Documenta Ophthalmologica **92**: 253–267, 1997.

Assessing abnormal rod photoreceptor activity with the a-wave of the electroretinogram: applications and methods

DONALD C. HOOD[1] & DAVID G. BIRCH[2]
[1]*Department of Psychology, Columbia University, New York, NY;* [2]*Retina Foundation of the Southwest, Dallas, TX, USA*

Received 9 November 1996; accepted in revised form 10 February 1997

Key words: a-wave, electroretinogram, phototransduction, rod receptor

Abstract. The impact of a disease on phototransduction can be assessed by fitting the leading edge of the rod a-wave to high-energy flashes with a quantitative expression. Two parameters of rod receptor activity are obtained, S (sensitivity) and Rm (maximum response). In this study, the meaning of these parameters and examples of conditions that change them were examined. In addition, a new protocol was developed for obtaining these parameters. A set of three to five white flashes were first presented in the dark and then on an adapting field (30 cd/m^2). Subtracting the light-adapted responses from the dark-adapted responses yielded isolated rod a-wave responses. A clinical protocol was developed based on a single white flash energy. It is possible to determine whether a disease is producing a change in S and/or Rm with this single flash energy without the use of any equations.

Abbreviations: CRVO – central retinal vein occlusion; NVI – neovascularization of the iris; Rm – maximum response; S – sensitivity.

Introduction

Receptor activity can be assessed in the human retina by means of the a-wave of the electroretinogram (ERG). Although it has long been recognized that the a-wave recorded from the vertebrate eye is associated with the massed electrical activity of the receptors [1, 2], it is now possible to relate parameters of the rod a-wave to parameters of rod photoactivity [3-8]. The purpose here is (1) to explain the meaning of these a-wave parameters and to present examples of conditions that change them, (2) to describe a new protocol for deriving estimates of these parameters and (3) to suggest a simplified protocol and analysis for use in the clinic.

The need to distinguish S (sensitivity) and Rm (maximum response) changes

The techniques described here are for the clinical investigator interested in the

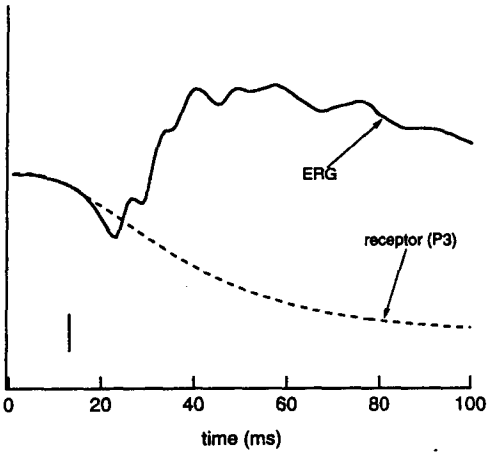

Figure 1. An ERG response to a 2.0-log scot td-s, blue (W47A), 10-μs flash presented in a ganzfeld to a dark-adapted eye. The dashed curve is the fit of a receptor model and provides an estimate of the receptoral contribution to the ERG [9].

following question: 'How does a particular disease or treatment affect human rod receptors?' The traditional way to answer this question is to measure the slope and/or the peak amplitude of the a-wave to flashes of moderate intensity. Figure 1 shows the ERG response to a flash of moderate intensity (2 log scot td-s) with an estimate of the receptor contribution labelled P3. Notice that the peak a-wave amplitude does not represent the peak receptor response. In addition, the rod a-wave of the human ERG to moderately intense flashes is partially postreceptoral in original [9], as was originally shown for the cone [10]. Further, as will be clear below, measures of the slope or amplitude of the a-wave to lights of moderate flash energy cannot distinguish between two different changes a disease can cause.

The two panels in Figure 2 illustrate two hypothetical, and very different, effects that a disease process could have on the rod a-wave. The dashed curves in both panels are the first 60 ms of the rod ERG to a brief, 1-ms, flash of light of about 4.0 log scot td-s. This flash produces a maximum a-wave response and is 100 times the intensity of the one used in Figure 1. First, assume a disease process that decreases the sensitivity of the rods without changing their maximum response. We will define a change in sensitivity S as one that acts as if the flash energy were decreased. A change in S is simulated in the normal subject of Figure 2 by showing the response (solid curve) to a flash of light that is one-fourth (0.6 log unit) less intense than the flash producing the dashed curve.

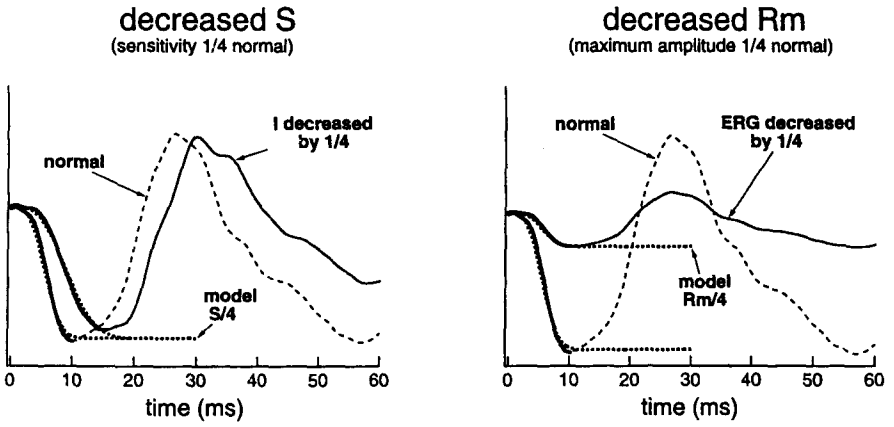

Figure 2. Two types of changes that a disease process could effect on the rod receptor and thus on the leading edge of the rod a-wave (shown as bold). The dashed curve is the dark-adapted, rod response to a flash of 4.0 log scot td-s. (Left) A change in sensitivity, S, is defined as a change that acts as if the flash intensity were decreased. The solid curve shows the ERG response to a flash that is one-fourth the intensity. The bold dotted curve labeled 'model' is the fit of eq. 1 assuming that the flash intensity has not changed. (Right) A decrease in the maximum response (Rm) is defined as a change that scales the entire leading edge (bold) by the same factor. The solid curve shows a hypothetical ERG response created by dividing the dashed curve by 4. The bold dotted curve labeled 'model' is the fit of eq. 1.

The right panel of Figure 2 illustrates a very different change in the rod ERG, a change in the maximum response Rm. A change in Rm is defined as one that decreases the a-wave at all times by a multiplicative factor. The solid curve in the right panel of Figure 1 is the normal curve divided by 4.

A disease process can produce changes in one or both of these parameters, S and Rm. The traditional measures of the a-wave (e.g., peak amplitude or slope of responses as in Figure 1) do not do a good job of distinguishing conditions that may produce one or both of these changes. First, in general, the flash energies (see Figure 1) used are insufficient to produce maximum rod a-wave responses, and thus S and Rm changes cannot be distinguished. Second, a measure of the slope, even if applied to a response of maximum amplitude, confuses S and Rm changes. Notice that the slope of the a-wave in Figure 2 is decreased with a change in either S or Rm. Below we show that S and Rm changes can be distinguished either by fitting a simple equation or by qualitatively comparing waveforms.

The rod model and the a-wave

The leading edges of the rod a-waves can be described by

$$P3(I,t) = \{1 - \exp[-I \cdot S \cdot (t - t_d)^2]\} \cdot Rm_{P3} \quad \text{for } t > t_d \tag{1}$$

where the amplitude names P3, named after Granit's receptoral component, is a function of flash energy I and time t after the occurrence of a brief, essentially instantaneous, flash. S is a sensitivity parameter that scales I (flash energy); Rm is the maximum amplitude; and t_d is a brief delay [5-8]. Values of t_d from different laboratories range from about 2.5 to 4 ms. Most of this delay is a constant that depends on the filtering of the recording apparatus and the duration of the test flash. The transduction process contributes only about 1 ms (see Breton et al. [7] and Cideciyan and Jacobson [11] for a discussion). Thus, in practice, t_d is a constant and studies of photoreceptor activity are concerned with only two parameters, S and Rm (see note 1). With care and the appropriate assumptions [8], these parameters can be related to parameters of phototransduction in the Lamb and Pugh model [12].

The dotted curves in Figure 2 show the fit of the model to the hypothetical curves. Note that eq. 1 is only fitted to the leading edge of the a-wave (bold part). From this fit, changes in S and Rm can be obtained. A change in the parameter S is equivalent to a change in flash energy (note the term $I \cdot S$ in eq. 1). Also, a change in Rm is equivalent to scaling the entire response P3 by a multiplicative constant. We will show below that these relationships allow estimates of changes in S and Rm to be made without the need of an equation.

Applications

Below we show three applications to illustrate conditions that affect only S, only Rm and neither S nor Rm. For each example, the responses and the fit of eq. 1 are presented in Figure 3. The responses to a single flash energy in Figure 4 illustrate that the key conclusions can be made with a single flash energy and without fitting a model.

Central retinal vein occlusion. The solid curves in upper panels of Figure 3 show the ERG responses from the normal and the affected eye of a patient with central retinal vein occlusion (CRVO) [13]. Each record is for a different flash energy (see figure caption). The dashed curves show the fit of the model (eq. 1). This patient had a large decrease in S (one-third of normal) and very little change in Rm. She developed neovascularization of the iris (NVI). In general, patients with CRVO who develop NVI have decreased values of S but relatively normal values of Rm [13]. The change in S in these patients may

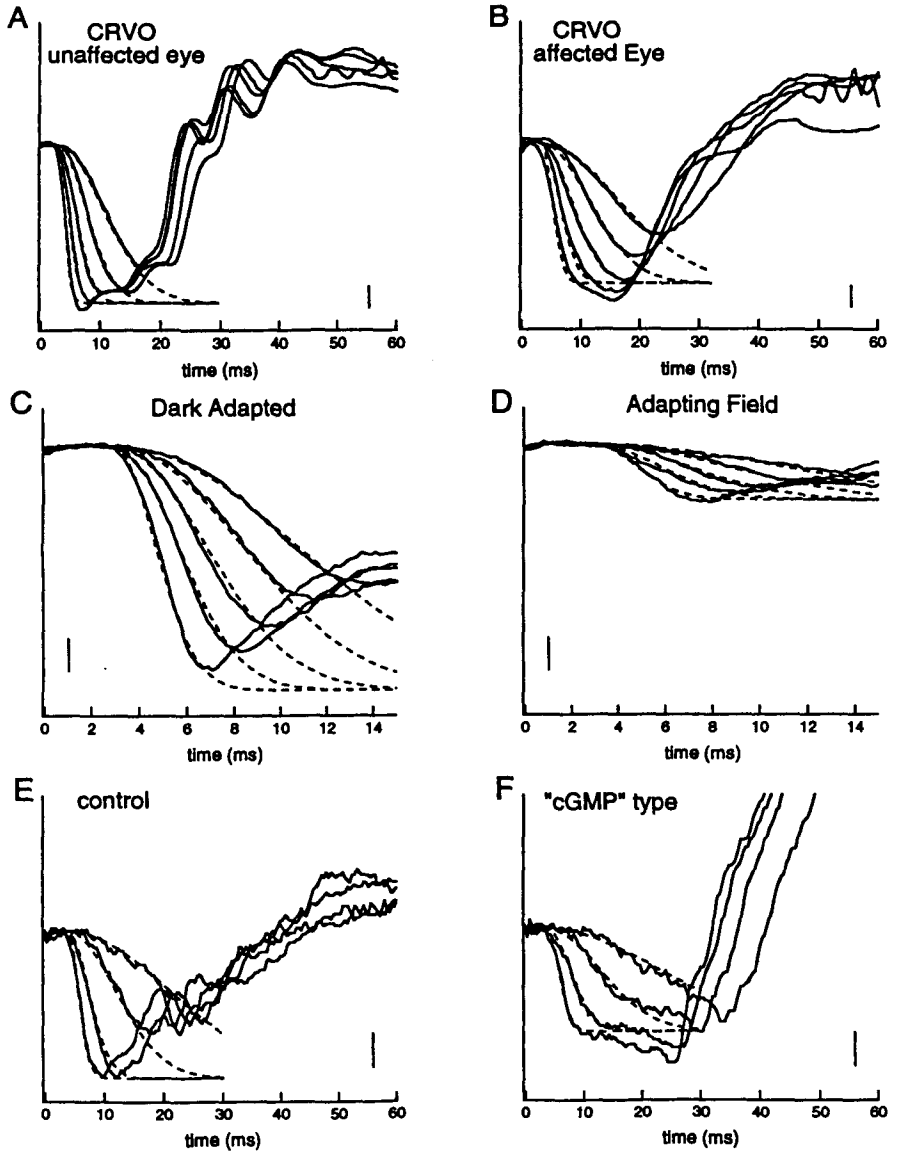

Figure 3. (A, B) Dark-adapted ERGs from a patient with CRVO who developed NVI. The stimuli were 1-ms, white flashes that ranged in energy from 2.6 to 4.3 log scot td-s. The dashed curves are the fit of eq. 1. The values of log S and log Rm were 1.34 and 2.59 in the unaffected eye and 0.87 and 2.54 in the affected eye. The calibration bar is 50 μV (modified from Johnson and Hood [13]). (C, D) Rod-only ERG responses to a blue (W47B), 1-ms flash presented in the dark (panel C) or on a 2.7-log scot td white background (panel D). The flash energies ranged from 3.2 to 4.5 log scot td-s (modified from Hood and Birch [19]). (E, F) Dark-adapted rod-only ERG responses to a blue (W47B), 1-ms flash that ranged in intensity from 2.0 to 3.9 log scot td-s are shown for a normal subject (panel E) and from a patient with so-called cyclic guanosine monophosphate (cGMP) supernormal b-waves and for three normal subjects. The dashed curves are the fit of eq. 1. The values of log S and log Rm were 1.26 and 2.63 in the normal subjects and 1.16 and 2.47 in the patient. The calibration bar is 100 μV (modified from Hood et al. [20]).

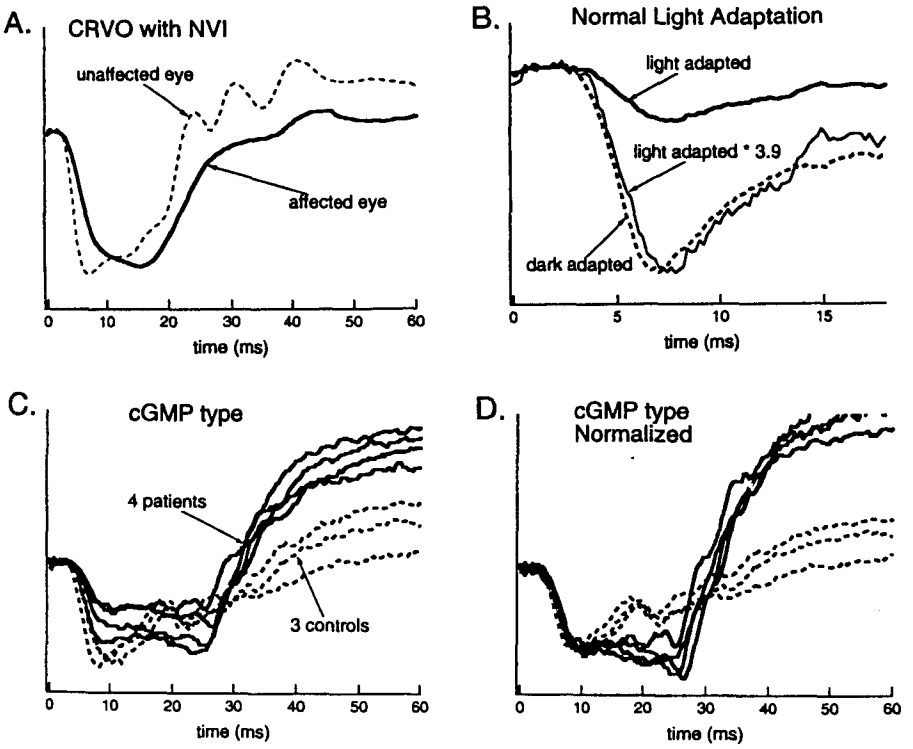

Figure 4. (A) CRVO. The responses are from Figures 3A and B to a 4.3-log scot td-s flash. (B) Adapting field. The responses labeled 'dark-adapted' (dashed) and 'light adapted' (bold solid) are the responses to the 4.5-log scot td-s flash from Figures 3C and D. The other curve is the solid curve multiplied by 3.9 to bring the peak in line with the dark-adapted response. (C) Cyclic guanosine monophosphate (cGMP) type. The rod-only responses to a 3.9-log scot td-s, blue (W47B), 1-ms flash are shown for four patients with so-called cCMP type supernormal b-waves and for three normal subjects (modified from Hood et al. [20]). (D) cGMP type. The records from panel C normalized to have the same maximum a-wave at 10 ms.

result from a slowing of one or more of the steps of phototransduction such that the amplification or sensitivity of transduction is decreased. Presumably these changes are secondary to an oxygen gradient that has been compromised enough to affect the receptors. Interestingly, other conditions that may produce hypoxia of the receptors have also been shown to produce changes in S [14-17], and Reynaud et al. [18] suggested that metabolic acidosis may be the cause.

Figure 4A shows that the change in S in the affected eye can be detected with the response to a single flash and without fitting eq. 1. The responses from the unaffected and affected eyes are shown for a single flash energy of

4.3 log scot td-s. Note the similarity to Figure 2A. The value of Rm is about the same in both eyes, and S has clearly been decreased.

Steady adapting fields. Figures 3C and D show a condition that mainly changes Rm (modified from Hood and Birch [19]). The response from a normal observer to a range of flash energies (see figure caption) are shown for the flashes presented in the dark (C) and on an adapting field of 2.7 log scot td. The dashed curves are the fit of eq. 1 and show that Rm is reduced by more than 75% (0.64 log unit) while S changes by less than 10%. The reduced Rm was hypothesized to be caused by the polarization of the membrane by the steady field (response compression) [19]. As above, Figure 4B illustrates that this conclusion can be reached with a single flash energy and without fitting eq. 1. The bold dashed and solid curves in Figure 4B are the response from Figures 3C and D and to a 4.5-log scot td-s flash. The solid curve was produced by multiplying the response in the presence of the adapting field by 3.9 to normalize the response to the dark-adapted value. By comparing these two responses to Figure 2, we conclude that there is a large change in Rm and little or no change in S.

'Cyclic guanosine monophosphate type' delayed ERGs. Figure 3F shows records from a patient with delayed and supernormal rod b-waves (modified from Hood et al. [20]). This unusual retinal dystrophy was described in two siblings by Gouras et al. [21] in 1983 and has since been reported in a number of other studies [22-27]. Some had argued that the large delays of the b-waves were caused by a transduction process that has been slowed secondary to elevated levels of cyclic guanosine monophosphate in the rod photoreceptors [e.g., 21, 23, 25]. If the cause of these delays is a slowed transduction process, then this should result in a decreased value of S. A recent study [20] fitted eq. 1 to the rod a-waves from four of these patients and showed that S was normal. The results for one of the patients in this study are shown in Figure 3F. The fit of the model (dashed curves) shows an S value that was close to normal (see figure caption). Figure 3E shows the fit to a normal subject from the same study. Figures 4C and D illustrate how the same conclusion can be reached with the response to a single flash and without eq. 1. The records in panel C are the responses to a 3.9-log scot td-s flash from four normal subjects and four patients. In Figure 4D, these records are normalized to have the same amplitude at about 10 ms. We can conclude that although some of the patients have smaller values of Rm, they all have normal values of S.

Protocols

Background

To study rod receptor activity by fitting eq. 1, protocols have been designed to isolate rod a-waves to relatively high flash energies. Protocols devised to estimate the parameters S and Rm have to be concerned with the following three factors: One, the flashes must be intense enough to allow a good estimate of Rm. (If flash energies are too high, then the value of S changes and this must be taken into consideration [7, 11].) Two, cones can contribute to the a-wave, and their contributions can be substantial in the case of patients with selective damage to the rods [8]. Three, preretinal filtering secondary to yellowing of the lens or cornea can affect the estimate of S, especially if blue flashes are used and older populations are studied. The procedures for addressing these concerns vary among studies and are partially influenced by commercial equipment that in some cases limits the range of flash energies available and/or the use of spectrally filtered light.

The protocols in the literature fall into two categories: some use white flashes and assume that the cone contamination is relatively minor [7] or at least unimportant for the condition under study (e.g. [13]), while others use red flashes to explicitly measure the cone contributions (e.g. [4, 6, 8, 11]). The major advantage of the latter protocol is that it maximizes rod-cone separation by using blue and red lights and thus allows cone responses to be measured in essentially a dark-adapted state. One disadvantage is that it is difficult to implement on some commercially available systems because of insufficient light intensity and/or the difficulty involved in adding spectral filters. A second disadvantage involves the difficulty of obtaining a photopic match between the blue and red flashes for each subject. Matches will vary across subjects because of variations in preretinal screening. However, in practice, a single photometric match is usually assumed. Further, if the experimenter wants to obtain a series of cone a-waves that are suitable for fitting with a cone model [11, 28, 29], then these red flashes are not intense enough and an additional series of red flashes on a more intense background to suppress the rods must be run.

A protocol using white light

It is possible to measure both rod and cone a-waves by means of a single series of white flashes. In this protocol, a series of white flashes are first presented in the dark. The responses to flashes from 3.6 to 5.0 log scot td-s are shown in Figure 5 (left) as the solid curves; each is the average of two responses (see note 2). To obtain an estimate of the cone contribution to these responses, the same flashes are then presented on a steady field of about 30 cd/m^2 (ISCEV standard white background). Previous work suggests that this

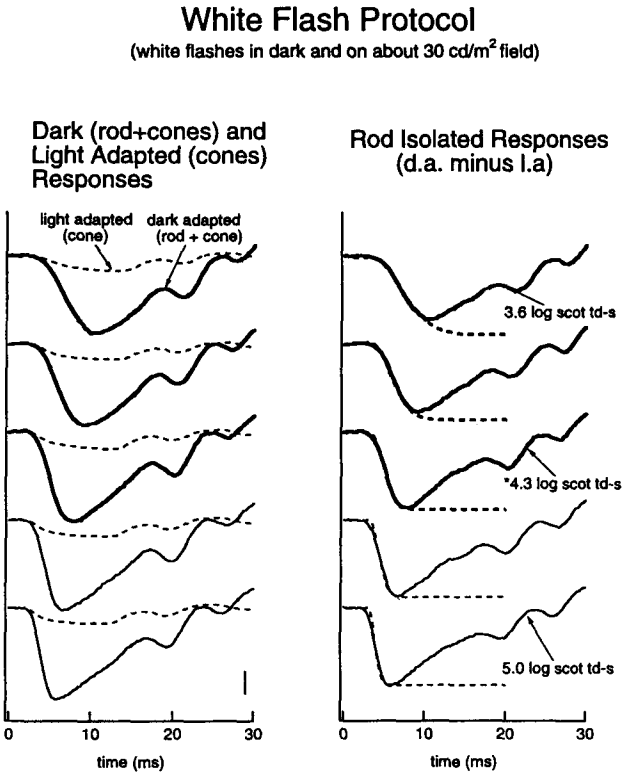

Figure 5. (Left) Dark-adapted (solid) and light-adapted (dashed) responses to 1-ms, white flashes ranging in energy from 3.6 to 5.0 log scot td-s. Each response is the average of two presentations. The calibration bar is 100 μV and applies to both panels. (Right) Rod-only responses created by subtracting the light-adapted (l.a.) responses from the dark-adapted (d.a.) responses. The dashed curves are the fit of eq. 1 to the three responses to the lowest flash energies shown as bold.

background of about 3.3 log scot td (8-mm pupil) reduces the rod a-wave to close to zero [5, 19] and has a very small effect on the cone a-wave [29]. The response to these white flashes (average of 12 in Figure 5) are shown as the dashed curves in the left panel. These same responses are shown in Figure 6 on an expanded response scale along with the response (solid curve) to a red (W26) flash set at the maximum intensity available. There is no sign of a rod contribution to the responses to the white flash. The response to the red flash matches the response (bold dashed curve) to the photometrically equal white flash. The waveforms of the responses have the characteristic shape of cone responses [28, 29]. Further, they cannot be fitted by the rod model but can be fitted by a model of cone phototransduction as previously described for responses to red flashes [28]. Although one cannot rule out the

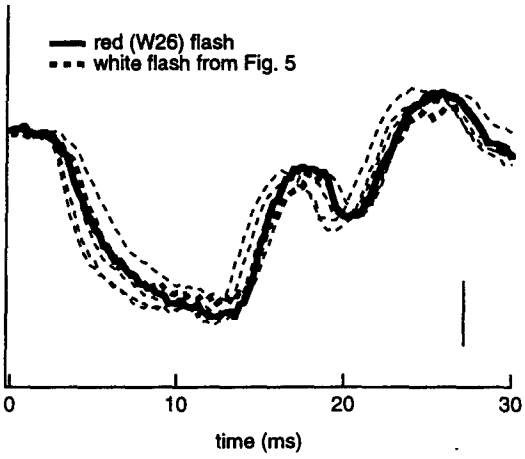

Figure 6. The dashed curves are the light-adapted responses from the left panel of Figure 5. The solid curve is the response to a red (W26) flash of 3.6 log td-s. The calibration bar is 25μV.

possibility that the responses in Figure 6 will be partially contaminated by rod contributions in some unusual disease states, this procedure for estimating the cone contribution should be adequate for nearly all conditions. When there is concern about rod contributions, monochromatic stimuli can be used and/or the two-flash technique described by Birch et al. [30] employed.

The solid curves in the right panel of Figure 5 are the rod-only responses obtained by subtracting the response in the light (dashed curves in the left panel) from the response in the dark (solid curves in the left panel). The dashed curves are the fit of eq. 1 to the responses to three lowest flash energies (bold curves). The range of flash energies could be extended to lower levels, but the three responses are sufficient to give good fits under most conditions. The model is fitted to the responses up to flashes of 4.3 log scot td-s for patients with normal values of S, but should be fitted to higher flash energies if S is substantially elevated (see note 2).

To summarize the protocol, the following are the key elements: (1) Use at least four flash energies — three at and below 4.3 log scot td-s and at least one above if the condition under study decreases S. (2) Present the same series in the dark and on a white background of about 30 cd/m^2. (3) Average one to three dark-adapted responses and 10 to 20 light-adapted responses; more may be needed when patients with retinal diseases that reduce a-wave amplitudes are studied. (4) Obtain rod-only response by computer subtracting the light-adapted from the dark-adapted responses. (5) Fit the rod model to the responses to flashes up to 4.3 log scot td-s, higher for a patient if the value of S is depressed (see note 2). (Note: the purpose of the flashes above 4.3

log td-s is to allow the same range of I·S to be fitted in patients and normal subjects.) (6) (optional) The maximum cone amplitude can be measured and compared to that of the rods. (7) (optional) One of the advantages of the white flashes is that the photopic effectiveness of these flashes is sufficient to produce maximal cone activity. Parameters of cone phototransduction can be obtained by fitting a model to the light-adapted series in Figure 6 [11, 28, 29].

A clinical protocol using a single white flash energy

It is clear from Figure 4 that changes in S and Rm can be distinguished with a single flash energy. For a clinical protocol, a single flash energy can be used. A white flash of about 4.3 log scot td-s (see asterisk in Figure 5) is a good choice. (This corresponds to a flash of 200 cd-s/m^2 when viewed with an 8-mm pupil.) This flash should be presented once or twice in the dark. Then the same flash is presented on an ISCEV steady background of 30 cd/m^2 and averaged until a clean record is obtained. The light-adapted cone a-wave provides an estimate of the cone contribution to the dark-adapted response. The dark-adapted responses with or without this cone contribution subtracted can be compared as in Figure 4 to a group of normal subjects without fitting an equation. By simply scaling the response as in Figure 4, an estimate of the change in Rm can be obtained. Further, by comparing the position of the scaled waveform to the responses to a few flash intensities, an estimate of the change in log S can also be obtained. Alternatively, with the use of any one of a number of spreadsheet programs, eq. 1 can be fitted to the dark-adapted or rod-only response and the values of S and Rm estimated. (The value of t_d can be held constant for this fit. See note 2.)

This protocol has three advantages: One, it is efficient in that a single flash energy gives information about both maximum rod and cone activity. Two, it is easy to implement on commercially available equipment. Three, it allows either a qualitative or a quantitative estimate of changes in S and Rm. Finally, note the advantage of this flash energy compared to the ISCEV standard white flash, which is about 100 times weaker. Now the complete view of the receptor-driven a-wave is possible (see note 3).

Distinguishing among alternative explanations of receptor damage

The procedures described above provide estimates of two parameters of the rod a-wave. With careful assumptions, these parameters can be related to parameters of the initial phases (activation) of rod phototransduction [8, 11, 31, 32]. However, there are only two parameters, and each can be modified by a number of possible disease mechanisms. Thus, by themselves these param-

eters cannot distinguish among a number of different alternatives for the changes. For example, in addition to changes in the amplification or speed of transduction, changes in S have been attributed to preretinal absorption and to a decrease in the density of rhodopsin in individual discs. In addition to response compression, mentioned above in the context of light adaptation, changes in Rm have been attributed to the loss of large sections of the retina and shortened outer segments. For example, most patients with retinitis pigmentosa [e.g. 6, 8, 31-34] as well as the animal models for retinitis pigmentosa [e.g. 35, 36] show changes in Rm presumably because of some combination of loss of regions of receptors and local losses of rod outer segment membrane. To distinguish among the various alternative hypotheses, other measures must be added. Among the other measures that have or could be used are measures of preretinal absorption, b-wave (or derived P2) implicit times and amplitudes [e.g. 31, 32, 37], densitometry, deactivation [30], visual fields [e.g. 32] and focal ERGs, as well as computer simulations [31, 38]. Thus, although the a-wave technique described here cannot by itself answer all questions about the mechanisms damaging rod photoreceptors, in conjunction with other techniques it offers a way to answer the question, 'How does a particular disease or treatment affect human rod receptors?'

Acknowledgements

Supported by National Eye Institute grants R01-EY-09076 and R01-EY-05235 and a grant from The Foundation to Fight Blindness. We thank Karen Holopigian, Mary Johnson, Marilyn Schneck, Wayne Verdon, and Tomoaki Usui for their help and feedback on the use of the protocol in Figure 5. Preliminary versions of this report were reported at the 1995 and 1996 ISCEV meetings in Athens and in Tübingen.

Notes

1. Three quantitative descriptions have been fitted to the leading edge of the rod a-wave. All three have parameters that can be equated to S and Rm. The modified Baylor et al. [39] model used by Hood et al. [4, 9, 32] has the advantage of describing the entire underlying receptor waveform, but it does not do as well at capturing the leading edge nor is it as easily related to the parameters of phototransduction of the single rod as are the other two. The Lamb and Pugh model on which eq. 1 is based is mathematically the simplest and is the one we use here. A recent version of the Lamb and Pugh model by Cideciyian and Jacobson [11] is computationally more difficult but has

the advantage of providing better fits to the responses to very high-energy flashes.

2. As a general rule of thumb, the range can be expressed in values of log (I·S) from about 4.6 to 6.0. This allows for a good selection of a range of flash energies even for animal work, where S is different from the value for normal human subjects but the equivalent value of I·S is not [35, 36]. Equation 1 will provide a good fit up to a value of log (I·S) of about 5.3 or more. The model of Cideciyan and Jacobson [11] can be used if fits to higher flash energies are desired.

Further, for this range of I·S values and for nearly all disease conditions, t_d will not change in any detectable way and will be constant for a given apparatus (see above). Thus, the best estimates of a patient's S and Rm values can be obtained if t_d is first determined for a group of normal subjects and then set to that value for the fitting of the patient data.

3. It has been suggested that the leading edge of the a-wave to the high-energy series has a nonreceptor component from the off-bipolars [40]. However, the leading edge of these a-waves, unlike the a-waves to lower flash energies (see Figure 1), behave in every way like the rod photoreceptors. In particular, both the leading [3-8] and trailing edges are described by receptor models [41], and the leading edge is affected only by background intensities that affect the rod receptors. Thus, if there is a nonreceptor component, it is behaving like the receptors and will not change the conclusion from the analysis here under most conditions.

References

1. Granit R. The components of the retinal action potential in mammals and their relation to the discharge in the optic nerve. J Physiol 1933; 77: 207–39.
2. Penn RD, Hagins WA. Kinetics of the photocurrent of retinal rods. Biophys J 1972; 12: 1073–94.
3. Hood DC, Birch DG. A quantitative measure of the electrical activity of human rod photoreceptors using electroretinography. Vis Neurosci 1990; 5: 379–87.
4. Hood DC, Birch DG. The a-wave of the human ERG and rod receptor function. Invest Ophthalmol Vis Sci 1990; 31: 2070–81.
5. Hood DC, Birch DG. Light adaptation of human rod receptors: the leading edge of the human a-wave and models of rod receptor activity. Vision Res 1993; 33: 1605–18.
6. Cideciyan AV, Jacobson SG. Negative electroretinograms in retinitis pigmentosa. Invest Ophthalmol Vis Sci 1993; 34: 3253–63.
7. Breton M, Schueller A, Lamb T, 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.
8. 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: 2948–61.
9. Hood DC, Birch DG. The b-wave of the scotopic (rod) ERG as a measure of the activity of human on-bipolar cells. J Opt Soc Am 1996; 13: 623–33.

10. Bush R, Sieving P. A proximal retinal component in the primate photopic ERG a-wave. Invest Ophthalmol Vis Sci 1994; 35: 635–44.
11. Cideciyan AV, Jacobson SG. An alternative phototransduction model for the human rod and cone ERG a-wave; normal parameters and variations with age. Vision Res 1996; 36: 2609–21.
12. Lamb TD, Pugh EN. A quantitative account of the activation steps involved in phototransduction in amphibian photoreceptors. J Physiol 1992; 499: 719–58.
13. Johnson MA, Hood DC. Rod photoreceptor transduction is affected in central retinal vein occlusion associated with iris neovascularization. J Opt Soc Am 1996; 13: 572–6.
14. Holopigian K, Kelly R, Greenstein V, Seiple W, Hood DC. Rod and cone photoreceptor analysis in patients with diabetic retinopathy. Invest Ophthalmol Vis Sci 1995; 36(suppl): S480. Abstract.
15. Reynaud XR, Chunguang RM, Hansen RM, Fulton AB, Aouididi S, Dorey CK. Morphological and ERG evidence of retinal hypoxia in interrupted oxygen induced retinopathy in the neonatal rat. Invest Ophthalmol Vis Sci 1994; 35: 1378.
16. Fulton AB, Hansen RM. Photoreceptor function in infants and children with a history of mild retinopathy of prematurity. J Opt Soc Am 1996; 13: 566–71.
17. Fulton AB, Hansen RM. Electroretinogram responses and refractive errors in patients with a history of retinopathy of prematurity. Doc Ophthalmol 1996; 91: 87–100.
18. Reynaud X, Hansen RM, Fulton AB. Effect of prior oxygen exposure on the electroretinographic responses of infant rats. Invest Ophthalmol Vis Sci 1995; 36: 2071–2079.
19. Hood D, Birch D. Computational models of rod-driven retinal activity. IEEE Eng Med Bio 1995; 14: 59–66.
20. Hood DC, Cideciyan AV, Halevy DA, Jacobson SG. Sites of disease action in a retinopathy with supernormal and delayed rod electroretinogram b-waves. Vision Res 1995; 36: 889–902.
21. Gouras P, Eggers M, MacKay C. Cone dystrophy, nyctalopia and supernormal rod responses. Arch Ophthalmol 1983; 101: 718–24.
22. Alexander K, Fishman G. Supernormal scotopic ERG in cone dystrophy. Br J Opthalmol 1984; 68: 69–78.
23. Yagasaki K, Miyake Y, Litao R, Ichikawa K. Two cases of retinal degeneration with an unusual form of electroretinogram. Doc Ophthalmol 1986; 63: 73–82.
24. Foerster M, Kellner U, Wessing A. Cone dystrophy and supernormal dark-adapted b-waves in the electroretinogram. Graefes Arch Clin Exp Ophthalmol 1990; 228: 116–9.
25. Sandberg M, Miller S, Berson E. Rod electroretinograms in an elevated cyclic guanosine monophosphate-type human retinal degeneration. Invest Ophthalmol Vis Sci 1990; 31: 2283–7.
26. Kato M, Kobayashi R, Watanabe I. Cone dysfunction and supernormal scotopic electroretinogram with a high-intensity stimulus. Doc Ophthalmol 1993; 84: 71–81.
27. Rosenberg T, Simonsen SE. Retinal dysfunction of supernormal rod ERG type. Acta Ophthalmol 1993; 71: 246–55.
28. Hood DC, Birch DG. Phototransduction in human cones measured using the a-wave of the ERG. Vision Res 1995; 35: 2801–10.
29. Hood DC, Birch DG. Human cone receptor activity: the leading edge of the a-wave and models of receptor activity. Vis Neurosci 1993; 10: 857–71.
30. Birch DG, Hood DC, Nusinowitz S, Pepperberg DR. Abnormal activation and deactivation mechanisms of rod transduction in patients with autosomal dominant retinitis pigmentosa and the pro-23-his mutation. Invest Ophthalmol Vis Sci 1995; 36: 1603–14.
31. Hood DC, Shady S, Birch DG. Heterogeneity in retinal disease and the computational model of the human rod response. J Opt Soc Am 1993; 10: 1624–30.
32. Shady S, Hood DC, Birch DG. Rod phototransduction in retinitis pigmentosa: distinguishing alternative mechanisms of degeneration. Invest Ophthalmol Vis Sci 1995; 36: 1027–37.

33. Jacobson S, Cideciyan A, Kemp CM, Sheffield VC, Stone EM. Photoreceptor function in heterozygotes with insertion or deletion mutations in the RDS gene. Invest Ophthalmol Vis Sci 1996; 37: 1662–74.
34. Birch DG, Hood DC. Abnormal rod photoreceptor function in retinitis pigmentosa. In: Anderson RE, La Vail MM, Hollyfield JG, eds. Degenerative diseases of the retina. 1995; 359-70. Plenum Press, NY.
35. Kedzierski W, Lloyd M, Birch DG, Bok D, Travis GH. Generation and analysis of transgenic mice expressing P216L-substituted rds/peripherin in rod photoreceptors. Invest Ophthalmol Vis Sci 1997; 38: 498–509.
36. Goto Y, Peachey N, Ziroli NE, Seiple WH, Gryczan C, Pepperberg DR, Naash MI. Rod phototransduction in transgenic mice expressing a mutant opsin gene. J Opt Soc Am 1996; 13: 577–85.
37. Hood DC, Birch DG. A computational model of the amplitude and implicit time of the b-wave of the human ERG. Vis Neurosci 1992; 8: 107–26.
38. Hood DC, Shady S, Birch DG. Understanding changes in the b-wave of the ERG caused by heterogeneous receptor damage. Invest Ophthalmol Vis Sci 1994; 35: 2477–88.
39. Baylor DA, Nunn BJ, Schnapf JL. The photocurrent, noise, and spectral sensitivity of rods of the monkey Macaca fascicularis. J Physiol 1984; 357: 575–607.
40. Robson JG, Frishman LJ. Photoreceptor and bipolar cell contributions to the cat electroretinogram: a kinetic model of the early part of the flash response. J Opt Soc Am 1996; 13: 613–22.
41. Pepperberg DR, Birch DG, Hood DC. Photoresponses of human rods in vivo derived from paired-flash electroretinograms. Vis Neurosci 1997; 14: 73–82.

Address for correspondence: D.C. Hood, Department of Psychology, Columbia University, 1190 Amsterdam Ave., Room 406, New York, NY 10027-7004, USA
Phone: (212) 854-4587; Fax: (212) 854-3609; e-mail:don@psych.Columbia.edu