Understanding Changes in the b-Wave of the ERG Caused by Heterogeneous Receptor Damage

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Purpose. To understand better the relationship between heterogeneous receptor damage and the changes in the b-wave of the rod ERG.

Methods. A computational model of the b-wave is used to simulate b-waves from retinas with two regions (a healthier and a more affected region) differing in area and sensitivity. The peak-to-peak amplitudes of the simulated b-waves are fitted with a Naka-Rushton equation, and the parameters log K and Vmax are estimated. Insights gained from these simulations are tested against rod ERGs and rod visual fields from patients with autosomal dominant retinitis pigmentosa (n = 11) and cone-rod dystrophy (n = 17).

Results. In the simulated retinas, Vmax decreases when the more affected region of receptors is less sensitive than the healthier region by more than 0.5 log unit. However, the relative change in Vmax does not match the relative area of the more affected region unless this region is depressed by 2.0 log units or more. As the more affected region loses sensitivity, log K at first increases but then decreases and approaches the log K of the healthier region for losses greater than 2.0 log units or so relative to the healthier region. For the patients' data, the simulations predict the general relationships observed between the summary statistics of the visual fields (e.g., area of field and mean of log sensitivity changes in the field) and the changes in log K and Vmax.

Conclusion. A decrease in Vmax indicates that regions of the patient's retina have lost 0.5 log unit or more of sensitivity. An increase in log K indicates that either the healthiest part of the patient's retina is abnormal by at most Δlog K, a large part of the retina has lost considerable sensitivity (i.e., 0.5 to 2.0 log units) but is still contributing to the response, or both. Invest Ophthalmol Vis Sci. 1994;35:2477-2488.

Since the Naka-Rushton equation was first shown to fit the growth in peak-to-peak b-wave amplitude with flash intensity, it has been fitted to b-wave data from a large number of patients. The parameters estimated from these fits, the semisaturation intensity (K) and the maximum response (Vmax), are affected in different ways by different diseases. A variety of retinal pathologic changes have been associated with changes in one or both of these parameters. Recently, computational models of the human rod ERG have been developed to relate the potential disease mechanisms to the change in these parameters. In particular, with these models, the timing and amplitude of the a- and b-waves can be quantitatively related to hypothesized retinal changes.

With the help of these models, it is relatively easy to predict changes in the a- and b-waves of the ERG caused by a disease process acting uniformly on all receptors. For example, using a computational model of the b-wave, Hood and Birch were able to simulate the changes in K and Vmax seen in some patients with retinal disease. These simulations assumed that the effects of the disease process were uniform across all functioning receptors. However, many diseases affect one region of receptors more than another, making the changes in the ERG parameters K and Vmax more difficult to interpret.

Recently, a-waves were simulated from a hypothetical retina that had two regions, a normal region and one affected by disease. The a-waves from each region were generated by a model of the rod response...
with the parameters set to mimic different degrees of disease. The simulated a-waves from the two regions were summed, and the summed "a-wave" fitted with the same rod model. This analysis suggested that if the uneven effects of a disease process are ignored, misinterpretations of ERG parameters are possible. If these effects are not taken into consideration, the fit of the receptor model will lead us to overestimate the change in the healthiest rods and to underestimate the change in the affected rods.

To understand better the relationship between the uneven effects of a disease process and the changes in the Naka-Rushton parameters, we simulated by computer the effects of a heterogeneous disease process using a computational model of the b-wave. Insights gained from these simulations were tested against rod ERGs and behaviorally measured rod visual fields from patients with autosomal dominant retinitis pigmentosa (ADRP) and cone-rod dystrophy (CRD).

PART 1: SIMULATIONS OF A HETEROGENEOUS DISEASE PROCESS

The Model of the b-Wave

The Hood and Birch computational model of the b-wave predicts the peak-to-peak amplitude and implicit time of the normal rod b-wave. The model assumes, after Granit, that the ERG is to a first approximation the sum of two potentials, P3 and P2. The P3 potential is the sum of the responses, p3, of the individual rod receptors. The P2 potential is the sum of the responses of the individual p2 generators. The P2 potential is the sum of the responses of the individual p2 generators. The ERG as a function of time is then defined as the sum of P3 and P2 (Fig. 1A).

A.

p3' generators (rods) p2 generators (bipolars/Muller cells)

$\text{ERG}(t) = \sum p3'(t) + \sum p2(t) = P3(t) + P2(t)$

B.

p3' generator p2 generator

$\text{ERG}(t) = p3'(t) + p2(t)$

C.

p3' generators p2 generators

$\text{ERG}(t) = \text{erg}_3(t) + \text{erg}_2(t) = P3(t) + P2(t)$

FIGURE 1. (A) A schematic of the model of the b-wave. (B) A schematic of the stages of the computational model that produce p3' and p2 of a single subunit in A. The components of the rod model are described in several earlier works. LF2 (linear filter 2) is the difference of two LP (low-pass) filters, and acts as a transfer function between the p3' and p2 generators. SNL2 is a static nonlinearity, described by a Naka-Rushton equation. The need for LF3, which slows p2, was determined empirically. In the simulations, the parameters of the P2 components were assigned values that gave good fits to data from normal observers. The p3' and p2 sum to produce erg(t), the subunit’s contribution to the ERG (see reference 18 for further details). (C) A schematic of the model describing the ERG of the two-region retina in the simulations. We assume that each region contains identical p3 and p2 generators. Thus, the response of each region can be represented by a single subunit, as described in panel A. The response of the two-region retina is the sum of the responses of the two subunits.
The response of the individual rod, p3, is computed using the model shown to fit the responses of individual primate rods as well as the human rod a-wave. The input to the p2 generator is the sum, p3′ (t), of a pool of individual rods feeding that particular p2 generator. The output of an individual p2 generator as a function of time is p2(t). Although the p2 generators can be associated with bipolar and Müller cell activity, unlike the rod response, there is no agreed upon computational model of p2. The computational model used to generate p3′(t) and p2(t) for the contribution, erg(t), of each subunit in panel A, is shown schematically in panel B of Figure 1 (see the figure caption and reference 18 for more details).

In the simulations described below, we assume that the abnormal retina has two regions, one region more affected by the disease process than the other. In each region, all rods are identical, as are all p2 generators. This allows us to represent the response of each region in terms of a single p3′ generator and a single p2 generator, as shown in panel C of Figure 1. The ERG of this two-region retina is the sum of the p3′ and p2 responses of the two regions.

By varying one or more parameters of the model, the effects of retinal disease can be simulated. For our purpose here, only the parameters of the rod receptor are important. The two parameters that were varied in this study were σp3 and rmP3. The parameter rmP3 is the maximum amplitude of the response of an individual rod. The parameter σp3 is an indicator of the sensitivity of the individual rod. Decreases in rmP3 act to scale down the rod response for all flash energies and at all times after the flash. Increases in σp3 represent a decrease in sensitivity to light and act as if the flash energy was decreased. For example, a doubling of σp3 (a change in log σp3 of 0.3) is equivalent to decreasing all flash energies by a factor of 2. Hypotheses about the action of the disease process can be couched in terms of one or both of these parameters (see Discussion).

The Simulated Retinas

The simulated retina was divided into two regions, the “healthier” and the “more affected” regions. All the rods in the healthier region were assumed to be identical with the same sensitivity (σp3) and a normal maximum response (rmP3). Likewise, all the rods in the more affected region were assumed identical but with either σp3 or rmP3 set to be abnormal.

Two groups of simulations were run. In one, the rods in the more affected region had a normal value of rmP3 and a log σp3 that could take on one of 10 values that ranged from 0.3 to 3.0 log units above the value of the healthier region. In the second group of simulations, the rods in the more affected region had a normal value of σp3 and a log rmP3 that took on one of 10 values ranging from 0.3 to 3.0 log units below the rmP3 of the healthier region. In each set of simulations, the more affected region was set at one of three sizes, 12%, 50%, or 88% of the total. Thus, there were 30 pairs of combinations of the two parameters (i.e., percentage of retina affected; Δlog σp3 (or Δlog rmP3)). For each pair of values, the ERGs for the healthier and more affected regions were generated using the computational model and summed together to produce a simulated ERG for this condition. The peak-to-peak b-wave amplitudes were measured and fitted with the Naka-Rushton equation as if they were from real ERGs (see note 1).

The simulations in which σp3 of the more affected region was elevated were repeated setting the healthier region 1.2 log units lower in sensitivity (higher σp3) than normal.

The flash energies used in the simulations were the same as those used for obtaining the ERGs from the patients, about −1.2 to 2.0 log scot td·s. Extending the range of flash energies would affect the outcome. For example, in simulations where the receptors in the more affected region have a normal value of rmP3, if we place no limit on the maximum flash energy, the more affected region will produce a normal Vmax for sufficiently high flash energies.

Results of the Simulations

Figures 2A and 2B present the results of the simulations when the healthier region is normal. Figure 2A shows the change in log Vmax as a function of the value of Δlog σp3 of the more affected region. When the decrease in receptor sensitivity of the more affected region is large enough, then Δlog Vmax approximates the proportion of the retina that is normal, shown as the horizontal dashed lines. To be within 10% of this value, the change in log σp3 must be greater than 2.7 log units when the retina is 12% normal and greater than 1.8 log units when it is 50% normal. When the change in the more affected region is smaller than these values, substantial decreases in Vmax are still observed. Notice, for example, that if 88% of the retina is decreased in sensitivity by about 1.5 log units, then Vmax is halved (Δlog Vmax = −0.3).

Figure 2B shows the values of Δlog K of the simulated retina as a function of the value of Δlog σp3 of the more affected region. The values of Δlog K are not monotonically related to the underlying values of log σp3. When the more affected region is very healthy or very sick, log K will approach the log K of a retina that is normal. For situations between these extremes (e.g., the more affected region down by 1.0 log unit in sensitivity), Δlog K will be greater than 0.0 (the normal value) but less than the weighted mean of the Δlog σp3 values of the two regions. The weighted means are shown as the dashed lines.
FIGURE 2. Parameters of the Naka-Rushton equation for simulated b-waves from heterogeneous retinas. The peak-to-peak b-waves from the simulated retinas were fitted with the Naka-Rushton equation and the parameters log K and log V_max estimated. The deviation in these parameters from the values obtained from a totally healthy retina are expressed as Δlog K and Δlog V_max. (A and B) The simulated retina contained a normal region and an affected region in which the rod sensitivity, σ_p3, was elevated by different values of Δlog σ_p3 relative to the normal value. The best fitting values of Δlog V_max (panel A) and Δlog K (panel B) are shown for different values of Δlog σ_p3 of the more affected region. The parameter in each panel is the percentage of the total retina occupied by the normal (healthier) region. See text for details. (C and D) Similar to panels A and B, except that the rods in the healthier region had a σ_p3 elevated by 1.2 log units, and the values of Δlog σ_p3 in the more affected region are expressed relative to this value. See text for details.

Panels C and D of Figure 2 show the results for the simulations when the healthier region is not normal but is decreased in sensitivity by 1.2 log units. The value of Δlog V_max follows a similar course (panel C) to that seen in panel A. For most values of Δlog σ_p3 of the more affected region, it makes relatively little difference whether the healthier region is normal or down by 1.2 log units. All values of Δlog K are equal to or greater than the value of Δlog σ_p3 of the healthier region, in this case 1.2 log units above normal. In particular, log K is never more than 0.5 log unit higher than the log K for a retina that is uniformly depressed by 1.2 log units. The value of Δlog K approaches the value of Δlog σ_p3 of the healthier region if the more affected region is close to or much worse than the sensitivity of the healthier region.

The simulations produce similar results with a change either solely in σ_p3 or solely in rm_p3 of the receptors. The dotted curves in Figure 3 show the results of the simulations in which log rm_p3 is changed. For comparison, the results from Figure 2A and 2B are shown as the solid curves. The changes in rm_p3 produce slightly smaller changes in log K and slightly larger changes in V_max than do the changes in σ_p3. But, overall, the results are remarkably similar. The reason for this similarity can be traced to the approximately linear behavior of the receptors over the range of flash energies used here, up to 2.0 log scot td-s. At higher flash energies, changes in rm_p3 and σ_p3 give different results.

DISCUSSION OF PART 1

Based upon the simulations, it is clear that when the effects of disease are uneven, the parameters of the Naka-Rushton equation fitted to patients' b-waves will
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FIGURE 3. Parameters of the Naka-Rushton equation for simulated b-waves from heterogeneous retinas. The peak-to-peak b-waves from the simulated retinas were fitted with the Naka-Rushton equation and the parameters log K and log V max estimated. The deviation in these parameters from the values obtained from a totally healthy retina are expressed as Δlog K and Δlog V max. The simulated retina contained a normal region and an affected region in which the maximum response of the rods, r mP3, was depressed by different values of Δlog r mP3 relative to the normal value. The dashed curves show the best-fitting values of Δlog V max (panel A) and Δlog K (panel B) for different values of Δlog r mP3 of the more affected region. The solid curves are the results from Figures 2A and 2B for equivalent changes in Δlog σP3. The parameter in each panel is the percentage of the total retina occupied by the normal region. See text for details.

not be simply related to the underlying pathology. However, the simulations lead to some general conclusions about the underlying pathology based upon these Naka-Rushton parameters.

What Does a Decrease in V max Indicate?

In general, previous investigators have attributed the decrease in V max to a loss of receptors secondary to the disease process.3-8,24-25 Of course, a loss of regions of receptors will decrease V max. In our simulated retina, an affected region with large changes (e.g., 2.0 to 3.0 log units) in σP3 or r mP3 effectively simulate a loss of a region of receptors. Under these extreme conditions, the relative value of V max nearly matches the proportion of the retina less affected (see dashed horizontal lines in Figures 2A, 2C, and 3A). However, the simulations suggest that V max can also be decreased by relatively small changes in the maximum response (r mP3) or sensitivity (σP3) of the rods. The magnitude of this decrease will depend upon both the number of the receptors affected and the degree to which they are affected relative to the healthier region in the retina (or the healthiest region if there are more than two regions). Significant decreases in V max can occur well before receptors cease to function. This probably explains why a decrease in V max is such a prominent early sign in diseases like retinitis pigmentosa.2,5,6

There are two conditions that have smaller effects on V max than one might expect. First, changes in r mP3 are not much more effective in decreasing V max than are changes in σP3.18,25 The explanation for this can be found in the relative values of the semisaturation parameters, σP3 and σP2, of the p3 and p2 generators. The semisaturation of the p2 generator occurs in the range of flash energies that is well below σP3 and, thus, where the receptor response is linear with flash energy. Therefore, changes in r mP3 or σP3 produce nearly equivalent changes in p1*, the input to the p2 generator in Figure 1; both act to scale down the input, resulting in an altered value of the semisaturation of P2 and ultimately a change in K in the Naka-Rushton fit. The parameter V max is affected only when there are drastic losses of receptor sensitivity in the more affected region.

The implication is that a local loss of rods, unlike regional losses, will not influence V max much. Local dropout of rods, as well as a decrease in a rod’s maximum response, would be represented in the model as a decrease in r mP3. For example, if half the retina lost all its rods, then half of the p2-generators would also be excluded from contributing to the ERG (see Fig. 1A), and V max would be one-half the normal value. However, if every other rod in the retina was missing, then all the p2 generators would still contribute to the ERG because each still receives some pooled p3 input (see Fig. 1A): V max would be essentially normal and K would be elevated by 0.3 log unit (see Fig. 3).

A second finding that may be surprising is that V max is unaffected by a uniform decrease in receptor sensitivity, unless sensitivity is down by well over 1.2 log units (see Note 2). But V max will decrease when there are retinal regions more depressed in sensitivity than others, whether the healthiest of these regions is normal or not. For example, in Figure 2, V max is nor-
normal when the full retina is down by 1.2 log units (panel C), but it is decreased by about 30% when half the retina is normal and half is down by 1.2 log units (panel A).

What Does an Increase in Log K Indicate?
According to the simulations, log K is not monotonically related to the underlying receptor pathology (see Figs. 2B, 2D). The simulations suggest that a patient’s log K value could increase as a region of the retina loses sensitivity and then, over time, decrease and return to normal as this region becomes nonfunctional. Breton et al.\textsuperscript{26} described a patient with CRVO that appears to show this pattern. However, this finding will tend to be the exception, not the rule, for the patients with a progressive, degenerative process like retinitis pigmentosa. In these patients, log K will tend to increase with time because, as the more affected regions become nonfunctional (losses greater than 2 log units), other regions previously normal will become affected. For a particular patient at any given time, the simulations suggest that an elevated log K will be observed either if the healthiest region of the retina has receptors less sensitive than normal or if a large proportion of the receptors is substantially decreased in sensitivity but is still functioning (e.g., decreased in sensitivity by about 0.5 to 2.0 log units; see Fig. 2B). Fulton and Hansen\textsuperscript{8} simulated this latter condition in a normal retina by decreasing the light reaching patches of the retina. In agreement with our simulations, log K was elevated and V\textsubscript{max} was decreased.

In general, patients with heterogeneous receptor damage show larger changes in log V\textsubscript{max} than in log K. For example, it is common to find patients with retinitis pigmentosa who show large decreases in V\textsubscript{max} with very small changes in log K.\textsuperscript{2,5} The simulations suggest an explanation: Until the healthiest region of the retina loses sensitivity, it is difficult to produce log K elevations greater than 0.6 log unit but easy to produce large decreases in V\textsubscript{max}.

PART 2: COMPARISON OF NAKA-RUSHTON PARAMETERS TO FIELD STATISTICS
In trying to relate the ERG to receptor pathology, several studies have measured visual fields and compared descriptive statistics of the fields to the Naka-Rushton parameters.\textsuperscript{3,6,24,25,27,28} In the case of retinitis pigmentosa, it has been long known that the ERG provides an early indicator of receptor damage.\textsuperscript{29-31} Further, Masof and colleagues\textsuperscript{32,33} showed that visual fields are a powerful tool for characterizing the nature and time course of retinodegenerative diseases. Until relatively recently, however, the quantitative correspondence between the ERG and visual fields was thought to be poor in patients with degenerative diseases of the receptors. Nondetectable ERGs were reported in some patients with full visual fields, and a poor correlation between field size and ERG parameters was reported in others.\textsuperscript{3,25,34,35} With the use of signal averaging and when procedures are used to assure that both the ERG and the visual fields are mediated by the rod system, a better correspondence is found between a number of measures of the rod field and the parameters of the rod ERG.\textsuperscript{6,24,25,27,28} However, attempts to relate the changes in the ERG to changes in the visual field based upon a common set of assumptions about the underlying receptor damage have met with limited success.\textsuperscript{29,37}

The simulations in Part 1 suggest that the parameters of the Naka-Rushton fit to patients’ b-waves will not be simply related to visual field changes. This helps explain the limited success of previous work in this area. However, the simulations do suggest some orderly relationships. To test the insights gained from the simulations in Part 1, ERGs and behaviorally measured visual fields from patients with autosomal dominant retinitis pigmentosa and cone-rod dystrophy are analyzed below.

METHODS
Subjects
Patients were selected from a larger group that is being tested annually, as part of a natural history study\textsuperscript{36} of rod loss in retinitis pigmentosa and CRD. We include all ADRP (n = 11) and CRD (n = 17) patients who had both rod ERG and rod visual fields measured within a reasonable time span, typically on the same day. The data analyzed are from the first year in which the patients had both tests performed. The ages of the patients ranged from 10 to 68 years, with a mean age of 33.4 years.

For the ERG, a group of 50 normal observers who ranged in age from 5 to 77 years, with a mean age of 35.8 years, served as the controls.\textsuperscript{37} For the visual fields, a group of 20 normal observers with a mean age of 34.2 years served as the controls.\textsuperscript{38}

All subjects or their guardians signed informed consent forms after the experiment and its potential risks were described to them. Tenets of the Declaration of Helsinki were followed.

Visual Fields
For all 28 patients, dark-adapted rod visual fields were measured on a modified Octopus 201 (Grass, Quincy, MA) automated perimeter using Program 21 (Grass) as described by Birch et al.\textsuperscript{9} This program measures 75 (74 without the blind spot) extrafoveal locations covering the entire visual field on a grid spacing of 15° with
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a test spot of 0.43°, and extending to 60° in the nasal field (temporal retina) and to 90° in the temporal field (nasal retina). These fields are compared to the average of 20 normal observers. Fields were measured with short-wave stimulation (W47A) to enhance detection by the rods. Typically, a second field was measured with a long-wave stimulus (W26). The relative intensities were set such that higher sensitivity to the short-wave stimulation (W47A) to enhance detection age of 20 normal observers. Fields were measured with the Naka-Rushton equation as previously described. For the group of normal observers, the values of log K and log V_max ranged from —0.25 to —1.28, with a mean of 0.32. As has been reported, the decrease in log V_max is often larger than the increase in log K in patients with ADRP and CRD.

ERGs

As previously described, a standard clinical ganzfeld dome, based on a Grass photostimulator, produced a 10 ms short-wavelength flash (Wratten 47A, Kodak, New York, NY) with a maximum retinal illuminance of 2.0 log scot td-s. Rod ERGs were isolated and fitted with the Naka-Rushton equation as previously described. For the group of normal observers, the values of log K ranged from —0.34 to 0.87, with a mean of 0.32. As has been reported, the decrease in log V_max is often larger than the increase in log K in patients with ADRP and CRD.

RESULTS

ERGs

For each patient, the changes in the Naka-Rushton parameters, V_max and K, were expressed as the log deviations from the normal values. In particular,

\[ \Delta \log K = \log \left( \frac{K_{\text{individual}}}{K_{\text{mean}}} \right) \]

and

\[ \Delta \log V_{\text{max}} = \log \left( \frac{V_{\text{max,individual}}}{V_{\text{max,mean}}} \right) \]

were calculated, where the K (mean) and V_max (mean) are the means for the 50 normal subjects. Thus, a value of 0.0 \( \Delta \log V_{\text{max}} \) or \( \Delta \log K \) is normal. The values of \( \Delta \log V_{\text{max}} \) ranged from —0.25 to —1.28, with a mean of —0.67. The values of \( \Delta \log K \) ranged from —0.34 to 0.87, with a mean of 0.32. As has been reported, the decrease in log V_max is often larger than the increase in log K in patients with ADRP and CRD.

Fields

For each of the 74 points in a patient’s visual field, the difference between the patient’s log threshold and the mean log threshold of the normal controls was calculated. We call these 74 differences the patient’s “difference field.” The difference field is a convenient way to express the patient’s visual field thresholds relative to the average of the normal subjects. For example, a difference field value of 0.0 log unit indicates that the patient’s threshold at this field location is normal, and a value of 1.0 indicates that the threshold is 10 times larger than normal. Difference field values less than 0.0 (i.e., more sensitive than normal) were set equal to 0. Figure 4 shows the difference fields for two of the patients (patients 22 and 23). The losses greater than 2.0 log units are coded by black, the losses less than 0.5 log unit by white, and the losses between these values by gray. Although the pattern of loss differs in these patients, the magnitudes of the field losses are similar (see below and Fig. 5) and the patients’ ERGs have comparable values of \( \Delta \log K \) (0.44 and 0.28) and \( \Delta \log V_{\text{max}} \) (—0.44 and —0.64).

Healthiest Regions

For each patient, the healthiest region of the field was defined as the seven points, roughly 10% of the field.
The patients in this study show changes in $V_{\text{max}}$ and $K$ when the Naka-Rushton equation is fitted to their ERG b-wave amplitudes. The simulations in Part 1, coupled with the visual field data, provide a foundation for understanding these changes. First, consider the patients with near-normal healthiest regions (filled symbols in Figure 5). According to the visual field data, a large region of the retinas of these patients

DISCUSSION OF PART 2

The filled symbols indicate the patients with healthiest regions within 0.2 log unit of normal. They have been identified separately because their healthiest regions, like the healthier region of the simulations in Figures 2A and 2B, are essentially normal. In this group, an average of 21% of the field was within 0.5 log unit of normal. All patients in this group had sizable regions with losses in the 0.5 to 2.0 log unit range; this region, on average in these patients, was 51% of the field.

In general, the simulations suggest that the loss relative to the healthiest region of the field is a more useful measure when assessing the effects on Naka-Rushton parameters. The display in Figure 6 is similar to that in Figure 5, but the loss in sensitivity is expressed relative to the loss in sensitivity in the healthiest region. For example, the bottom panel shows the proportion of the field with sensitivity losses within 0.5 log unit of the loss in the healthiest region. The pattern of results is similar to that in Figure 5. All patients show losses in the 0.5 to 2.0 log unit range, and in all but five, at least 30% of the field was in this range.

Heterogeneity of Field Loss

Figure 5 summarizes the losses in sensitivity as indicated by the difference fields. For each patient, the difference thresholds are divided into three categories: below 0.5 log unit, between 0.5 and 2.0 log units, and above 2.0 log units. The proportion of the 74 points in the field within 0.5 log unit of normal is shown in the lower panel of Figure 5. The 28 patients are numbered according to this proportion. Values ranged from 0 (patient 1) to 0.35 (patient 28) of the field. A few studies have operationally defined "nonfunctional areas" as the areas of the field showing sensitivity losses greater than some value for the purpose of predicting the change in $V_{\text{max}}$. The upper panel in Figure 5 shows the proportion of the fields with difference thresholds greater than 2 log units. The middle panel shows the proportion of the fields with difference thresholds between 0.5 and 2.0 log units. In general, these data indicate a range of field losses within each patient. In all but four of the patients (patients 1 to 4), some part of the field was within 0.5 log unit of normal, and in all but one (patient 21), some part of the field showed losses greater than 2.0 log units. In all the patients there were portions, usually sizable, that showed losses between 0.5 and 2.0 log units.

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DISCUSSION OF PART 2

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FIGURE 5. The proportion of the area of the difference field below 0.5 log unit (lower panel), between 0.5 and 2.0 log units (middle panel), and above 2.0 log units (upper panel) are shown for each of the 28 patients. The data for the patients with ADRP and CRD are shown by the triangles and circles, respectively. The patients are ranked ordered and numbered based upon the area of the difference field within 0.5 log unit. The filled symbols represent the patients whose healthiest regions were within 0.2 log unit of normal.

with the smallest difference values. The median of these seven differences was taken as the threshold elevation in the healthiest region.

This procedure has the advantage of producing an estimate of the sensitivity of the healthiest region of the field that is uninfluenced by one or two extreme points. It will tend to overestimate the loss at the healthiest point, especially when the number of points near normal is small. (In one patient in whom only four points in the difference field were below 2.0 log units, the healthiest region was defined as the single healthiest point.)

In a majority of the patients, there were regions of the fields that were close to normal in sensitivity. In 16 of the 28 patients, threshold elevations for the healthiest region were within 0.2 log unit of normal, and in all but four patients, one or more points in the fields were normal.

Heterogeneity of Field Loss

Figure 5 summarizes the losses in sensitivity as indicated by the difference fields. For each patient, the
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In general, though, we are dealing with a disease of the receptors, and the loss in receptor function should be highly correlated with the losses measured behaviorally.

Comparison of the Decrease in $V_{\text{max}}$ to the Change in the Visual Field

Previous studies have attributed the decrease in $V_{\text{max}}$ to a loss of regions of the visual field.\(^6\) These studies argued that a loss of large regions of rods will both reduce the size of the visual field and decrease $V_{\text{max}}$. When the “nonfunctional area” of the field was defined as the percentage of the field that has lost substantial sensitivity (usually 2 to 3 log units), the decrease in $V_{\text{max}}$ correlated with an increase in this non-functional area.\(^{6,24,25}\) However, there was a consistent tendency for the decrease in $V_{\text{max}}$ to be larger than predicted.\(^{3,6,24,25}\) For example, if 50% of the field was nonfunctional based upon this criterion, then the decrease in $V_{\text{max}}$ was usually much more than 50%. Our data show the same trend. Although this finding has led some to postulate other non-receptoral causes for the decrease in $V_{\text{max}}$, our simulations supply an explanation based strictly upon receptor changes.

Figure 7 shows the change in log $V_{\text{max}}$ versus the log of the proportion of the field area within 2.0 log units of normal for the 28 patients in this study. Con-

shows losses in sensitivity between 0.5 log unit and 2.0 log units above normal (middle panel, Fig. 5). There also are regions that show losses greater than 2.0 log units (top panel, Fig. 5). According to the simulations, the decrease in $V_{\text{max}}$ in these patients is due to the large regions with losses greater than 0.5 log unit. And the increase in log K is largely attributable to the large region with losses between 0.5 and 2.0 log units. On the other hand, for the patients in whom the healthiest region is well below normal, the simulations suggest that part of the elevation in log K is attributable to the decrease in sensitivity of this region. Thus, the simulations provide a common explanation for both the field and the ERG changes.

To attempt a more quantitative comparison of the ERG and field data, we make two assumptions. First we assume that, to a first approximation, all parts of the retina, with the exception of the fovea and the blind spot, contribute equally to the production of the rod ERG. This is a common assumption that seems reasonable.\(^{40}\) Second, we assume that the difference fields provide a measure of the change in the receptors at each point in the field. This is a more tenuous assumption. Practice effects can improve a patient’s sensitivity,\(^{38}\) and the disease process can also act at post-receptoral sites to contribute to the losses measured.

Figure 7 shows the change in log $V_{\text{max}}$ versus the log relative area of the patient’s difference field that is within 2.0 log units of normal. The values 0.0 $\Delta \log V_{\text{max}}$ or log relative area represent the values for the mean normal observer. The diagonal line has a slope of 1.0 and represents the locus of points for which the change in log $V_{\text{max}}$ matches the change in the log relative area within 2.0 log units. The data for the patients with ADRP and CRD are shown by the triangles and circles, respectively. The filled symbols represent the patients with healthiest regions within 0.2 log unit of normal.

FIGURE 6. Similar to Figure 5, except that the difference thresholds are expressed relative to the difference value for the patient’s healthiest region (defined as the median of the seven smallest difference thresholds) rather than to normal.
sistent with previous studies, the relative decrease in \( V_{\text{max}} \) is greater than the proportion of the retina with losses greater than 2.0 log units. (A criterion of 3.0 log units would show more extreme deviations.) Patients whose data are represented by the filled symbols have a healthiest region that is near normal (within 0.2 log unit). According to the simulations (Fig. 2A), if, in addition to the near-normal region, there is a sizable region of the retina in these patients between about 0.5 and 2.0 log units less sensitive than normal, then the relative change in \( V_{\text{max}} \) will be greater than the “non-functional” portion of the retina (i.e., the portion down by more than 2.0 log units). The difference fields for these patients show sizable regions between 0.5 and 2.0 log units (middle panel, Fig. 5). Consistent with the simulations, they also have values of \( V_{\text{max}} \) that are smaller than the proportion of the fields within 2.0 log units of normal. Thus, in these patients, the decrease in \( V_{\text{max}} \) can be attributed both to the field area “lost” due to a sensitivity change greater than 2.0 log units and to the region with less drastic losses in sensitivity. Although we cannot rule out non-receptor contributions to a decrease in \( V_{\text{max}} \), the analysis thus far requires no such explanation.

A similar analysis can be made for patient data represented by the open symbols. Strictly speaking, these patients should have their \( V_{\text{max}} \) changes compared to the proportion of their field area within 2.0 log units above their healthiest region (see Figs. 2C, 2D, and 6). This would generally move the open symbols in Figure 7 to the right. Although several of these patients (patients 1, 7, 10, and 11) have \( V_{\text{max}} \) changes largely attributable to the region with losses greater than 2.0 log units, most of these patients, like those whose data are represented by the filled symbols, have \( V_{\text{max}} \) changes attributable to the region with losses between 0.5 and 2.0 as well.

**Comparison of Log K Increases to Visual Field Data**

There is no clear agreement in the literature on the best approach to relating aspects of the visual field data to changes in \( K \). A model developed by Arden et al.\(^{25} \) assumed that the local \( K \) of each region in the field was elevated relative to normal by the same factor as that region’s behavioral threshold. Their model produced a predicted \( K \) and \( V_{\text{max}} \) for patients based upon their visual fields. Although their predicted increases in \( K \) correlated with the observed values, the predicted changes were in general far larger than the observed changes.

Our simulations suggest that no single field statistic will predict the change in \( \log K \). However, the simulations, coupled with the assumptions above, make two predictions. First, the change in \( \log K \) should be less than or equal to the mean of the difference thresholds (counterpart to the weighted mean (dashed lines) in Figures 2B, 2D, and 3B). Second, the change in \( \log K \) should be greater than or equal to the change in the healthiest region of the field. The first prediction is well documented in Figure 8. Here are plotted the changes in \( \log K \) versus the means of the points in the difference fields. (Only points below 2.0 log units were included in the means.) As predicted, the points fall below the diagonal line. The data, in general, also support the second prediction from the simulations.

Twenty-two of the 28 patients, including all the patients who have their healthiest regions near normal (the filled symbols in Figs. 7 and 8), have \( \Delta \log K \) values equal to or greater than the elevation in the healthiest region of their fields. The fact that the values from six of the patients do not agree with this second prediction is undoubtedly due, on one hand, to the variability inherent in both ERG and field measures and, on the second hand, to the simplification involved in our modeling of the ERG (see Note 3).

**SUMMARY**

If a disease process affects the receptors unevenly, what can we say about the state of the retina based upon the ERG parameters? Our working hypothesis is that the healthiest part of the retina has a sensitivity within \( \Delta \log K \) of normal (for example, if \( \Delta \log K \) is 0.3 log unit, the rods in the healthiest part have a sensitiv-
ity that is no worse than 0.3 log unit above normal and is, in all likelihood, considerably closer to normal); and the region of receptors that is functioning (e.g., contributing to the ERG) is larger than suggested by V\text{max}. For example, if \( \Delta \log V_{\text{max}} = 1.0 \), the functioning area is larger, probably much larger, than 10%.

NOTES

1. The fitting of the Naka-Rushton equation to the simulated b-waves is based upon a least squares fit to the log of the peak-to-peak amplitude. Fitting the linear values of the amplitudes, a method that weighs more heavily the larger amplitudes, produces a pattern of results much like the one in Figures 2 and 3 but with larger changes in log K and smaller changes in log V\text{max}.

2. This is because a retina that is homogeneous and increased in \( e_{\text{pr}} \) by 1.2 log units produces peak-to-peak b-wave amplitudes fitted by a Naka-Rushton equation with a normal V\text{max} and a log K elevated by 1.2. A retina that is half normal and half dead has a normal log K and a V\text{max} that is one-half of the normal value. If half of the retina is more affected than the healthier half by 1.2 log units, this results in a \( \Delta \log K \) between 0 and 1.2 log units and a V\text{max} between normal and one-half normal. Because the responses from the more affected region add a larger increment to the response at the higher flash energies than at the lower flash energies, the log K value will be relatively closer to the value in the healthier region and V\text{max} relatively closer to the normal V\text{max}.

3. The six patients who do not conform to the predictions are among the most extremely affected patients; in these patients, less of the retina is normal and more of the retina shows losses greater than 2.0 log units. These deviations are understandable on several grounds. We are assuming that the threshold elevation at each point is a measure of the extent of the receptor damage. In the more advanced stages of the disease, inner nuclear layer changes may also contribute to the loss in field sensitivity. Evidence for post-receptoral changes in sensitivity has been found by others.\textsuperscript{41-45}

The loss in sensitivity in the healthiest region of the patients showing the most extreme field changes may overestimate the loss of receptor sensitivity. Alternatively, there is inherent variability in both the ERG and field measures. This variability, combined with our procedure for determining the healthiest region, may help produce these deviant points. More work is needed to distinguish among these possibilities.

**Key Words**

ERG, b-wave, visual fields, rods, human

**References**


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