Temporal Summation in Children With a History of Retinopathy of Prematurity

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PURPOSE. To assess temporal summation in children with a history of retinopathy of prematurity (ROP) by determining the critical duration (tCRIT) 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 tCRIT 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 tCRIT 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, tCRIT 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). For stimulus durations shorter than the critical duration (tCRIT), a reciprocal relation between log threshold and log stimulus duration is evidence of complete temporal summation. For stimuli longer than tCRIT, there is little change in threshold with increasing duration. In psychophysical studies in healthy adult subjects, tCRIT is approximately 100 ms under dark-adapted conditions.

The psychophysical tCRIT may be related to the temporal properties of photoreceptor activity. Electroretinographic (ERG) studies have demonstrated that temporal summation occurs in both rod and cone photoreceptors. 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.

Low rod photoreceptor sensitivity (SROD) is evidence of slow transduction kinetics in the rod outer segment. Low SROD is found in subjects years after the resolution of retinopathy of prematurity (ROP). We hypothesize that ROP is associated with an increase in tCRIT.

We measured dark-adapted thresholds for a range of stimulus durations, determined tCRIT and compared tCRIT 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. Based on these examinations, each subject was categorized according to maximum acute-phase ROP based on the ICROP system: 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...
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 using a previously reported method.18 Specifically, tCRIT was defined as the intersection of a regression line with slope $-1.0$ fit to thresholds for the 10- to 80-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 tCRIT 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 $P < 0.01$.

RESULTS

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

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Gestational Age, wk</th>
<th>Birth Weight, g</th>
<th>Age at Test, y</th>
<th>logMAR VA OU</th>
<th>Spherical Equivalent, Diopters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OD</td>
</tr>
<tr>
<td>No ROP</td>
<td>15</td>
<td>29.0 (25.0–32.0)</td>
<td>1255 (715–2065)</td>
<td>16.7 (13.0–17.4)</td>
<td>0.12 (0.06 to −0.22)</td>
</tr>
<tr>
<td>Mild ROP</td>
<td>23</td>
<td>26.0 (23.5–30.0)</td>
<td>790 (535–1860)</td>
<td>15.2 (10.8–17.1)</td>
<td>0.06 (0.08 to −0.22)</td>
</tr>
<tr>
<td>Severe ROP</td>
<td>7</td>
<td>26.0 (24.0–27.0)</td>
<td>700 (560–850)</td>
<td>12.5 (11.2–16.5)</td>
<td>0.04 (0.10 to −0.14)</td>
</tr>
</tbody>
</table>

VA OU, binocular visual acuity.

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, tCRIT 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 tCRIT, were not included in the regression.

TABLE 1. Subject Characteristics, Median (Range)
Lamb and Pugh presented a model of the biochemical steps phototransduction became understood in molecular terms, time constants of events in the rod outer segment. Harris controls. Each point represents an individual subject. The mean $t_{\text{CRIT}}$ value for each group is indicated by the horizontal bar.

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

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

The average slope of the regression line through thresholds for 10- to 80-ms stimuli was $-0.04$ ($SD = 0.27$), and the average slope of the regression line through thresholds for 100- to 640-ms stimuli was $-0.054$ ($SD = 0.16$). Thus, use of the classic temporal summation function is appropriate for these pediatric patients with retinal disease.

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

### Table 2. Summary of Critical Durations ($t_{\text{CRIT}}$), ms

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SD</th>
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</thead>
<tbody>
<tr>
<td>Term</td>
<td>101.0</td>
<td>19.47</td>
</tr>
<tr>
<td>No ROP</td>
<td>101.1</td>
<td>16.46</td>
</tr>
<tr>
<td>Mild ROP</td>
<td>127.5</td>
<td>19.89</td>
</tr>
<tr>
<td>Severe ROP</td>
<td>147.6</td>
<td>18.88</td>
</tr>
</tbody>
</table>

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, the temporal summation results reported herein add to the evidence that ROP has long-term effects on vision.

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### References

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