The Development of the Rod Photoresponse From Dark-Adapted Rats
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Purpose. To study electroretinographic a- and b-wave responses of rats at the ages during which rod outer segment length (ROS) and rhodopsin content increase.

Methods. Electroretinographic responses to brief, full-field stimuli were recorded from dark-adapted young (ages 12 to 30 days) and adult rats. The amplitude of the a-wave and the amplitude and implicit time of the b-wave were examined as a function of stimulus intensity. Sensitivity (S), saturated amplitude (Rm), and delay (τ) of the rod cell responses were calculated from the a-waves.

Results. The developmental increase in saturated a-wave amplitude parallels, but lags behind, growth of outer segment length, whereas the saturated b-wave amplitude increases with about the same course as rhodopsin content of the retina. The sensitivity, S, depends on rhodopsin content, and the developmental decrease in the flash energy required to produce a half-maximum b-wave amplitude is inversely proportional to the developmental increase in rhodopsin content. No significant age-dependent variation in τ can be detected.

Conclusion. During development, ROS length and rhodopsin content of the retina are significant determinants of a- and b-wave response parameters. Invest Ophthalmol Vis Sci. 1995; 36:1038-1045.

The electroretinographic (ERG) responses of infants are smaller and less sensitive than those of adults, and visual sensitivity is lower in infants than in adults. In the scotopic domain, photoreceptor and more proximal immaturities are postulated determinants of infantile retinal and visual sensitivities. We examined the ERG responses of rat rod photoreceptors to consider further the rod photoreceptor’s role in controlling the development of retinal response amplitude and sensitivity.

Rod outer segments (ROS) are the last structures to develop in the mammalian retina. The developmental courses of ROS and rhodopsin are summarized in Figure 1. In the immature retina, ROS are short, and rhodopsin content is low. Outer segment length develops more rapidly than does rhodopsin content. For instance, ROS length in 12- to 13-day-old rats is half that of adults, but it is not until 18 to 19 days of age, when ROS length nearly equals that of adults, that rhodopsin content is half that of adults (Fig. 1B).

The rod responds to light by closing the cGMP-regulated ionic channels in the ROS cell membrane. In the dark, current circulates through the open channels. The reduction in dark current by light is the photocurrent. In the ROS cell membrane of mature rods, the density of channels is uniform along the length of the ROS, at least in toad rods, and the amplitude of the photocurrent is proportional to ROS length. If channel density and operation are the same in immature and mature rods, the saturated photocurrent must be smaller in the infant than in the adult in proportion to ROS length. The a-wave voltage is considered proportional to the photocurrent. Thus, the specific prediction is that, during development, the saturated photoresponse, derived from the a-wave voltage, increases as ROS length increases.

When rhodopsin content is low, photon capture will be low. For instance, when the rhodopsin content of an infant’s eye is half that of an adult’s, then, disregarding for the moment factors such as media density
A.

B.

C.

FIGURE 1. Rod outer segment (ROS) development. (A) Central (circles) and peripheral (triangles) ROS lengths are shown as a function of age. The plots are logistic growth curves fitted to the data. All parameters were free to vary. In this equation, C is the age of which y is 50% of the adult value s_{\text{max}}. For the curve fitted to central ROS length, C is 12.5 days (95% confidence interval, 11.7 to 13.1 days) and n is 16.4; for peripheral ROS, C is 12.8 days (95% confidence interval, 12.5 to 13.1 days) and n is 16.7. When normalized, central (solid line) and peripheral (dashed line) curves are similar (not shown). To estimate ROS growth throughout the retina, the normalized central and peripheral data are fitted by a single curve in panel B. (B) The logistic growth curves fitted to normalized ROS lengths (n = 37) and the previously fitted curves for rat rhodopsin values (n = 45) extracted from whole retinas are shown. Rod outer segment length at 12.5 (95% confidence interval, 12.1 to 12.8) days is half the adult value. The exponent of the fitted growth curve is 10.3. Rhodopsin content is half the adult value at 18.7 (95% confidence interval, 18.2 to 19.2) days; the exponent of the fitted growth curve is 3.3. (C) Developmental increases in the relative amounts of transducin and phosphodiesterase. According to the growth curves shown, 50% of adult amounts of α-transducin are present at age 13.2 days; phosphodiesterase (PDE) at 14.8 days. At 9.1 days, cGMP (not shown) is estimated to be 50% that of adults. The exponents of the growth curves are transducin, 11.9; PDE 10.6; cGMP, 3.2. The transducin and PDE curves were fitted to data from mouse; nonquantitative and less complete data indicate similar developmental courses for rat. Also shown is the growth curve for rhodopsin.

and self-screening, photon capture can be no more than half that of an adult's. In this instance, if rhodopsin content were the only determinant of sensitivity, the infant's sensitivity would be 0.3 log units less than that of the adult's. Indeed, the scotopic sensitivity of the a- and b-wave response from developing rats and the gain of the photocurrent of isolated, immature rat rods is accounted for by low rhodopsin content.

The main steps leading to the photoresponse start with light activation of rhodopsin (retinal bound to opsin). Activated rhodopsin diffuses laterally in the disk membrane to the G-protein, transducin, on the disk membrane. Activated transducin then diffuses to phosphodiesterase, with subsequent closure of the channels in the rod cell membrane.

Opsin, the photostable protein part of rhodopsin, accounts for 90% of ROS disk protein and increases along the same developmental course as ROS length (Fig. 1B) with opsin mRNA preceding the protein by approximately 1 day. Transducin and phosphodiesterase have developmental courses (Fig. 1C) similar to ROS length development, as does cGMP. Therefore, the developmental courses of each of the three principal proteins involved in the activation of phototransduction (opsin, transducin, phosphodiesterase) appear to antedate that of rhodopsin. It has been concluded that infant rat rods have a low concentration of rhodopsin with naked opsin present, because rods taken from immature retinas treated with 9-cis retinal (an active homologue of 11-cis retinal) have sensitivities equivalent to those of the adult.

A concentration of rhodopsin lower in infants than in adults also is predicted by the growth curves in Figure 1B. The photolabile compound, rhodopsin, which is opsin bound to retinal, has a slower developmental course than ROS length. Therefore, the amount of rhodopsin per unit length of ROS is low during development. Rod outer segment diameters change little with development; therefore, the curves in Figure 1B indicate that the average rhodopsin concentration is low in infants. The proteins opsin, transducin, and phosphodiesterase have developmental courses indistinguishable from those of ROS length (Figs. 1B, 1C), and, therefore, do not appear to undergo appreciable age-dependent changes in concentration.

Besides the a-wave, which represents the processes involved in the activation of phototransduction in the rod cell by which a single activated rhodopsin molecule activates hundreds of phosphodiesterase molecules (amplification), ERG records display the b-
wave. The rod-mediated b-wave represents the retinal response proximal to the photoreceptors that may be attributable to ON-bipolar cell activity. The ERG response parameters to be evaluated include those representing sensitivity, saturated amplitudes, and implicit time of b-wave. The developmental courses of ROS length and rhodopsin (Fig. 1B) will be compared to the parameters derived from the a- and b-wave responses.

METHODS

Electroretinography

The ERG responses of young (12 to 30 days of age) and adult (60 to 90 days of age) albino rats (Sprague-Dawley strain from Charles River) to flashes were recorded (AC coupled, 1 to 1000 Hz; 1000 gain). Twelve days is the youngest age at which a range of ERG responses can be recorded from rats. Forty-two young and six adult rats were tested. The rats were dark adapted overnight and then prepared for recording under dim red illumination. The rat was lightly anesthetized (sodium pentobarbital, 5 mg/100 g, intraperitoneally), and the left pupil was dilated with 1% cyclopentolate. Corneas were anesthetized with proparacaine. A bipolar Burian-Allen-type electrode was placed on the cornea, and a ground electrode was placed on the tail. This investigation adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

White stimuli (Novatron [Dallas, TX] strobe, series 2100, <1 msec duration) were delivered through a 41-cm integrating sphere, controlled in intensity by calibrated neutral-density filters, and ranged from a 41-cm integrating sphere, controlled in intensity by calibrated neutral-density filters, and ranged from a 41-cm integrating sphere, controlled in intensity by calibrated neutral-density filters, and ranged from a 41-cm integrating sphere, controlled in intensity by calibrated neutral-density filters, and ranged from 10^3 to 10^4 flashes per flash in the adult. S is a sensitivity parameter in units sec^{-1}. $R_{m,31}$ is the estimated saturated rod response amplitude, and $t_d$ is a brief delay. The value of $t_d$ calculated for a-waves exceeds that of the overall delay in the biochemical processes involved in the activation of the G-protein cascade of phototransduction that leads from photosensorization of rhodopsin to hyperpolarization of the rod cell membrane. This model has been shown to describe the photoreceptor response of several species, including that derived from the a-waves of humans.

Equation 1 has similarities with the quantitative model of the activation of phototransduction described by Lamb and Pugh. The Lamb and Pugh model formulates the rising phase of the photocurrent in terms of the biochemical processes involved in the activation of the G-protein cascade of phototransduction that leads from photosensorization of rhodopsin to hyperpolarization of the rod cell membrane. This model has been shown to describe the photoreceptor response of several species, including that derived from the a-waves of humans.

In equation 1, $i$ is the number of isomerizations per flash in the adult. $S$ is a sensitivity parameter in units sec^{-1}. $R_{m,31}$ is the estimated saturated rod response amplitude, and $t_d$ is a brief delay. The value of $t_d$ calculated for a-waves exceeds that of the overall delay in the biochemical processes involved in the activation of phototransduction, designated $t_d$, in the equations of Lamb and Pugh, as does the delay observed in responses of isolated rods unless under voltage clamp. To estimate the number of isomerizations for this calculation, the prereceptor absorbance and ROS diameters and lengths (Fig. 1) of adult rats were taken into account. For adults, an average ROS length of 20 μm, a specific axial pigment density of 0.016 μm^{-1}, and quantum efficiency of isomerization of 0.67 were assumed. In adults, therefore, the maximum stimulus was estimated to produce ~10^6 isomerizations per flash. For purposes of calculation of $S$ with equation 1, at all ages the value of $S$ estimated for adults was used because prereceptor absorbance and specific axial pigment density have not been measured during rat development. Because rhodopsin content is low in infants, $S$ is expected to be low in infants. In view of previous reports that low rhodopsin content

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with consequent low photon capture accounts for low infantile rod sensitivity, the relationship of $S$ to rhodopsin content (Fig. 1B) was examined.

A least squares minimization (fmin) procedure based on the simplex algorithm in the Matlab (The Math Works, Natick, MA) package was used to estimate $S$, $R_{nips}$, and $t_d$. Fitting was restricted to the $a$-wave response before obvious intrusion of the $b$-wave. In practice, the first 40 msec of the record were displayed, and the model was fitted to the leading edge of the $a$-wave (Fig. 2B).

The Michaelis-Menten function

$$V/V_{\text{max}} = \frac{i^n}{i^n + \sigma^n}$$

was fitted to the $b$-wave amplitudes of each rat with an iterative procedure that minimized the mean square deviation of the data from the equation. Each parameter was free to vary. In this equation $V$ is the $b$-wave amplitude, $V_{\text{max}}$ the saturated amplitude, $i$ is the number of photoisomerizations per flash in the adult, and $\sigma$ is the value of $i$ that evoked a half-maximum $b$-wave amplitude. Hence, $\sigma$ may vary if rhodopsin is low, as it is known to be in infants (Fig. 1B). For the $b$-wave, the exponent $n$, indicating the steepness of the function at $\sigma$, is approximately unity for infants and adults.

To summarize, the parameters derived from the $a$-wave were saturated amplitude $R_{nips}$ (equation 1), sensitivity $S$ (equation 1), and $t_d$. The parameters derived from the $b$-wave were saturated amplitude, $V_{\text{max}}$ (equation 2), $\log \sigma$ (equation 2), and implicit time at $\log \sigma$. For comparison to the development of ROS length and rhodopsin (Fig. 1B), developmental changes in ERG parameters were fitted with the logistic growth curve

$$y/y_{\text{max}} = \frac{\text{Age}^n}{(\text{Age}^n + C^n)}$$

where $C$ is defined as the age at which $y$ is 50% of the maximum value, $y_{\text{max}}$. The exponent, $n$, indicates the steepness of the function at $C$. All parameters in the equation were free to vary. The parameters of the growth curves fitted to the ERG parameters were compared to those describing ROS length and rhodopsin (Fig. 1B).

**RESULTS**

The saturated $a$- and $b$-wave amplitudes increase systematically from 12 to 30 days of age (Fig. 3). The growth of saturated $a$-wave amplitude, as previously reported for photocurrents, lags behind growth of ROS length (Fig. 3, inset). The maximum saturated $a$- and $b$-wave amplitudes are found not among adults but among the 18- to 30-day-old rats. In this age range, ROS lengths have become equal to those of adults, but rhodopsin content continues to increase (Fig. 1). If logistic growth is assumed from ages 12 to 30 days, the half-maximum saturated $a$-wave amplitude, $R_{nips}$, is reached at 17.5 days (95% confidence interval, 15.0 to 19.9 days), and the half-maximum saturated $b$-wave
FIGURE 3. Development of saturated a- and b-wave amplitudes. Saturated a-wave (○) and b-wave (●) amplitudes are shown as a function of age. The logistic growth curve fitted to the a-wave is 50% of maximum (358 µV; SE = 47 µV) at age 17.5 days (95% confidence interval, 15.0 to 19.9); fitted the b-wave, it is 50% of maximum (848 µV; SE = 56 µV) at age 20.8 days (19.0 to 22.6). For adults, the mean saturated a-wave amplitude, R\text{max}_a, is 142 µV (SE = 24 µV), and the mean saturated b-wave amplitude, R\text{max}_b, is 198 µV (SE = 54 µV). The inset shows the normalized growth curves fitted to the saturated a- and b-wave amplitude data, with normalized mean (±SE) saturated amplitude of the response from isolated rods (thin dashed line) and rhodopsin (thin solid line) growth curves.

amplitude, V\text{max}, is reached at 20.8 days (confidence interval, 19.0 to 22.6 days). The normalized curves in Figure 3 (inset) show growth of the saturated a- and b-wave amplitudes, previously reported photocurrents,7 and ROS length and rhodopsin.

Sensitivity, S, is shown as a function of age in Figure 4. There is a significant increase in S with age (r = 0.81; df = 46; P < 0.01). In accord with the previous report that the gain of isolated, immature rods is caused by a low amount of retinal,7 the increase in S is correlated with rhodopsin content (r = 0.82; df = 46; P < 0.01). A logistic growth curve fitted to S as a function of age estimates the maximum value of S to be 11.2 sec⁻² (95% confidence interval 9.95 to 12.45 sec⁻²), which is in reasonable agreement with the values obtained for the individual adults (median, 10.21 sec⁻²; range, 7.80 to 15.2 sec⁻²). The age at which the fitted growth curve estimates S to be half-maximum is 17.9 days (95% confidence interval, 16.2 to 19.6 days). These ages overlap the 95% confidence interval (18.2

FIGURE 4. The development of sensitivity, S, and log b-wave sensitivity. (top panel) The sensitivity, S, in units sec⁻², calculated using the estimate of i for adults in equation 1, is shown as a function of age. The smooth curve is a logistic growth curve; the age at which S is 50% of adults' is 17.9 (95% confidence interval, 16.2 to 19.6) days. (middle panel) The log stimulus producing a half-maximum b-wave amplitude (log | in equation 2) is shown as a function of age. The logistic growth curve estimates for adults that a flash causing 1.88 log photoisomerizations per flash produces a half-maximum b-wave amplitude (log | in equation 2). The age at which the curve is 0.3 log units below the adult value is 180.0 days. (lower panel) The growth curves for S and 1/σ, normalized to the calculated maximum (adult) values of S (upper panel) and σ (middle panel), are compared to the rod outer segment length and rhodopsin growth curves.
to 19.2 days) for the age at which rhodopsin content of the eye is 50% of adults. The stimulus that produces a half-maximum b-wave amplitude (log \( \sigma \) in equation 2) decreases significantly with age \((r = -0.41; df = 46; P < 0.01)\). The logistic growth curve fitted to the log \( \sigma \) versus age function is 0.3 log units below the adult value of log \( \sigma \) at age 18 days (Fig. 4, middle panel). Thus, the stimulus producing a half-maximum b-wave amplitude at 18 days is twice that producing a half-maximum b-wave response from adults. The development courses for S and \( \frac{1}{\sigma} \) are similar to that of rhodopsin (Fig. 4, lower panel). The developmental course of b-wave implicit time at log \( \sigma \) is similar to the developmental course for rhodopsin. The age at which b-wave implicit time at log \( \sigma \) is twice that of adults is 18.2 days (95% confidence interval, 16.6 to 19.8 days).

The values of \( t_A \) do not differ significantly in any age group. No significant age-dependent change in \( t_A \) is detectable. For instance, the mean values of \( t_A \) for the 13 day olds \((4.2 \pm 0.61 \text{ msec; } n = 6)\) and adults \((4.1 \pm 0.44 \text{ msec; } n = 6)\) do not differ significantly.

**DISCUSSION**

The physical properties of the developing rods, namely ROS length and rhodopsin content, have significant relationships to parameters of the infants' a- and b-wave responses. Some of the variances of a- and b-wave parameters that are unaccounted for by the development of ROS length and rhodopsin content may be caused by noise inherent in ERG recordings and to intersubject variability of developmental rates.

Saturated a-wave amplitude and photocurrent increase at the ages during which ROS length increases, but both lag behind the development of ROS length. A saturated response of a rod means that the photocurrent has saturated by closing available channels. The lag in development of the saturated response with respect to ROS length could, therefore, be attributable to a lower density of functional channels in infants or to immaturities of channel function despite early expression of the channel gene, with channel mRNA increasing approximately in concert with ROS length.65

Available data do not allow one to determine if the developmental courses of saturated a-wave voltage and photocurrent clearly differ (Fig. 3 inset). Some differences in these courses might be expected if the saturated a-wave voltage reflects developmental changes in the conductances of the rod cell as a whole or in the extracellular milieu, whereas the photocurrent of the isolated rod assesses events in the outer segment that follow photon capture by rhodopsin. During development, the saturated photoresponse, whether the metric is the a-wave voltage or the photocurrent, would likely be dependent, at least in part, on the number of channels available for closure. Possibly the number of channels that can be closed is limited by the relative amount of rhodopsin present. The development of the photocurrent of isolated rods may have a course more like that of rhodopsin than ROS length (Fig. 3, inset). It seems unlikely, however, that the low amount of rhodopsin will provide a complete explanation of the developmental course for the amplitude of the response because saturation of the current, at least in mature rods, depends on activation of only a small proportion of the approximately \(10^8\) molecules of rhodopsin in a mammalian rod.2

Another related possibility is that rhodopsin concentration is not uniform along the length of the developing outer segment. Rhodopsin, which comes to the outer segment disks from the inner segment, might have a higher concentration of chromophore at the base of the rapidly developing outer segment than at the tip. Ratto et al, however, did not find "...a striking difference in sensitivity in experiments where the base and tip of neonatal outer segments were illuminated with transversely oriented slits of light..." and concluded that active rhodopsin was uniformly distributed along the length of the outer segment. Whatever the complete explanation for the physical basis of the saturated photoresponse amplitude, the developmental courses (Fig. 3, inset) suggest that an interaction of ROS length and rhodopsin content will have a role.

Saturated b-wave amplitude has a developmental course from 12 to 30 days that is more like that of rhodopsin than ROS length (Fig. 3). Saturated b-wave amplitude and sensitivity \((\sigma \text{ in equation 2})\) and implicit time at log \( \sigma \), then, may depend on quantum capture by rhodopsin in the outer segments.

Saturated a- and b-wave amplitudes are larger in the 18- to 30-day age range than in adults. Again, physical events limited by the developing outer segment length and rhodopsin content may interact so that the amplitudes of responses from 18- to 30-day-old rats are larger than those of adults. Although it is possible that extracellular resistance changes with age and causes decreases in both a- and b-wave amplitudes, the saturated a-wave amplitude approaches its maximum soon after maximum ROS length is reached (Fig. 3, inset). But b-wave implicit time continues to speed up as rhodopsin doubles between 18 days and adulthood. Thus, a- and b-wave potentials of opposite polarities may come to overlap more completely, in effect diminishing the amplitudes of both a- and b-waves as rhodopsin reaches adult value.

Consistent with the previous report that the gain of the immature rod is attributable mainly to a low amount of 11-cis retinal, a significant proportion \((r = 0.82; P < 0.01)\) of the developmental variation in sensitivity, S, in equation 1 is accounted for by the
rhodopsin content of the eye. Immaturities of rhodopsin itself appear unlikely. Extracted rhodopsin in solution has the same characteristics, whether from infant or adult,39 and in situ photosensitivity of infants and adults is indistinguishable.14 Sensitivity, S, has a developmental course (Fig. 4, lower panel) similar to that of b-wave sensitivity ($1/\sigma$ in equation 2), which is in accord with the previous observation24 that during development dark adapted a- and b-wave sensitivities are proportional to the rhodopsin content of the retina.

The low concentration of rhodopsin has yet to be explained. Even during early development, the rods are well apposed to the pigment epithelial cells, the suppliers of 11-cis retinal.35,37 The presence of intracellular and extracellular vitamin A carrier proteins antedates the appearance of the rod outer segments,36 and the developmental course of interphotoreceptor binding protein, though showing some variation across techniques and laboratories,38,39 suggests that interphotoreceptor binding protein stands ready at an early age to transport 11-cis retinal to the rods. The development of the retinoid system in the pigment epithelium,41 which includes the enzymes to convert 11-cis retinal to the rods. The developmental course of interphotoreceptor binding protein stands ready at an early age to transport 11-cis retinal to the rods. The development of the retinoid system in the pigment epithelium,41 which includes the enzymes to convert 11-cis retinal to the rods. Therefore, human infants must have low rhodopsin concentration as well. The processes involved in the activation of phototransduction in the rods control rod sensitivity, as deduced from the a-wave. The differences between infants’ and adults’ scotopic sensitivities are the same whether measured with the a-wave, b-wave,42 or visually evoked cortical potential.43 Therefore, the processes involved in the activation of phototransduction may also be among the determinants of visual sensitivity. Of course, these a-wave measures of activation processes in the rod, and b-wave measures of ON-bipolar cell activity, do not assess deactivation or inhibitory processes. These responses of dark-adapted, developing retinas to brief, diffuse, full-field stimuli do not assess development of lateral interactions. Hence, these results do not rule out maturation of postreceptor function in the ages studied.

Key Words

rods, phototransduction, development, rats, electroretinogram

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