

Deactivation of the rod response in retinopathy of prematurity

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Abstract It is known that retinopathy of prematurity (ROP) alters the activation of rod photoreceptors, but the effect of ROP on deactivation has not been investigated. We studied deactivation using an electroretinographic (ERG) paired flash procedure in 22 subjects (12 infants and 10 older subjects) with a history of preterm birth and ROP. The amplitude of the rod-isolated a-wave response to a flash presented 2–120 s after a test flash was measured, and the time at which it reached 50% of the single flash amplitude (t_{50}) was determined by linear interpolation. Deactivation results were compared to those in former preterms who never had ROP ($n = 6$) and term-born controls. In infants, t_{50} values of ROP subjects did not differ from those in subjects who never had ROP or term-born controls. Among mature ROP subjects, eight of 12 had t_{50} values longer than any control subject. Prolonged deactivation in these mature ROP subjects may indicate lack of maturation of the deactivation process (t_{50}) or progressive compromise of retinal function with increasing age.

Keywords Electroretinogram · Retinopathy of prematurity · Rod photoreceptor · Deactivation

Introduction

Abnormal activation of rod phototransduction has been reported in subjects with a history of retinopathy of prematurity (ROP) [1]. The more severe the ROP, the lower rod photoreceptor sensitivity, S_{ROD} [1]. S_{ROD} depends on the time constants of the biochemical steps from photon capture by rhodopsin to closure of the channels in the rod outer segment. Low S_{ROD} indicates slow kinetics of the molecular processes in the activation of phototransduction, possibly due to subtle alteration in the rod outer segment [2].

Following activation, the rod must deactivate in a timely manner to prepare for response to the next stimulus. The rod recovers by stepwise deactivation of rhodopsin, transducin, and phosphodiesterase in a series of biochemically complex processes [3–7]. In term-born infants and infant rats, the kinetics of both activation and deactivation of the photoresponse are slower than in adults [5, 8–14]. If activation in ROP is slower than in age-matched term-born control subjects, is deactivation also abnormally slow? We used an electroretinographic (ERG) paired flash technique to study deactivation in ROP subjects in infancy and at older ages.

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Methods

Subjects

Twenty-eight subjects with a history of preterm birth were studied (Table 1). All had been monitored in the newborn intensive care nursery following schedules for examination that were modeled on those used in the multi-center ROP treatment trials [15–17]. Based on a review of the results of these examinations, the subjects were categorized by ROP history as either mild ROP or no ROP. Those with mild, untreated ROP ($n = 22$) had Stage 2 or 3 in Zone II or III that resolved spontaneously [18]. The others ($n = 6$) had serial examinations but never had ROP. Gestational age at birth ranged from 23 to 32 (median 27) weeks and birth weight from 550 to 1,590 (median 910) grams. None had active ROP at the time of the ERG test. Thirteen subjects were tested as infants at median age 10 (range 7–18) weeks post term. Fifteen older subjects were tested at median age 13 (range 11–21) years. The parameters of rod activation in these preterm subjects have been reported [1]. Results from term-born 10-week-old infants ($n = 15$) and mature subjects ($n = 10$) provide control data for comparison. Data from the term-born infants and most of the mature control subjects (8 of 10) were reported previously [11].

This study conformed to the tenets of the Declaration of Helsinki and was approved by the Children's Hospital Committee on Clinical Investigation. Informed consent was obtained from the parents of the infants and children, assent from the older children, and consent from those 18 years and older.

ERG procedure

Parents stayed with infants and children throughout the procedure. One pupil was dilated with cyclopentolate

1% and the subject dark-adapted for 30 min. Then, under dim red light, proparacaine 0.5% was instilled and a bipolar Burian–Allen electrode was placed on the cornea. A ground electrode was placed on the skin over the ipsilateral mastoid.

Twenty-four subjects were tested using a Compact 4 system (Nicolet, Madison, WI), and four subjects were tested using an Espion system (Diagnosys, Lowell, MA). Rod responses were recorded using a Wratten 47B filter ($\lambda < 510$ nm) in the Nicolet system and a 470 nm LED (half bandwidth 30 nm) in the Espion system. The gain was 1,000 and bandpass in both systems was 0.5–1000 Hz. The digitization rate was 2,564 Hz for the Nicolet and 2,000 Hz for the Espion. In adult control subjects, rod activation and deactivation parameters do not differ between the Espion and Nicolet systems [13, 19]. Therefore, data obtained using the two systems have been combined.

Deactivation of phototransduction in rods

The recovery of the rod's response to light was evaluated using a paired flash paradigm [5, 9, 20]. After a +3.3 log scotopic troland second (scot td s) test flash, an equal intensity probe flash was presented at seven selected inter-stimulus intervals (ISI 2–120 s). For each test–probe pair, the amplitude (R) of the rod-isolated a-wave response to the probe was measured at 8 ms. The response to the probe flash provides a measure of the circulating current in the rods [9, 10, 20]. For each ISI, R was expressed as proportion of R_{MAX} , the amplitude of the a-wave to the probe alone. Linear interpolation was used to determine the time, t_{50} , at which a-wave amplitude was half R_{MAX} . Between each test–probe pair, 2 min in the dark was allowed. Control experiments in term-born subjects showed that 2 min were sufficient for

Table 1 Subjects with a history of preterm birth [median (range)]

	<i>N</i>	Test age	Gestational age at birth (weeks)	Birth weight (g)
Infants				
ROP	10	73 (68–81) days	28 (26–31)	970 (626–1,170)
No ROP	3	73 (52–131)	29 (25–30)	1230 (740–7,360)
Mature				
ROP	12	13 (11–21) years	26 (23–28)	815 (550–1,077)
No ROP	3	13 (10–18)	31 (26–32)	1510 (1,430–1,590)

full recovery to the amplitude of the dark-adapted response [11]. To obtain the rod-isolated response, the amplitude of the a-wave to a photopically matched red flash was subtracted from the response to the probe flash.

Rod ERG

Activation was also studied in all subjects. Responses to full-field, brief (<3 ms), blue stimuli ranging from +2.1 to +3.3 log scot td s were recorded. The rod photoresponse parameters (S_{ROD} and R_{ROD}) were calculated by fit of the Hood and Birch [21] formulation of the Lamb & Pugh model [22, 23] to the a-waves. The equation is

$$R(i, t) = [1 - \exp\{-0.5 I S_{\text{ROD}}(t - t_d)^2\}] R_{\text{ROD}}$$

where I is the flash (scot td s), S_{ROD} a sensitivity parameter [(scot td) $^{-1}$ s $^{-3}$] that depends on the time constants of the steps in activation of phototransduction [23], R_{ROD} the saturated response amplitude (μV), and t_d a brief delay (ms). All three parameters, (S_{ROD} , R_{ROD} , and t_d) were free to vary [24].

Calibrations

Stimuli were measured with a detector and appropriate photopic or scotopic filter (IL 1700, International Light, Newburyport, MA) placed at the position of

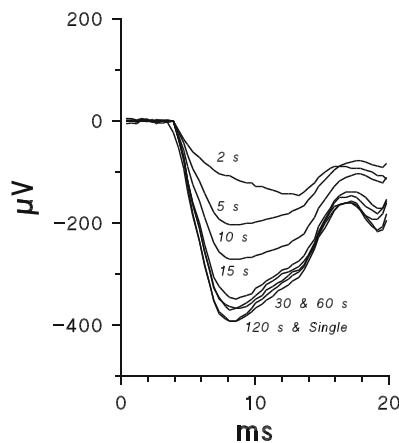


Fig. 1 Sample results from a 14-year-old subject with a history of mild ROP and t_{50} value (10 s) close to the ROP median. Rod-isolated ERG a-wave responses are shown in the *left panel*; the responses to the single flash and to the probe flash at the indicated inter-stimulus intervals (*ISI*) are shown. In

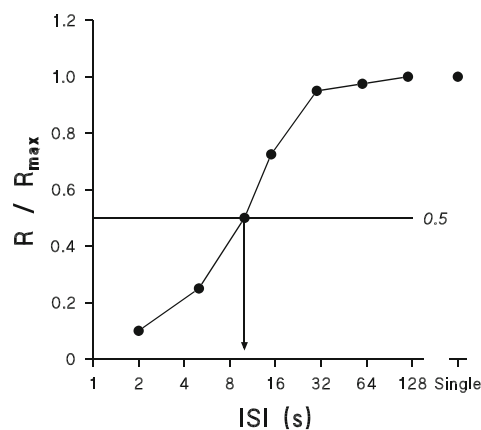
the subject's cornea. Retinal illuminance varies directly with area of the pupil and the transmissivity of the ocular media and inversely with the square of the posterior nodal distance [25]. We used the area of each infant's dilated pupil, published estimates of the ocular media density, and measures of the axial length of the eye. In summary, equal intensity stimuli produced approximately equal retinal illuminance in both infants and control subjects [1, 11, 26–30]. The maximum intensity stimulus produced a retinal illuminance of approximately +3.3 log scot td s in both infants and mature subjects.

Statistical analyses

For each age group, the Mann–Whitney test was used to compare the deactivation parameter (t_{50}) of the ROP and no ROP subjects. Spearman rank order correlation was used to evaluate the relationship between t_{50} and S_{ROD} . The level of significance was $P < 0.01$.

Results

On records such as those in Fig. 1 (left panel), a-wave amplitude was measured 8 ms after the stimulus. For each test–probe flash pair, R/R_{MAX} was plotted as a function of inter-stimulus interval (right panel).



the *right panel*, a-wave amplitude (R) expressed as a proportion of the response to the single flash (R_{MAX}) is plotted as a function of ISI. The ISI (*arrow*) that would produce a half maximum response was determined by linear interpolation

The t_{50} values in infants and mature subjects are plotted in Fig. 2. Table 2 summarizes the median deactivation (t_{50}) and activation (S_{ROD}) parameters of the former preterms and control subjects. The t_{50} values in mature ROP subjects were significantly longer (Mann–Whitney $U = 0$, $P < 0.01$) than in

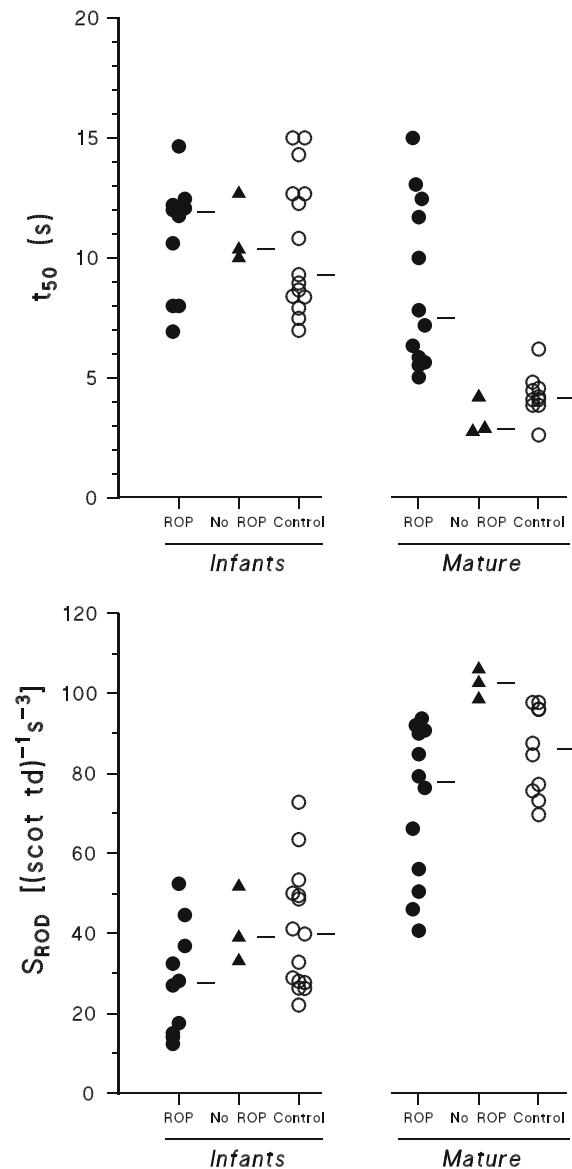


Fig. 2 Values of t_{50} and S_{ROD} . *Upper panel* Values of t_{50} are plotted for the mild ROP subjects (filled circles), the no ROP subjects (filled triangles), and term-born control subjects (open circles). The horizontal bars indicate the median for each group. *Lower panel* Values of S_{ROD} are plotted for the same subjects; all features are as described for the upper panel. S_{ROD} values for these subjects were reported previously [1]

those who never had ROP. In eight of the 12 mature ROP subjects, t_{50} was longer than in any of the mature controls. The t_{50} values in ROP infants did not differ (Mann–Whitney $U = 15$, ns) from those in prematurely born infants who never had ROP and were similar to those previously reported for term-born infants. In both age groups, the t_{50} values of the former preterm subjects who never had ROP were similar to those of the control subjects. The t_{50} values in the mature controls are similar to those in the two subjects tested by Friedburg et al. [10] who also used equal intensity test and probe flashes ($\sim +3 \log \text{td s}$).

In term-born subjects, higher values of S_{ROD} are associated with shorter t_{50} values [11]. However, this is not the case in the ROP subjects ($\rho = -0.262$; ns). In Fig. 3, deactivation (t_{50}) and activation (S_{ROD}) values for each ROP subject are shown. In the majority of mature ROP subjects (5 of 7) with normal S_{ROD} (>69.7 [(scot td)⁻¹ s⁻³]), deactivation was slower than normal ($t_{50} > 6.2$ s); t_{50} was also abnormal in three of the five mature ROP subjects who had low S_{ROD} . Two had normal t_{50} and low S_{ROD} . Both parameters were normal in only two. Thus, a mismatch occurred in seven of the 12 mature ROP subjects. In contrast, all ten infant ROP subjects had normal t_{50} for age and S_{ROD} was normal in six. For preterm subjects, neither t_{50} nor S_{ROD} varied significantly with either gestational age at birth or birth weight.

Discussion

The results are evidence that the kinetics of deactivation (t_{50}) in the majority of the mature ROP subjects were abnormally slow, even in cases with normal kinetics of activation (S_{ROD}). Furthermore, two with normal t_{50} had low S_{ROD} . In normal development, t_{50} and S_{ROD} are correlated; higher S_{ROD} is associated with more rapid recovery, that is, shorter t_{50} . This is not necessarily the case in disease. For example, re-analysis of data in patients with Smith-Lemli-Opitz Syndrome and mitochondrial disease [31, 32] indicated no relationship between t_{50} and S_{ROD} . In the present sample of mature ROP subjects, we found no significant correlation. These data raise the possibility that the ROP rod's capacity to recover from light stimulation did not mature in eight of the subjects with mild ROP, even among those in whom S_{ROD} was normal (Fig. 3).

Table 2 Deactivation (t_{50}) and activation (S_{ROD}) parameters [median (range)]

	ROP	No ROP	Control
t_{50} (s)			
Infant	11.9 (6.9–14.7)	10.4 (10.0–12.7)	9.3 (7.0–15.0)
Mature	7.5 (5.0–15.0)	2.9 (2.8–4.2)	4.2 (2.6–6.2)
S_{ROD} [(scot td) $^{-1}$ s $^{-3}$]			
Infant	27.6 (12.4–52.5)	39.0 (33.2–51.8)	39.9 (22.1–72.8)
Mature	77.9 (40.7–93.8)	102.7 (98.6–106.1)	86.1 (69.7–97.8)

Alternatively, the deactivation of the rods in some older ROP subjects may have suffered progressive compromise; long t_{50} is associated with photoreceptor degeneration [9]. S_{ROD} was abnormally low in five subjects due to either lack of maturation or progressive loss. The data do not distinguish between these two explanations. There is evidence of progressive compromise of rod driven post-receptor retinal function in subjects with a history of severe ROP [1, 33]. All ROP infants had deactivation kinetics that were normal for age; their t_{50} values were within the range of age-matched controls.

In healthy control subjects, activation and deactivation are coupled; higher S_{ROD} values are associated with lower t_{50} values [11, 34]. Studies of deactivation in healthy infants [11, 34] and adults [5, 9, 11, 34, 35] have shown that the brighter the stimuli, the slower the recovery. In healthy infant and adult rat retina, t_{50} varies with the proportion of rhodopsin isomerized [8]. A similar relationship appears to pertain to deactivation in human rods. We have measured [36] the length of peripheral human rod outer segments (ROS) shown in Hendrickson [37]. The peripheral ROS length in the 5-day-old infant was 43% of that in the adult. Assuming that there are 7×10^7 molecules of rhodopsin in the adult ROS [23], there are $\sim 3 \times 10^7$ molecules of rhodopsin in the 5-day-old ROS. If the axial density of rhodopsin in the ROS is proportional to the rhodopsin content of the retina, the ratio of infant to adult isomerizations is proportional to $(1-10^{-D_{\text{infant}}})/(1-10^{-D_{\text{adult}}})$. The rhodopsin content of the retina in a 10-week-old infant is $\sim 68\%$ of that in the adult retina [38]. Therefore, D_{infant} is $\sim 0.68 \times D_{\text{adult}}$ and 1 scot td would isomerize 6.6 molecules of rhodopsin in the infant retina [11]. The $+3.3 \log$ scot td s flash would isomerize $\sim 13,200$ molecules of rhodopsin (0.044%) in the infant retina compared to $\sim 17,000$ (0.024%) in the adult. Thus, isomerization of a higher proportion of rhodopsin in

the infants is consistent with the longer t_{50} values found in infants. This explanation may pertain to the ROP infants. The amount of rhodopsin extractable from the whole retina did not differ between ROP and control rats [2].

The stimuli used in the present study bleach only a small fraction ($<1\%$) of the rhodopsin in the ROS. The double flash method we have used [10] was designed to evaluate the time course of stepwise deactivation of rhodopsin, transducin, and phosphodiesterase. The rate-limiting step in recovery of the photoresponse (deactivation) is hydrolysis of guanosine triphosphate (GTP), which is catalyzed by a membrane-associated multi-molecular complex [7]. Slow diffusion of the activation and deactivation proteins in ROS could account for long t_{50} and low S_{ROD} values found in three of the mature ROP subjects. However, a mismatch (normal activation and abnormal deactivation or abnormal activation and normal deactivation) was found in seven of the mature ROP subjects. Normal kinetics of activation (normal S_{ROD}) is evidence of normal molecular movements in the disc membrane and in the cytosol leading to closure of the channels in the outer segment membrane [39]. As for the kinetics of deactivation, possibly the re-supply of retinoid is sluggish. Alternatively, those molecules dedicated to recovery may be selectively affected in some ROP subjects. These molecular issues will be more readily approached in rats with oxygen-induced retinopathy [40–44], which is known to model key features of ROP [45]. To our knowledge, deactivation of phototransduction has yet to be studied in rat models of ROP.

Further study of the kinetics of deactivation in mature ROP subjects using a range of stimulus levels, along with measurement of rhodopsin density and kinetics of regeneration [46, 47] and dark adaptation, might help explain the abnormal results. The final dark-adapted thresholds of some ROP subjects are

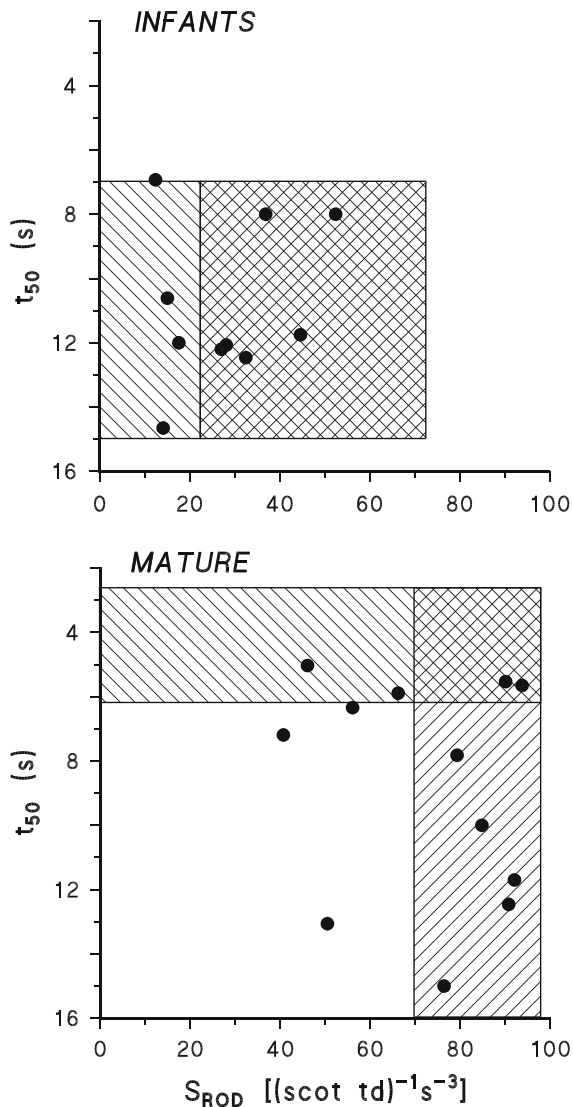


Fig. 3 Deactivation parameter (t_{50}) versus activation parameter (S_{ROD}). In both panels, the shaded bands indicate the range of t_{50} and S_{ROD} values in control subjects; the cross-hatched area represents the locus of control data [11]. Data from infant ROP subjects ($n = 10$) are plotted in the upper panel and from mature ROP subjects ($n = 12$) in the lower panel. The same scales are used in both panels to facilitate comparison across age groups

elevated [48]; the kinetics of dark adaptation and rhodopsin density and regeneration have not been studied.

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