The A-Wave of the Human Electroretinogram and Rod Receptor Function

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The amplitude of the leading edge of the a-wave of the human electroretinogram (ERG) was compared with predictions from a computational model of the light-induced responses of rod mammalian receptors. According to this model, a linear process describes the amplitude and time course of the response to relatively low flash intensities and at brief times after the onset of the flash. At higher flash intensities, a nonlinear process, described by the Naka-Rushton function or a saturating exponential, is involved. The primary focus here is on intensity-response data recorded with a clinical ganzfeld apparatus. The leading edge of the rod a-wave recorded from normal observers and patients with congenital stationary night blindness (CSNB) was described by a linear process for flash intensities up to the maximum available flash intensity, 2.0 log scot td-sec. This finding is consistent with the model of the rod’s response. It suggests, however, that when ERGs are recorded with clinical systems limited to 2.0 log scot td-sec, these data cannot be used to distinguish between changes in the parameters (eg, semisaturation intensity versus maximum response) of the human rod receptors. Responses to flash intensities up to 3.4 log scot td-sec were recorded using a custom, high-intensity ganzfeld system. Both the linear and nonlinear components of the model were needed to fit the ERGs recorded with this system. This suggests that changes in different receptor parameters can be distinguished with higher intensity flashes. Invest Ophthalmol Vis Sci 31:2070–2081, 1990

The vertebrate electroretinogram (ERG) shows two prominent peaks in potential, the a- and b-waves. For over 50 years, the leading edge of the a-wave has been associated with receptor activity. Uncertainty remains, however, about the answers to two basic questions. First, to what extent does the a-wave reflect receptor activity? For example, can we assume that the amplitude of the a-wave is linearly related to the size of the receptor’s response? Second, can we associate specific defects in receptor function with alterations in the leading edge of the a-wave? In this report we address these questions by comparing the leading edge of the a-wave to responses predicted by a computational model of the rod receptor response.

The amplitude of the leading edge of the a-wave varies with both the intensity of the flash and the time after the onset of the flash. The a-wave grows in amplitude during the first 30 msec or so of the ERG and is larger for more intense lights. To determine the relationship of the a-wave to rod receptor activity requires a model of the receptor’s response that incorporates both the time course of the response and the intensity of the flash. There is general agreement on the basic components of such a model.

Two landmark studies of the mammalian rod include models of the time course of the response of the rod receptor as a function of flash intensity. Although these studies used different techniques and studied different species, they came to similar conclusions. Penn and Hagins recorded the voltage across the receptors of a rat retina. With their technique the electrical activity of a large number of receptors was measured. Baylor et al. recorded the current flow of single rod outer segments in a monkey retina. Both studies conclude that the light-induced rod response can be described by a two-component model. The first component is a linear process which describes transduction, and the second component is a static (instantaneous) nonlinearity.

The Model

The Penn and Hagins and the Baylor et al. models are described as if they are different models. In fact, they are only slightly different versions from a class of models shown in Figure 1. This class of models has two components, a linear process and a static nonlinear process. Transduction is described by the linear process and is represented in the model by a low-pass filter with n stages. The output of the low-pass filter is linearly related to intensity. Doubling the intensity of

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The response \( R(I,t) \) of the rod is a nonlinear function of \( (I,t) \), the output of the low-pass filter. Penn and Hagins\(^6\) assumed a nonlinear function (equation 3) and Baylor et al\(^7\) (equation 4). In particular, for brief flashes:

\[
R(I,t) = \frac{1}{1 + \left[K_0/r^*(t)\right]} R_{\text{max}}
\]

or

\[
R(I,t) = \frac{1}{1 + \left[K_0/r^*(t)\right]} R_{\text{max}}
\]

where \( k_0 \) (scot td-sec) is the semisaturation constant for the response function at its time of peak response, \( t_p \). These nonlinear components in the two models are similar. Equations 3 and 4 produce functions similar in form, and the semisaturation parameters given by the two studies are very close, 20–40 isomerization (i)/rod/flash (Baylor et al\(^7\)) and 30–50 i/rod/flash (Penn and Hagins\(^6\)). A semisaturation constant of 30 i/rod/flash corresponds to about 0.85 log scot td-sec.

In this study, the predictions of this model were compared with ERG responses recorded in a typical clinical ERG apparatus with a ganzfeld dome and a strobe flash. The primary focus is on the information contained in these data about receptor function. The more general question of what is knowable about receptor activity from the ERG recordings is also considered. To address this question, data were collected with a high-intensity ganzfeld system built for this study. In particular, we asked whether the leading edge of the a-wave has properties consistent with the model of the light-induced rod response and whether rod receptor function can be assessed from human a-wave data. A preliminary report of these findings was presented at the ARVO meeting in May 1989.

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* Baylor et al\(^7\) specify that the rod response can be fitted by the impulse response of a Poisson filter given by equation 2 in this report. This filter, like that proposed by Fuortes and Hodgkin,\(^8\) is a chain of \( n \) delay stages or low-pass RC (resistor-capacitor) filters, each with the same time constant, \( \tau \). The time to peak of the filter, \( t_p \), is given by \((n - 1)\tau\). Baylor et al estimate that \( n \) equals 6, and \( t_p \) equals 190 msec ± 38 msec.

Penn and Hagins\(^6\) also assume a filter made up of a chain of low-pass RC filters. However, they assume four stages and that the first two stages have one time constant, \( \tau_a \), and the second two a different time constant, \( \tau_B \). For 33°C, the values of these time constants were estimated to be 35.2 and 89.3, respectively. From our simulation of this filter, its output over the time range in the current study effectively is indistinguishable from a four-stage filter with equal time constants of 57.7 msec and a \( t_p \) equal to 173 msec. Thus our predictions for the Penn and Hagins model are based on equation 2 in the text with \( n \) and \( t_p \) set equal to 4 and 173, respectively.
Materials and Methods

Stimulus Conditions

Two stimulating systems were used. A “clinical ganzfeld dome,” based on a Grass photostimulator, produced a 10-μsec short-wavelength flash (Wratten 47A, Eastman Kodak, Rochester, NY) with a maximum retinal illuminance of 2.0 log scot td-sec. To achieve flashes of higher retinal illuminance, a “high-intensity ganzfeld dome” was built on an optical bench. Light from a 1000-Watt xenon arc lamp was shuttered to produce 10-msec flash durations and directed to a small (10-cm diameter) integrating sphere. A bite-bar assembly was used to hold the head steady. The eye was placed at an opening in the sphere that was approximately 90° from the entrance point of the light. The subject therefore received diffuse full-field illumination from the highly reflective (Kodak White reflective coating; Eastman Kodak, Rochester, NY) surface of the globe. The maximum retinal illuminance of a short-wavelength flash (Wratten 47A) was 3.4 log scot td-sec.

Recording Techniques

The methods used for obtaining full-field ERGs were relatively standard.9 One eye was dilated (1% cyclopentolate hydrochloride and 2.5% phenylephrine hydrochloride) and dark adapted for 45 min before testing. Responses were obtained from the anesthetized cornea with a Burian-Allen bipolar contact lens electrode. Approximately 20 responses to each flash were computer averaged. Responses were initially obtained to an ascending series of short-wavelength flashes (Wratten 47A; X max, 470 nm; half-bandwidth, 55 nm). A second series of responses was obtained to long-wavelength flashes (Wratten 26; λ50% cutoff, 605 nm) that were photometrically matched to the short-wavelength flashes. The rod component to flashes above 1.0 log scot td-sec was subsequently derived by computer subtracting the photometrically matched short-wavelength stimulus.9

Subjects

Normal subjects and patients understood the purpose of the study and signed consent forms after the potential risks were explained.

Normal subjects: The ERG data from ten normal subjects were selected from a group of 180. In particular, these subjects were selected to represent the range of normal a-wave amplitudes from largest to smallest. Full-field rod ERGs were obtained over a 4 log unit range of retinal illuminance (approximately, 0.3 log unit steps) from one eye. Ages ranged from 11-48 yr (mean, 27 yr).

Patients: Patients with X-linked congenital stationary night blindness (CSNB) were referred by ophthalmologists and included in this study because their ERGs have normal or near normal a-waves and markedly reduced b-waves,10-17 conditions which may allow us to assess more of the a-wave response before b-wave intrusion. All six patients were male and had high (>6 diopters) myopia, an elevation in their final dark-adapted threshold of greater than 2.5 log units, minimally reduced cone amplitudes, and markedly reduced or unrecordable rod b-waves. Thus all patients showed the complete type of CSNB.17

One patient with X-linked blue-cone monochromacy served as a control for the rod isolation procedure.

Results

The Clinical Ganzfeld Dome

Normal observers: Computer-averaged ERG responses from a normal observer are shown in Figure 2A. Each trace is the ERG response for a different intensity of a 10-μsec, blue (Wratten 47A) flash. Notice that as the flash was increased in retinal illuminance from 0.8–2.0 log scot td-sec, there was a substantial change in the size of the a-wave. Over this range of flash intensities, the leading edge of the a-wave becomes larger and steeper, although there is little change in the peak-to-trough amplitude of the b-wave. The first 30 msec of these responses is shown in Figure 2B. These responses are truncated at the point that the b-wave intrudes. Because the cone contribution has been computer subtracted, we assume that these responses are rod driven. To evaluate whether the leading edge of the a-wave is linearly related to rod receptor activity, a model that incorporates both the time course of the response and the intensity of the flash must be specified.

Figures 3A–B show predicted receptor responses to a strobe flash. Each curve is for a different flash intensity. Baylor et al17 and Penn and Hagins6 specify the average values for the parameters n, tp, and Ka. In generating the theoretic responses in Figure 3 only Rm, the maximum response amplitude, must be specified. For the theoretical curves in Figures 3A–B, the value of Rm was set at 100 for both models.

A particularly useful way of comparing the predictions of these models to each other and to the ERG data is to divide the response at any point in time, R(I,t), by the intensity of the flash. Figures 3C–D show the predicted responses from panels A and B divided by flash intensity. (Technically, the ordinate is for flash energy not intensity.) This figure requires some explanation. First, only the first 30 msec of the response is shown because this is the range over which the leading edge of the a-wave can be observed (Fig. 2B). Second, the curves for all intensities super-
impose immediately after the onset of the flash. This is due to the fact that immediately after the onset of the flash, the output of the low-pass filter is sufficiently small so as to be uninfluenced by the static nonlinearity. For weak intensities and/or at times immediately after the onset of the flash, the receptor's output is a linear function of flash intensity.\(^\dagger\) When the response amplitude is a linear function of intensity, then the value of \(R(t,t)/I\) is the same for all intensities. Third, the curves deviate from the common curve at shorter times as the flash intensity is increased. Finally, the primary difference between the predictions of the two models is the slope of the leading edge of the curves (Fig. 3).

Results from the clinical ganzfeld dome and the model: In Figure 4A the data from Figure 2B are plotted as response amplitude divided by the intensity of the flash. For graphic clarity, only the data for the three most intense flashes are shown. Figures 4B–D show the data for three additional normal observers.

These clinical ganzfeld data are in qualitative agreement with the models of the rod receptor. The models predict that the curves for the three intensities should fall together immediately after the onset of the flash. The data do fall along a common curve when plotted as response divided by intensity. For this range of intensities and times, there is clear evidence of a linear process. There is also a suggestion in Panels B and D that the response to the 2.0 log scot td-sec flash is influenced by the nonlinear process beyond 20 msec.

Before considering how the data from the clinical ganzfeld dome can be analyzed to assess receptor function, we asked whether the nonlinear process can be observed with more intense stimulation. If it cannot, then the analysis of the a-wave in terms of these models must be questioned.

The High-Intensity Ganzfeld Dome

The high-intensity ganzfeld dome was built to extend the range of flash intensities. Computer-averaged ERG responses to a 10-msec, blue (Wratten 47A) flash are shown in Figure 5A for the same observer whose records appear in Figure 2. Each trace is the ERG response to a different flash intensity. Note that as the flash was increased in intensity from 1.3–3.4 log scot td-sec there was a substantial change in the size of the a-wave. Over this range of flash intensities, the leading edge of the a-wave becomes larger and steeper. The first 30 msec of these responses is shown in Figure 5B as data points. The responses are truncated at the point that the b-wave intrudes.

For the clinical ganzfeld data, the cone contribution is a small percentage of the response to the “blue” test flash. For the higher intensity flashes, the cone response becomes a significant factor. Figure 6 illustrates, with records from a normal observer and a patient with blue-cone monochroma, the technique for isolating the rod a-wave. The first column shows responses to the most intense blue flash (3.4 log scot

\(^\dagger\) From equations 3 and 4 when:

\[
1 \cdot r^*(t) \leq K_a
\]

\[
R(l,t) \equiv \frac{1 \cdot r^*(t)}{K_a} \cdot R_m
\]

and

\[
\frac{R(l,t)}{I} \approx r^*(t) \cdot \left(\frac{R_m}{K_a}\right)
\]

A(1)
Fig. 3. Predicted receptor responses for the Baylor et al (A, C) and Penn and Hagins models (C, D). (A, B) 400 msec of the response for six flash intensities. (C, D) the first 30 msec of these responses divided by the energy of the flash. For a 10-μsec flash, the ordinate should be multiplied by 10^{-5} to be in terms of intensity.

d-t-sec). The second column contains the responses to photopically matched long-wavelength flashes. To confirm that the a-wave elicited by the long-wavelength flash is largely a cone response, the fourth column shows the responses to scotopically matched short-wavelength stimuli. The rod-isolated responses (column 3) are obtained by computer subtracting column 2 from column 1. It is these responses that are plotted in Figure 5.

Figure 7 shows the data from Figure 5B plotted as in Figure 4. The response to each flash intensity was divided by the intensity of the flash. The data resemble the predictions of the models in Figure 3. First, the data fall together along a common curve for the weaker intensities and shorter times. As predicted by the model, a linear process describes the response under these conditions. Furthermore, as in Figure 3, the data deviate from the linear prediction at earlier times for the higher flash intensities. These data show good qualitative agreement with the models.

A quantitative fit: The smooth curves in Figures 5B and 7 show a fit to the class of models schematized in Figure 3. To obtain this fit we assumed that equation 2 described the linear transduction process and that equation 3 described the static nonlinearity. The value of Ka was set to 0.85 log scot td-sec (Baylor et al\(^7\) and Penn and Hagins\(^6\)). The value of Rm was set at 130 μV, just larger than the maximum response. Using these equations and parameters, values of n and tp were determined that would provide a good fit to the data.\(^6\) For the smooth curves n equals 4.5, tp equals 123 msec, and the fit is good.

One minor but consistent deviation from the

\(^6\) Since the flash duration of 10 msec is long relative to the time course of the low-pass filter, the approximation in equation 1 could not be used. To derive the predictions in Figures 5B and 7 a convolution was used.

Reasonable fits could be obtained with n ranging from 4.3–4.7. It was not possible to obtain a plausible fit for a value of n larger than 5. Thus the a-wave suggests that the human rods show a faster onset than the Baylor et al\(^7\) model and are more in line with the Penn and Hagins\(^6\) model in terms of time course.
model is seen in the responses 20–30 msec after the onset of the weaker flashes. They are also present in the 10-μsec data in Figure 2B. These small “ripples” may be residual cone responses or small artifacts introduced by our subtraction technique. However, they resemble low-voltage, fast-oscillation potentials (oscillatory potentials) described by others on the leading edge of the b-wave and may be the potential labeled OP2 by Lachapelle et al.\textsuperscript{18} These oscillatory potentials have been reported to be missing in many CSNB patients\textsuperscript{10–13,18} and were not present in our CSNB patients. In either case, they represent a small and unimportant deviation from the model.

This analysis suggests that the hypothesis that the leading edge of the a-wave is linearly related to the pooled response of the rod receptors cannot be rejected. We can return to the question of what can be said about abnormal receptor responses from clinically available data.

Clinical Ganzfeld Data From Normal Observers and Patients With CSNB

The a-wave responses recorded in the clinical ganzfeld dome show little or no influence of the static nonlinearity. As will be discussed, these data do not
allow separate estimates of changes in the receptor's parameters. This does not mean, of course, that we cannot distinguish normal from abnormal rod receptor activity. It does mean, however, that the same information is contained in each response over the intensity ranges used in Figure 2. In the linear range, all responses divided by intensity are the same. To analyze whether a patient's receptor responses are normal, only the response to a single intensity is needed. As the responses are largest to the 2.0 log scot td-sec flash, we present these data from normal controls and patients with CSNB.

The first 25 msec of the responses from ten normal controls to the flash of maximum intensity, 2.0 log scot td-sec, are shown in Figure 8. These were selected from a sample of 180 normal subjects to represent the range of normal a-wave amplitudes from largest to smallest. The leading edge of the a-wave appears to show considerable variability in amplitude and waveform for these observers. The causes of this variability are analyzed best in a plot in which the log of the response is plotted. The response at each time was multiplied by −1 to make the leading edge of the a-wave positive (the log of a negative number is undefined). The logs of these values are shown against log time in Figure 9. For clarity, the data are presented in two panels, each containing the results for five subjects. Each symbol is for a different observer. Notice that the responses in Figure 9 appear
Fig. 8. The first 25 msec of the ERG response from ten normal observers. The intensity of the 10-μsec flash was 2.0 log scot td-sec, the maximum flash intensity in Figure 2. Each symbol represents a different observer.

more similar than those in Figure 8. The smooth curve is the mean curve and the dashed curves show this curve displaced vertically by ±0.5 log unit. The curve turns down when the b-wave enters. To a first approximation, the data for different observers have the same shape but are displaced vertically and thus differ by a multiplicative constant. This constant will be related to the parameters of the model of the rod receptor.

CSNB patients: The intrusion of the b-wave makes it impossible to follow the a-wave from normal observers beyond approximately 25 msec for the most intense flashes. As patients with CSNB are said to have little or no rod b-wave and a near normal a-wave, data from six patients with CSNB were analyzed to see if more of the receptor response could be followed. These data also provide an illustration of a new approach for assessing whether receptors are affected by retinal abnormalities.

Figure 10A shows the ERGs from six patients with CSNB for a single flash intensity (2.0 log scot td-sec). As expected, the b-wave is markedly reduced in these patients. Figure 10B shows the first 30 msec of the ERGs in Figure 10. To determine whether the amplitude of the leading edge of the a-wave is within the normal range, the data are presented in Figure 11 on a log-log plot with the curves for the mean and range of the normal from Figure 9. Notice how similar the responses from the six patients are. Furthermore, the CSNB responses have the same time course and fall within the normal range but are, on average, about 0.25 log unit lower.

Since the CSNB patients have very small b-waves and normal or near normal a-waves, it was anticipated that more of the a-wave could be studied in these patients than in the normal subjects. Although the a-wave appears normal and the b-wave is greatly reduced in these patients, the b-wave still intrudes at about the same time. For the ten normal subjects, the leading edge of the b-wave elicited by the 2.0-log scot td-sec flash occurred between 22–26 msec; for the six CSNB patients it was around 25–35 msec. At best the a-wave can be followed for another 10 msec or so for these patients. The data from these patients do, however, illustrate the value of the log-log plot in assessing receptor function.

Fig. 9. The ERG responses from Figure 8 are plotted on log-log axes. The responses from the ten observers are shown in two panels for clarity. The symbol convention from Figure 8 is maintained. The solid curve is the average for all ten normal subjects. The dashed curves are this curve shifted vertically by −0.5 or 0.5 log unit.
Discussion

The amplitude of the leading edge of the a-wave varies with time and flash intensity in ways consistent with the current model of the light-induced response of the mammalian rod. The qualitative agreement between the model and the data is good. As predicted, the responses to relatively weak lights and at brief times after the onset of a flash are linearly related to intensity. The evidence for this linear process can be seen in both the 10-μsec (Fig. 4) and 10-msec (Fig. 7) data. With the more intense flashes available with the high-intensity ganzfeld dome, there is evidence that a nonlinear process occurs.

The ERG data also show reasonable quantitative agreement with the computational model of the rod’s response. Our purpose in fitting the model to the 10-msec data (Figs. 5B, 7) was to establish that the class of models used by the physiologist could be fitted to the a-wave data with plausible parameters. This model is computational in the sense that it predicts a response waveform for any temporal variation in light intensity. It is not a model of the biochemical or biophysical processes. The model is, however, consistent with the current biochemical theory of transduction. The molecular events initiated by quantal absorption and culminating in a change in the amount of an internal transmitter, cyclic guanosine monophosphate (GMP), are approximated by a linear process over a wide range of intensities. The instantaneous nonlinear component is associated with the limited number of light-sensitive conductance channels that are rapidly opened and closed by cyclic GMP.

Based on the current study, the hypothesis that the amplitude of the leading edge of the a-wave is proportional to the underlying receptor response cannot be rejected.

Estimating Rod Receptor Parameters
From Human A-Wave Data

The model of the rod has four parameters: (1) the number, n, of stages in the low-pass filter, (2) the time-to-peak response, tp, which can be related to the time constant of the individual stages, (3) the semi-
saturation constant, $K_a$, of the nonlinear mechanism, and (4) the amplitude of the response of the individual rods, $R_m$. We assumed that the amplitude of the a-wave was linearly related to the underlying response of the individual receptors. In particular, we assumed that the amplitude of the a-wave $A(I, t)$ is given by:

$$A(I, t) = \alpha c R(I, t) \quad (5)$$

and the maximum a-wave amplitude $A_m$ by:

$$A_m = \alpha c R_m \quad (6)$$

where $R(I, t)$ is the amplitude of the potential of a single rod, $c$ is a constant that depends on the number of rods recorded, and $\alpha$ is a constant that depends on the placement of the electrode, the size of the eye, and other factors in the recording situation that may produce variations among individuals with normal rods. We assume that for normal observers only $\alpha$ varies.

With these simple assumptions, the effects of changing one or more of the receptor's parameters can be assessed. Different hypotheses about the cause of sensitivity loss make different predictions about changes in $R_m$ or $K_a$.\textsuperscript{24-26} For example, a simple loss of quantal absorbing ability secondary to pigment loss or preretinal filtering acts like an increase in $K_a$. On the other hand, a less responsive rod secondary to hypoxia may result in a decrease in $R_m$. To determine whether a change in $K_a$ can be distinguished from a change in $R_m$, we assume that the model fitted to the 10-msec data describes the human rod response. Figure 12 shows the effects of increasing $K_a$ or decreasing $R_m$ by a factor of four. The first 25 msec of the predicted a-wave responses to a flash of 2.0 log scot td-sec (panels A and C) and 3.5 log scot td-sec (panels B and D) are shown. The predicted responses are in linear coordinates in panels A and B and in the log-log coordinates in panels C and D. For the 2.0 log scot td-sec flash, changes in $K_a$ cannot be distinguished from changes in $R_m$. Thus, clinical domes must allow for the recording of rod-isolated responses to flashes in excess of 2.0 log scot td-sec for the parameters of the rod receptor to be estimated reliably.

For the 3.5-log scot td-sec flash, the changes in $K_a$ and $R_m$ produce different predictions. On the log-log plot (panel D) the change in $R_m$ appears as a vertical shift in the normal curve and the change in $K_a$, a horizontal shift. Although it is possible to distinguish $R_m$ from $K_a$ changes, changes in the transduction process can mimic $K_a$ changes. For example, increasing $tp$ from 123–185 msec produces a response indistinguishable from the increase in $K_a$ over the first 25 msec. It should be possible, however, to obtain estimates of three parameters, $n$, $A_m$, and ($K_a/tp$) from these data.

A deceptively simpler approach to estimating the receptor's parameters involves the slope of the leading edge of a-wave. Some investigators\textsuperscript{27,28} estimated $R_{max}$ and $K_a$ of normal observers by measuring the slope of the leading edge of the a-wave elicited by flashes of different intensities and then fitting a static nonlinear function to this measure. Hood and Birch\textsuperscript{5} recently argued that this slope measure does not allow a straightforward estimate of the receptor's parameters. To estimate these parameters requires a model of the time course of the receptor response.

**Analyzing Existing Clinical Ganzfeld Data**

Most clinical protocols include a full-intensity "white" flash. Compared with the blue flash, the white flash is about 0.2 log unit more effective for the rods and about 1.3 log units more effective for the cones. Thus the response to this white flash will have a sizable cone contribution, adding little to the range over which the rods can be studied. Consequently, we do not recommend using the response to a white flash for quantitative assessment of rod sensitivity loss. Although it is preferable to remove the cone contribution with a subtraction procedure, the response to the blue flash of 2.0 log scot td-sec contains a sufficiently small cone contribution to make the measurement of rod receptor activity feasible.

The two most common measures of receptor function are the peak a-wave amplitude and the slope of the leading edge of the a-wave. Both measures have potential problems. The peak amplitude has long been recognized as being contaminated by the intrusion of the b-wave, which may be of varying influence depending on the stimulus conditions and the nature of the process affecting retinal sensitivity. The slope of the leading edge of the a-wave has been suggested as an alternative measure to peak amplitude.\textsuperscript{27} This measure does not entirely avoid these problems. Even for a flash of fixed intensity, there is no single value of the slope of the a-wave when ERGs are displayed on a linear time axis. Thus, the measure of slope will be influenced by how much of the a-wave is available for analysis. This interval of analysis is determined in part by the size of the b-wave. Consequently, retinal abnormalities that affect the b-wave may influence the measure of slope without affecting the receptors.

The log-log plot introduced in Figure 9 offers an alternative to the slope measure. Since the responses are in the linear range for intensities of 2.0 log scot td-sec or less, all responses divided by intensity are the same, and when plotted as log response ampli-
Fig. 12. (A) The first 25 msec of the response predicted from the model in Figure 9 to a 2.0-log scot td-sec flash. The solid curve is the normal response for the parameters used in the fit to the data in Figure 9. The interrupted curves show the effects on this response of increasing $K_a$ or decreasing $R_m$ by a factor of four. (B) As in (A) for a 3.5-log scot td-sec flash. (C) Responses in (A) on log-log axes. (D) Responses in (B) on log-log axes.

Thus, although the response to flashes of different intensities can be plotted together on the log–log plot, only the response to a single flash intensity must be analyzed. The response to the most intense flash contains all the information available about receptor function. For the linear range of flash intensities, 2.0 log scot td-sec or less, the average curve for the normal subjects can be fitted to the patient data with a vertical displacement. The vertical displacement needed for best fit provides a measure of the log of the decrement in the a-wave. This analysis has the advantage of using all the appropriate data in the response and of supplying a number that can be related to hypotheses about receptor malfunctioning. Two important caveats must be added. First, these data alone cannot be used to distinguish different causes for the abnormal a-wave. Changes in $R_{max}$ or $K_a$ will both produce vertical shifts (Fig. 12C). Second, the wide range of normal data in Figure 9 may limit the use of any measurement of the a-wave for detecting changes in receptor function. This analysis holds some hope that ERGs elicited with more intense flashes will yield separate measures of $K_a$ and $R_{max}$, which should allow independent estimates of the variability of $K_a$ and $R_{max}$ in normals and estimates.
of the changes in these parameters with retinal abnormalities.

Key words: ERG, a-wave, human rod receptor, CSNB

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References