not differ significantly (Figure 5, top right). The mean amplitudes of OP_3 and OP_4 in patients and adults are shown as a function of log relative stimulus energy (Figure 5, left middle and lower panels). The amplitudes of OP_3 and OP_4 did not vary significantly with stimulus energy, and, therefore, for each subject have been averaged across stimuli. The mean average OP_3

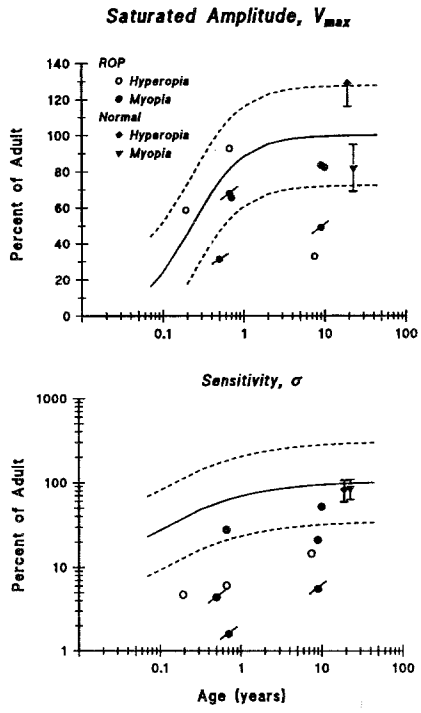

Figure 4. The patients' b-wave stimulus/response parameters (from fit of equation 2) as a function of age. The vertical axes indicate σ and *Vmax* relative to mean values in adults. The solid curves show the mean normal values of σ or *Vmax* as a function of age [29] and the dashed lines indicate the 95% prediction intervals [39] for normal. These growth curves and prediction interval are based on b-wave stimulus/response data from 101 normal, full-term subjects, aged 4 weeks to 40 years [29]. As in Figure 3, open circles indicate patients with hyperopia at time of ERG; closed circles, myopia at time of ERG; and slashed circles, those who had laser or cryotherapy. Also shown are the mean (± SEM) values of σ and *Vmax* in previously studied [30] subjects with myopia and hyperopia, none of whom had a history of preterm birth or preschool myopia.

amplitude in patients was 35% of that in adults, and that of OP_4 was 20% of that in adults.

Patient 1 had no detectable OP responses. All normal full-term 10-week-olds had detectable OP_2, OP_3 and OP_4 wavelets. Their mean maximum amplitude of OP_2 was 130 ± 49 μV; their mean amplitude of OP_3 was 15 ± 7 μV, and of OP_4, 6 ± 2 μV

The eight patients' OP_3 and OP_4 amplitudes, relative to adults' mean amplitudes, are shown in Figure 6. The point at coordinates (17%, 17%) represents the normal 10-week-olds. Patients' points below the diagonal line had larger relative OP_3 than OP_4 amplitudes, and the two above the line had larger OP_4 amplitudes. Patients 2 and 6, who had relative larger OP_4

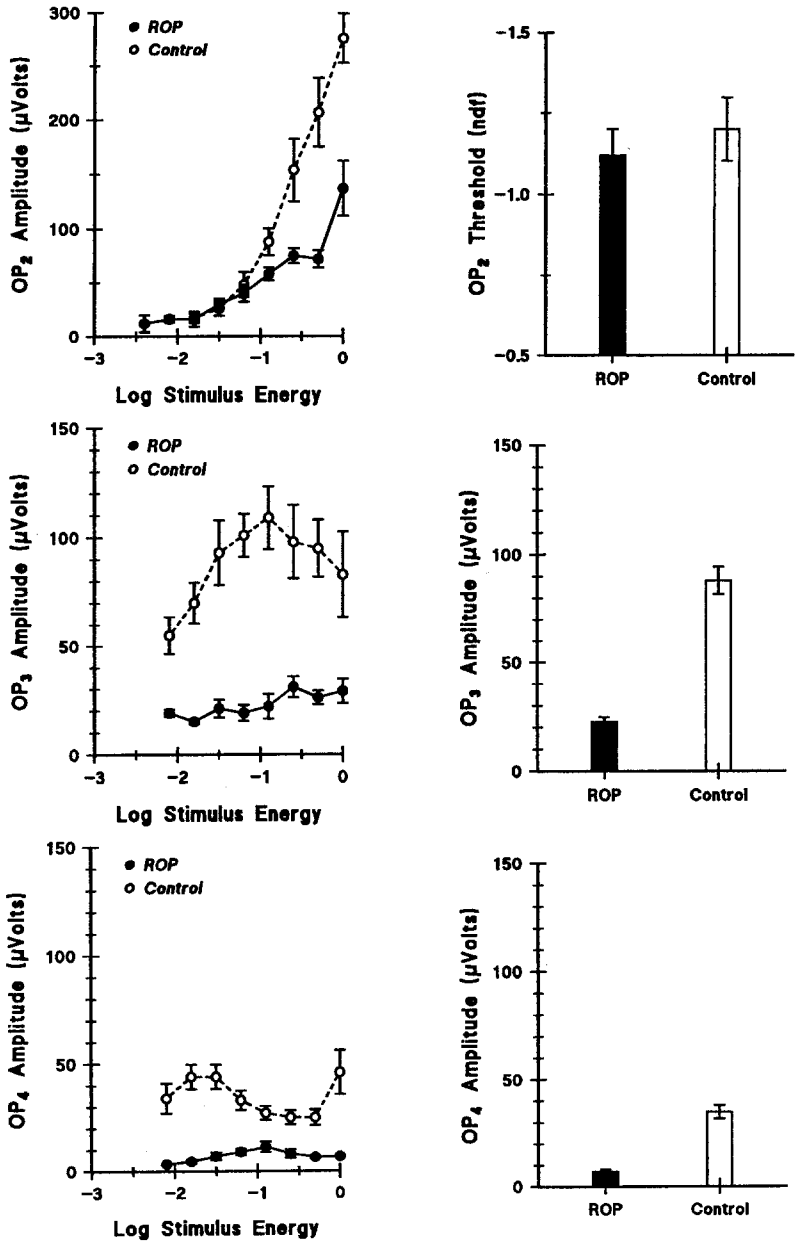

Figure 5. Mean amplitudes of OP_2, OP_3 and OP_4 in the patients with ROP and adult controls. The error bars indicate ± 1 SEM. Left panels, mean OP amplitudes as a function of log relative flash energy. For both patients and adults, the amplitude of OP_2 increased with log stimulus energy, but OP_3 and OP_4 amplitudes varied little with log stimulus energy. Right panels log OP_2 thresholds (50-μV criterion) in patients and adults did not differ significantly. Mean OP_3 amplitude was 35% and OP_4 amplitude was 20% of adult values.

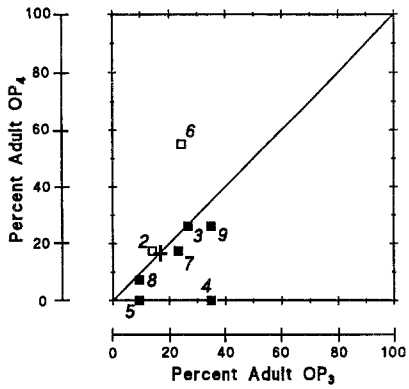

Figure 6. Amplitudes of OP_3 and OP_4 relative to the adults' mean amplitudes. The patients represented by solid squares (below the diagonal line) had relatively larger OP_3 than OP_4, while OP_4 was relatively larger in those with open squares (above the diagonal line). The patient's number is indicated by each symbol. The mean amplitudes in normal 10-week-olds are at the coordinates (17%, 17%).

amplitudes, had courses toward increasing hyperopia. The other patients with larger relative OP_3 amplitudes had courses toward increasing myopia. Patients 4 and 5 had, in fact, no detectable OP_4. In patient 4, with OP_3 about one third of the adults' mean amplitude, OP_4 must be relatively smaller than OP_3 because a third of the mean adult OP_4 amplitude (34 μV; Figure 5) is a detectable potential. In patient 5, with OP_3 less than 10% of the adult mean, the relative amplitude of OP_4 could be nearly 15% of the adult mean without detection. Thus, in patient 5 it is uncertain that OP_3 is relatively more robust than OP_4.

Discussion

All nine patients, whether hyperopic or myopic, had low values of saturated rod photoreceptor response amplitude (Rmp_3) or gain of activation of rod phototransduction (S), or both (Figure 3). The magnitude of attenuation was not correlated with refractive error in these patients.

The a-wave reflects the sum of the processes involved in the activation of phototransduction [23]. The present results (Figure 3), therefore, suggest that ROP has a long-term effect on the photoreceptors and the activation of phototransduction. Possibly ROP leaves the rods in a state of relative functional immaturity. Short rod outer segments and low rhodopsin account for low values of Rmp_3 and S in the developing normal retina [24]. The a-wave analysis does not evaluate processes involved in the deactivation of phototransduction, which could be regarded as the 'OFF' processes in the photoreceptor.

According to the dynamic b-wave model of Hood and Birch [31], low amplitude and gain of the photoreceptor response predict low b-wave sensitivity and normal saturated b-wave amplitude. In these patients, low b-wave sensitivity is found with little alteration of saturated b-wave amplitude (Figure 4). In other words, the observed changes in b-wave sensitivity may be secondary to the alterations in photoreceptor activity rather than indicative of inner retinal dysfunction. Laser and cryotherapy do not necessarily cause marked attenuation of *Vmax*; one treated patient had *Vmax* within the 95% prediction interval for normal (Figure 4).

The mechanisms by which the retina exerts its control on eye growth and refractive development [6, 7, 32] remain to be defined. Multiple mechanisms are likely [11]. An imbalance of 'ON' and 'OFF' signals in the retina may be involved. In kittens given intravitreal 2-amino-4-phosphonobutyric acid, which blocks the 'ON' bipolar response and the b-wave, the treated eye does not grow as much and remains more hyperopic than the untreated fellow eye [33]. Intravitreal kainic acid, which blocks the 'OFF' pathways in the retina [34], causes myopia in chicks [35]. Thus, as a provisional hypothesis, it is reasonable to postulate that a low 'ON' signal will be associated with small eyes that do not grow and, as a corollary, a high 'ON' signal will be associated with large eyes. Eyes with axial myopia, such as those found in the children with myopia [36] included in this study, are large.

The OPs of these patients offer some preliminary evidence that 'ON' and 'OFF' imbalance is associated with ametropias. OP_3 is known to represent 'ON' activity and OP_4 to represent 'OFF' activity in the inner retina [37, 38]. The patients with hyperopia (+5.50 diopters spherical equivalent) had OP_3, the 'ON' signal, relatively more attenuated than OP_4, the 'OFF' signal. Those who were myopic or on a course toward myopia had relatively stronger 'ON' (OP_3) than 'OFF' (OP_4) signals. Thus, a predominance of 'ON' over 'OFF' signals, may predict myopia in patients with a history of ROP.

Acknowledgements

This study was supported by National Institutes of Health grants EY 05329 and EY 10597.

Presented at the 33rd Symposium of the International Society for Clinical Electrophysiology of Vision, Athens, Greece, June 17, 1995.

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