Temporal Summation in Children With a History of Retinopathy of Prematurity

Ronald M. Hansen, Anne Moskowitz, Jena L. Tavormina, Jennifer N. Bush, Garima Soni, and Anne B. Fulton

Department of Ophthalmology, Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts, United States

Correspondence: Ronald M. Hansen, Department of Ophthalmology, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115; ronald.hansen@childrens.harvard.edu.

Submitted: November 19, 2014
Accepted: January 5, 2015

Citation: Hansen RM, Moskowitz A, Tavormina JL, Bush JN, Soni G, Fulton AB. Temporal summation in children with a history of retinopathy of prematurity. *Invest Ophthalmol Vis Sci*. 2015;56:914–917. DOI:10.1167/iov.14-16102

PURPOSE. To assess temporal summation in children with a history of retinopathy of prematurity (ROP) by determining the critical duration (t_{CRIT}) for complete temporal summation under rod-mediated conditions. From prior ERG studies, it is known that the kinetics of activation of phototransduction are prolonged in the ROP rod photoreceptor.

METHODS. Dark-adapted thresholds for detecting 10° diameter stimuli with durations from 10 to 640 ms were measured. A two-alternative, spatial, forced-choice psychophysical procedure was used. The t_{CRIT} for complete summation was estimated in former preterm subjects with a history of severe ROP ($n = 7$), mild ROP ($n = 23$), and no ROP ($n = 15$). The subjects ranged in age from 10.4 to 17.6 (median 15.6) years. Age-similar term-born control subjects ($n = 5$) were also tested.

RESULTS. Critical duration was significantly longer in subjects with a history of ROP than in subjects who never had ROP or who were born at term. Mean t_{CRIT} in the mild ROP group [127.5 (SD = 19.9) ms] and severe group [147.6 (SD = 18.9) ms] did not differ significantly, but both were significantly longer than in former preterms who never had ROP [101.1 (SD = 16.5) ms] and in term-born controls [101.0 (SD = 19.5) ms].

CONCLUSIONS. In ROP subjects, t_{CRIT} is significantly prolonged. This is likely due to abnormal kinetics in the rod outer segment.

Keywords: retinopathy of prematurity, temporal summation, scotopic visual threshold, photoreceptors, psychophysics

Threshold for detection of light depends on the total energy in the stimulus up to a critical duration (Bloch's law).^{1–6} For stimulus durations shorter than the critical duration (t_{CRIT}), a reciprocal relation between log threshold and log stimulus duration is evidence of complete temporal summation. For stimuli longer than t_{CRIT} , there is little change in threshold with increasing duration. In psychophysical studies in healthy adult subjects, t_{CRIT} is approximately 100 ms under dark-adapted conditions.^{1–6}

The psychophysical t_{CRIT} may be related to the temporal properties of photoreceptor activity.⁷ Electroretinographic (ERG) studies have demonstrated that temporal summation occurs in both rod and cone photoreceptors.^{8–10} Rod sensitivity in models of the activation of phototransduction is related to the amplification constant, which in turn is set by time-dependent biochemical events in the rod outer segment.^{11,12} Low rod photoreceptor sensitivity (S_{ROD}) is evidence of slow transduction kinetics in the rod outer segment. Low S_{ROD} is found in subjects years after the resolution of retinopathy of prematurity (ROP).¹³ We hypothesize that ROP is associated with an increase in t_{CRIT} .

We measured dark-adapted thresholds for a range of stimulus durations, determined t_{CRIT} , and compared t_{CRIT} values among children with a history of ROP, children who were born prematurely but never had ROP, and term-born children.

METHODS

Subjects

Thresholds were measured in 45 subjects with a history of preterm birth (Table 1). The subjects were 10.4 to 17.6 (median 15.6) years of age when tested. Their gestational ages at birth ranged from 23.5 to 32 (median 26) weeks and their birth weights from 535 to 2065 (median 850) g. Among these three preterm groups, there was considerable overlap of characteristics (Table 1). Five healthy, term-born subjects age 9.2 to 17.1 (median 12.8) years served as controls.

In the newborn intensive care nursery, all 45 preterm subjects had serial fundus examinations similar to those used in the multicenter ROP treatment trials.¹⁴ Based on these examinations, each subject was categorized according to maximum acute-phase ROP based on the ICROP system¹⁵: severe ROP ($n = 7$), mild ROP ($n = 23$), or no ROP ($n = 15$). The retinal location of ROP is specified by zone. Zone I is the most posterior; it is centered on the optic nerve and includes the macula. Zone II forms an annulus around zone I that reaches to the nasal ora serrata. Zone III is the most peripheral, consisting of a temporal crescent. Stage specifies the severity of the ROP, with higher numbers indicating greater severity. The extent of involvement is specified by number of affected clock hours. Our subjects in the severe category had been treated by laser ablation of peripheral avascular retina; the maximum severity was stage 3 with 6 to 8 clock hours of involvement. Those in

TABLE 1. Subject Characteristics, Median (Range)

Group	N	Gestational Age, wk	Birth Weight, g	Age at Test, y	logMAR VA OU	Spherical Equivalent, Diopters	
						OD	OS
No ROP	15	29.0 (25.0–32.0)	1235 (715–2065)	16.7 (13.0–17.4)	−0.12 (0.06 to −0.22)	−0.63 (−4.00 to +1.13)	−0.19 (−3.81 to +1.81)
Mild ROP	23	26.0 (23.5–30.0)	790 (535–1860)	15.2 (10.8–17.1)	−0.06 (0.08 to −0.22)	−0.75 (−3.00 to +1.81)	−0.22 (−3.06 to +4.38)
Severe ROP	7	26.0 (24.0–27.0)	700 (560–850)	12.5 (11.2–16.3)	0.04 (0.10 to −0.14)	−1.75 (−4.81 to +0.50)	−1.38 (−5.31 to +1.13)

VA OU, binocular visual acuity.

the mild category had ROP that did not require treatment; by clinical criteria, their ROP resolved completely. Their maximum severity of ROP was stage 1 to 3 in zone II or III. (Only one subject in the mild group had stage 3, which occurred in only 2 clock hours in zone II.) In each subject, ROP severity was symmetric in right and left eye. Subjects in the no ROP category had serial examinations, and ROP was never detected. No subject had retinal surgery other than laser treatment.

The study conformed to the tenets of the Declaration of Helsinki and was approved by the Children's Hospital Committee on Clinical Investigation. Written informed consent was obtained from the parents and assent from the subjects.

Procedure

We measured rod-mediated dark-adapted thresholds using a two-alternative, spatial, forced-choice procedure.¹⁶ The stimuli were 10° diameter blue (Wratten 47B, $\lambda < 440$ nm) spots presented 20° to the left or right of a dim red flickering fixation target at the center of a dark rear projection screen. Stimuli of seven durations (10, 20, 40, 80, 160, 320, 640 ms) were used. Calibrated neutral density filters controlled the intensity of the stimuli. Luminance was measured using a calibrated photodiode (IL 1700; International Light, Newburyport, MA, USA) placed in the position of the subject's eye. The scotopic troland values of the stimuli were calculated taking each subject's measured pupil diameter into account.

After 30 minutes of dark adaptation, the subject, positioned 50 cm in front of the rear projection screen, was asked to look at the central fixation target using both eyes. Then, the fixation target was extinguished and a stimulus was presented. On every trial, the subject reported stimulus position (right or left) and received feedback. Threshold was determined using a transformed up-down staircase (step size 0.3 log unit) that estimates the 70.7% correct point of the psychometric function.¹⁷ The staircase started with a stimulus 2 to 3 log units above the anticipated threshold.¹⁶ Threshold for each stimulus duration was estimated as the average of the stimulus intensities at 4 to 12 response reversals (median 6). The median number of trials per staircase was 37 (range, 20–51). In healthy adult subjects ($n = 26$), the mean threshold for a 10° diameter 50-ms stimulus is -3.9 (SD = 0.12) log scotopic troland seconds.¹⁶

Analyses

Temporal summation functions were constructed by plotting log threshold (scotopic trolands) as a function of log stimulus duration (ms) and t_{CRIT} determined using a previously reported method.¹⁸ Specifically, t_{CRIT} was defined as the intersection of a regression line with slope -1.0 fit to thresholds for the 10- to 40-ms stimuli and a horizontal line drawn through the average of the thresholds for the 320- and 640-ms stimuli. Previous psychophysical results have demonstrated little change in threshold for stimulus durations between 320 and 640 ms in healthy control subjects.¹⁹

We also applied linear regression to log threshold as a function of log duration for 10- to 80-ms stimuli and to log threshold as a function of log duration for 160- to 640-ms stimuli and estimated the slopes of these two line segments for each subject.

Analysis of variance was used to evaluate differences among the groups (severe ROP, mild ROP, no ROP, and control) in t_{CRIT} and in the threshold for the 640-ms stimulus. The Scheffé test was used to make post hoc comparisons between groups. For all tests, the level of significance was $P \leq 0.01$.

RESULTS

Temporal summation functions from a representative subject from each group are plotted in Figure 1. For each of these subjects, t_{CRIT} was near the median for the group.

The t_{CRIT} values for all subjects are shown in Figure 2 and summarized in Table 2. Analysis of variance showed that t_{CRIT} varied significantly with group ($F = 13.07$; $df: 3, 46$; $P < 0.001$). Most (5 of 7) t_{CRIT} values in those with severe ROP were longer than the median of the mild ROP subjects. However, post hoc testing showed that the t_{CRIT} values of these two groups did not differ significantly from each other ($P = 0.203$). This is in

FIGURE 1. Representative temporal summation functions. Log threshold is plotted as a function of log stimulus duration for a subject from each of the three groups of former preterm subjects (severe ROP, mild ROP, no ROP) and for a term-born control subject. For each of these subjects, t_{CRIT} was near the median for the group and is indicated by the arrow. The intersection of a line with slope -1.0 fit to the 10-, 20-, and 40-ms stimuli and a line with slope $= 0$ through the average threshold for the 320- and 640-ms stimuli is the critical duration (arrow). Thresholds for the 80- and 160-ms stimuli, which are near t_{CRIT} , were not included in the regression.

FIGURE 2. Critical duration (t_{CRIT}) values in former preterm subjects with a history of severe ROP, mild ROP, and no ROP and in term-born controls. Each point represents an individual subject. The mean t_{CRIT} value for each group is indicated by the horizontal bar.

contrast to previous ERG results,²⁰ which show that the long-term effect of ROP on photoreceptor and postreceptor function varies with the severity of the antecedent ROP.

The t_{CRIT} values of both mild and severe ROP subjects were significantly longer than t_{CRIT} in preterm subjects who never had ROP and in term-born controls ($P < 0.001$). There was no difference in t_{CRIT} between preterm subjects who never had ROP and term-born controls ($P = 0.267$).

The average slope of the regression line through the thresholds for 10- to 80-ms stimuli was -1.04 ($\text{SD} = 0.27$), and the average slope of the regression line through thresholds for 160- to 640-ms stimuli was -0.054 ($\text{SD} = 0.16$). Thus, use of the classic temporal summation function⁴ is appropriate for these pediatric patients with retinal disease.

Threshold for the 640-ms stimulus did not differ significantly among the groups ($F = 2.92$; $df: 3,46$; $P = 0.091$).

DISCUSSION

In ROP subjects, as in controls, detection thresholds depend on the total energy of the stimulus up to a critical duration, t_{CRIT} (Fig. 1). We found that t_{CRIT} was significantly longer in subjects who had ROP, whether mild or severe, than in subjects who were born prematurely but never had ROP or in term-born control subjects. In this sample, t_{CRIT} did not vary significantly with the severity of ROP (Fig. 2). There was no difference in t_{CRIT} between those who never had ROP and term-born control subjects; their values agree with those reported in other studies of temporal summation in healthy adults.^{1-3,5,6}

Classic ERG studies suggested that temporal processes are limited by events at the level of the photoreceptor.⁸⁻¹⁰ As phototransduction became understood in molecular terms, Lamb and Pugh¹² presented a model of the biochemical steps in the activation of rod phototransduction. Rod photoreceptor sensitivity derived from the a-wave of the ERG is proportional to the amplification constant,¹¹ which in turn depends on the time constants of events in the rod outer segment.^{12,21} Harris et al.¹³ found low rod photoreceptor sensitivity in ROP subjects many years after their active disease had resolved. In 10- to 11-year-old children with a history of mild or severe ROP, median rod sensitivity ($6.9 \text{ isoms}^{-1} \cdot \text{s}^{-2}$) was approximately two-thirds of the normal adult value ($10.2 \text{ isoms}^{-1} \cdot \text{s}^{-2}$).¹³ In the models of activation, photoreceptor sensitivity (S_{ROD}) is

TABLE 2. Summary of Critical Durations (t_{CRIT}), ms

Group	Mean	SD
Term	101.0	19.47
No ROP	101.1	16.46
Mild ROP	127.5	19.89
Severe ROP	147.6	18.88

related to the time constants (τ) in the outer segments by the relation $S_{\text{ROD}} = 1/\tau^2$. For the above values of S_{ROD} , the corresponding time constants are 381 ms in ROP compared to 312 ms in our healthy adult control subjects. Thus, the long t_{CRIT} values in ROP subjects may be a consequence of changes in the function of the rod outer segment. Our data do not permit exact comparison of critical duration and the time constants of activation of phototransduction. Proximal to the rod outer segment, the visual pathway further integrates information. The present results, however, suggest that the rod outer segment has a role in setting the critical duration for complete temporal summation.

We conclude that ROP has a significant long-term effect on temporal summation, perhaps as a consequence of altered rod photoreceptor function. Taken together with our recent report that altered postreceptor retinal circuitry underlies abnormal scotopic spatial summation,²² the temporal summation results reported herein add to the evidence that ROP has long-term effects on vision.

Acknowledgments

Supported by National Eye Institute Grant R01 EY010597 and Massachusetts Lions Eye Research Fund.

Disclosure: R.M. Hansen, None; A. Moskowitz, None; J.L. Tavormina, None; J.N. Bush, None; G. Soni, None; A.B. Fulton, None

References

- Barlow HB. Temporal and spatial summation in human vision at different background intensities. *J Physiol.* 1958;141:337-350.
- Baumgardt E, Hillmann B. Duration and size as determinants of peripheral retinal response. *J Opt Soc Am.* 1961;51:340-344.
- Graham H, Margaria R. Area and intensity time relation in the peripheral retina. *Am J Physiol.* 1935;113:299-305.
- Hood DC, Finkelstein MA. Sensitivity to light. In: Boff K, Kaufman L, Thomas J, eds. *Handbook of Perception, Vol 1: Sensory Processes and Perception*. New York: Wiley; 1986: chap 5, 16-22.
- Sharpe LT, Stockman A, Fach CC, Markstahler U. Temporal and spatial summation in the human rod visual system. *J Physiol.* 1993;463:325-348.
- Sperling H, Jolliffe C. Intensity-time relationship at threshold for spectral stimuli in human vision. *J Opt Soc Am.* 1965;46: 845-850.
- Daly SJ, Normann RA. Temporal information processing in cones: effects of light adaptation on temporal summation and modulation. *Vision Res.* 1985;25:1197-1206.
- Alpern M, Faris JJ. Luminance-duration relationship in the electric response of the human retina. *J Opt Soc Am.* 1956;46: 845-850.
- Hood DC, Grover BG. Temporal summation of light by a vertebrate visual receptor. *Science.* 1974;184:1003-1005.

10. Rosenblum RA. Electroretinographic evaluation of the Bunsen-Roscoe law for the human eye at high energy levels. *Invest Ophthalmol*. 1971;10:904-910.
11. Breton ME, Schueller AW, Lamb TD, Pugh EN Jr. Analysis of ERG a-wave amplification and kinetics in terms of the G-protein cascade of phototransduction. *Invest Ophthalmol Vis Sci*. 1994;35:295-309.
12. Lamb TD, Pugh EN Jr. A quantitative account of the activation steps involved in phototransduction in amphibian photoreceptors. *J Physiol*. 1992;449:719-758.
13. Harris ME, Moskowitz A, Fulton AB, Hansen RM. Long-term effects of retinopathy of prematurity (ROP) on rod and rod-driven function. *Doc Ophthalmol*. 2011;122:19-27.
14. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. *Arch Ophthalmol*. 2003;121:1684-1694.
15. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. *Arch Ophthalmol*. 2005;123:991-999.
16. Hansen RM, Eklund SE, Benador IY, et al. Retinal degeneration in children: dark adapted visual threshold and arteriolar diameter. *Vision Res*. 2008;48:325-331.
17. Wetherill GB, Levitt H. Sequential estimation of points on a psychometric function. *Br J Math Stat Psychol*. 1965;18:1-10.
18. Friedman LJ, Yim MH, Pugh EN Jr. Temporal integration of the π 1/ π 3 pathway in normal and dichromatic vision. *Vision Res*. 1984;24:743-750.
19. Fulton AB, Hansen RM, Yeh YL, Tyler CW. Temporal summation in dark-adapted 10-week old infants. *Vision Res*. 1991;31:1259-1269.
20. Fulton AB, Hansen RM, Moskowitz A, Akula JD. The neurovascular retina in retinopathy of prematurity. *Prog Retin Eye Res*. 2009;28:452-482.
21. Hood DC, Birch DG. Rod phototransduction in retinitis pigmentosa: estimation and interpretation of parameters derived from the rod a-wave. *Invest Ophthalmol Vis Sci*. 1994;35:2948-2961.
22. Hansen RM, Tavormina JL, Moskowitz A, Fulton AB. Effect of retinopathy of prematurity on scotopic spatial summation. *Invest Ophthalmol Vis Sci*. 2014;55:3311-3313.