Cone and Rod ERG Phototransduction Parameters in Retinitis Pigmentosa

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PURPOSE. To analyze cone and rod phototransduction parameters from ERG a-waves in patients with RP and to determine the relationships among these parameters, age, and mode of inheritance.

METHODS. Sets of four white flashes (3.2–4.4 log scotopic troland [scot td-s]) were presented in the dark. The same stimuli were later presented against a rod-saturating background and the generated cone a-waves were subtracted from the dark-adapted responses to produce rod-only a-waves. The rod-only and cone a-waves were fit with computational models.

RESULTS. Of 418 consecutive patients with retinitis pigmentosa (RP), cone a-waves were quantifiable in 136 (33%), whereas rod a-waves were quantifiable in 125 (30%). Cone $R_{\text{max}}$ (maximum response) and cone $S$ (sensitivity) parameters were significantly below normal in all RP subgroups. Cone $R_{\text{max}}$ was lower in XlRP than in other forms of inheritance ($P < 0.05$). Cone $S$ was abnormal in 77.9% of all patients with RP and in 96.8% of those with XlRP. More than 95% of the rod $R_{\text{max}}$ values were abnormal, whereas rod $S$ was abnormal in 61.6% of these patients.

CONCLUSIONS. The efficiency of cone phototransduction appears to be affected in all forms of RP, even in some patients in whom the sensitivity of rod phototransduction is normal. In this cross-sectional sample, there was no evidence that transduction efficiency decreased with increasing age of the patient. The X-linked mode of inheritance is associated with greater abnormalities in cone and rod photoreceptor function at a younger age compared with the other modes of inheritance. (Invest Ophthalmol Vis Sci. 2003;44:3993–4000) DOI: 10.1167/ iovs.02-1104

Retinitis pigmentosa (RP) is a heterogeneous group of eye diseases showing progressive photoreceptor and retinal pigment epithelial damage. Electroretinography (ERG) is useful in diagnosis and in observing the progression of the disease.¹,² It will continue to have a major role as an outcome measure in treatment trials as rational interventions become available.³ The ERG provides direct, objective information about retinal function. The initial portion of the a-wave reflects the process of light-induced hyperpolarization of the photoreceptor outer segments.⁴–⁹ With appropriate high-energy stimulation and computational modeling of the leading edge of the a-wave, parameters can be derived that provide information about the number of functioning photoreceptors, their visual pigment content, and the efficiency (sensitivity) of the phototransduction amplification process.⁵–¹⁰

Recent studies have used information derived from the leading edge of the a-wave to investigate transduction defects in patients with specific genetic mutations.¹¹–¹⁶ However, studies analyzing cone function have typically involved a small number of patients, and it is not clear how these results would generalize to the larger population of patients with RP, in which all modes of inheritance are represented. One purpose of the present study was to determine whether the percentage of patients from whom cone and rod a-wave parameters can be obtained differs by inheritance pattern.

Studies of photoreceptor transduction parameters in normal subjects indicate that rod and cone sensitivities (reflected by the $S$ parameter in computational models) decrease linearly with age, whereas the maximum response is stable through age.⁹,¹⁷ In contrast, very little is known about the effect of age on the $S$ parameter in patients with RP. Thus, the second goal of the study is to determine whether there is an added decrease in phototransduction efficiency ($S$) due to retinal degeneration superimposed on the normal age-related decline.

Finally, little is known about the properties of cone phototransduction in RP.¹⁸,¹⁹ Is cone sensitivity affected in early stages of the disease? Is there any relationship between the extent to which rods deteriorate and the loss in cone sensitivity? A third goal of the present study was to evaluate relationships between cone and rod phototransduction parameters in patients with different modes of inheritance.

METHODS

Subjects

Data were reviewed from high-energy a-wave recordings on 418 consecutive patients with RP attending the Retina Foundation of the Southwest. Most were patients who were referred immediately after their diagnosis by an ophthalmologist specializing in retinal diseases. A few were repeat visits of patients with previously diagnosed disease. Only nonsyndromic cases were considered. Patients were considered to have autosomal dominant RP (adRP) if three or more generations of direct transmission of the disease were identifiable and if the clinical phenotypic signs were similar in males and females. Patients with RP of autosomal recessive inheritance (arRP) had comparably affected siblings or multiple-affected members in a pedigree in which X-linked (XlRP) and adRP could be ruled out. Alternately, arRP was considered if there was evidence of parental consanguinity. Patients with XlRP had to have an affected maternal male relative, and the mother and/or daughter had to show evidence of the carrier state of RP. In isolated cases, there was no evidence of parental consanguinity and no family history of the disease.

Previously published normative data were available from 100 volunteers (ages 5–75 years) with normal eye examination results who were tested concurrently.¹⁷ The tenets of the Declaration of Helsinki were observed, and written consent was obtained after all procedures were fully explained.
Evaluation of the Phototransduction Process

After 45 minutes of dark adaptation, a-waves to high-energy achromatic stimuli were obtained as previously described in detail. A set of four white flashes (3.2, 3.7, 4.0, and 4.4 log scotopic troland [scot td]-s) was presented in the dark. This range extends well above the retinal illuminance necessary to elicit a maximum a-wave before b-wave inactivation mechanisms, but to the best of our knowledge, no such patients were included in the present sample. The same four retinal illuminances (but calibrated in photopic units as 2.8, 3.3, 3.6, 4.0 log photopic [phot]td-s) were later presented against a rod-saturating background (3.3 log scot td-s). This background eliminates the rod photoresponse in normal subjects, but changes log $R_{\text{max}}$ and log $S$ values in cones by less than 0.1 log unit. Patients with sensitivity ($S$) so reduced that the background may not completely saturate also had severely reduced rod amplitudes. Thus, no patient showed any evidence of a rod response in the presence of this background. Five responses were averaged for each retinal illuminance (interstimulus interval 3–5 seconds), and the resultant cone a-waves were subtracted from the dark-adapted responses to produce rod-only a-waves. The rod-only a-wave ensemble was truncated before the peak (i.e., before any indication of postreceptor processes) and fit with a computational model based on the original model of Lamb and Pugh (also reported in Breton et al.) describing the response ($R$) as a function of time ($t$) and retinal illuminance ($I$):

$$R(t, I) = R_{\text{max}} [1 - \exp(-I S(t - t_0)^2)]$$

where $R_{\text{max}}$ is the maximum amplitude, $S$ is a sensitivity parameter, and $t_0$ is a brief delay before the response onset. The $t_0$ was fixed at 3.2 ms for the rods and 1.7 ms for the cones. Cone a-waves were also truncated before the peak and ensemble-fit with a computational model. Truncation times for both rod- and cone-mediated responses were fairly standard (see the Results section) and were based on our 10 years of experience with a large number of patients. The cone model contained an additional time constant (1.6 ms) to reflect the capacitance of the cone outer segment.

Because the quality of the fit worsened as $R_{\text{max}}$ decreased, only the records of patients with cone a-wave responses with maximum a-wave amplitudes greater than 6 µV were analyzed. Similarly, rod responses with maximum a-wave amplitudes less than 9 µV were considered too small for modeling. In addition, for all records that met the minimum amplitude criterion, a least-squares goodness-of-fit criterion (statfit $< 0.5$) was used to exclude noisy data. The statfit parameter can be defined as:

$$\text{Statfit} = \frac{\sqrt{\sum (x_i - m_i)^2}}{\sqrt{\sum (x_i - \mu)^2}}$$

where $x_i$ is the value of the response in point $i$ in time, $m_i$ is the value of the model fit at the same time point, and $\mu$ is the mean of the response for the time interval evaluated. A perfect fit to the model would produce a statfit of 0.0, whereas a value of 1.0 indicates that the model does no better than using the mean of the data.

Statistical Analysis

Logarithmic transformation was applied to all the values of $R_{\text{max}}$ and $S$. The normality of the data distribution was checked for all subgroups of patients with the Shapiro-Wilk test. Despite the logarithmic transformation of the data, the values for some subgroups were not distributed normally. In this situation, nonparametric tests (Mann-Whitney and Kruskal-Wallis) were used to assess possible significant differences among all groups. Linear regression analysis (with determination of the 95% prediction lines) was performed with SigmaPlot 7.0 (SPSS Inc., Chicago, IL); other statistical analyses were performed with SPSS 7.5.

RESULTS

Representative responses from a normal subject are shown in Figures 1A and 1B. Figure 1A shows rod-only responses to four retinal illuminances of 3.2, 3.7, 4.0, and 4.4 log scot td-s obtained after 45 minutes of dark adaptation. In normal subjects, the model began to break down as the slope saturated above 4.0 log scot td-s. Thus, only the lower three responses were used in the ensemble fit. The portions of the leading edges used to fit the model are indicated by heavy lines. The three lower responses were used in the ensemble fit. The portions of the leading edges used to fit the model are indicated by heavy lines. In normal subjects, the leading edge was typically truncated at 13.4, 11, 9, and 7.6 ms (if used) for the increasing series of four illuminances. Figure 1B shows responses to the same four
TABLE 1. Analyzable Cone and Rod a-Waves for Each Mode of Inheritance

<table>
<thead>
<tr>
<th>Mode</th>
<th>adRP</th>
<th>arRP</th>
<th>XIRP</th>
<th>Isolated</th>
<th>RP Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients (n)</td>
<td>117</td>
<td>71</td>
<td>84</td>
<td>146</td>
<td>418</td>
</tr>
<tr>
<td>Patients with usable cone a-waves (n)</td>
<td>45</td>
<td>12</td>
<td>31</td>
<td>48</td>
<td>136</td>
</tr>
<tr>
<td>Patients with usable rod a-waves (n)</td>
<td>50</td>
<td>13</td>
<td>19</td>
<td>43</td>
<td>125</td>
</tr>
<tr>
<td>Mean age of patients with recordable cone a-waves (y)</td>
<td>44</td>
<td>46</td>
<td>16</td>
<td>37</td>
<td>36</td>
</tr>
</tbody>
</table>

retinal illuminances from the same subject in the presence of a rod-saturating background (3.5 log scot td). For cone fits, it is particularly important to limit the fit to the early portion of the response (heavy line) because of the proximal retinal contributions to the later portion of the response, although this postreceptoral contribution appeared to be smaller in many of the patients. Typical truncation values in normal subjects were 10.6, 10.6, 10, and 9.6 ms (if used).

Representative responses of a patient with RP are shown in Figures 1C and 1D. Figure 1C shows the rod-only responses (note expanded vertical scale) and Figure 1D shows cone responses. Because both log rod S and log cone S are decreased below the age-adjusted normal limit, all four responses were used in the ensemble fits. Darkened lines indicate the portion of each leading edge used for fitting. The truncation points in patients were often later than in normal subjects, because postreceptoral processes were typically delayed. Representative times for rod photoresponses were 17.1, 13.6, 11.3, and 10.1 ms (if used) for the increasing series of four illuminances. For the cone responses in patients, we typically truncated at 12.6, 12.6, 12, and 11.6 ms. Note the large decrease (~84%) in rod R_max compared with normal values and the moderate decrease (~50%) in cone R_max.

This protocol using white light was attempted in 418 consecutive patients with RP referred to the Retina Foundation of the Southwest. In this population, 151 had cone a-waves of sufficient amplitude for analysis and 139 had rod a-waves of sufficient amplitude. The data from 11% of the patients with cone responses and 11% of the patients with rod responses did not meet the goodness-of-fit criterion. Therefore, 136 (33%) patients provided reliable cone parameters and 125 (30%) provided rod parameters. Table 1 shows the number of patients in the study with each inheritance pattern and the number with each inheritance pattern retaining sufficient cone or rod ERG amplitudes for analysis.

As reported previously, rod and cone S parameters show a linear decrease with age. For rods, the linear regression equation describing the relationship between the lower 5% limit and age in the normal population is: \( y = 1.055 - 0.0035x \), where \( y \) is the log S value and \( x \) is age in years. The corresponding age-adjusted lower limit for cone log S can be derived from: \( y = 1.514 - 0.0043x \).

The regression line and the 95% prediction intervals (derived from a linear regression model applied to the data) for S values in normal subjects are indicated with dashed lines in Figure 2. Cone log S values as a function of age are shown in the top panel of Figure 2B for the subset of all patients with analyzable cone a-waves. Mean cone log S values were significantly lower than normal (\( P < 0.01 \), Mann-Whitney). Cone log S showed a borderline significant relationship to age, but the \( R^2 \) was very low (\( R^2 = 0.03, P < 0.05 \)), indicating that only a very small fraction of the cone S variation can be explained by age.

Cone a-wave sensitivity values for the different modes of inheritance and their relationship with age are summarized in the bottom panels of Figure 2B. Mean cone log S was lowest in the XIRP group, and the difference from mean log S in other modes of inheritance was statistically significant (\( P < 0.01 \)). Cone log S was not significantly related to age in any of the inheritance subgroups.

As shown in Table 2, 83.8% of the cone R_max values in patients with analyzable rod a-waves were abnormal (96%), whereas rod S was abnormal in 61.6% of the cases. Rod a-wave sensitivity values as a function of age for the entire RP cohort are summarized in the top panel of Figure 2A with normal regression and 95% and 5% prediction limits shown as dashed lines. Although most of the values were below the lower limit of normal, there was no significant variation with age. There were no significant differences in rod log S among different modes of inheritance. The only parameter in any genetic subgroup that demonstrated a significant age effect was log rod S in arRP (Fig. 2A, middle row).

For further analysis of the possible relationships among rod and cone a-wave parameters, a linear regression model was applied to the data (Fig. 3). There was a strong correlation between rod and cone R_max values in RP patients (Fig. 3B) in contrast with the weaker correlation observed with values in normal subjects (Fig. 3A; \( R^2 = 0.43 \) vs. 0.17). The reverse trend was present with rod and cone S parameters, which were significantly correlated in normal subjects (Fig. 3C) but showed a much weaker correlation in patients with RP (Fig. 3D; \( R^2 = 0.46 \) vs. 0.05). We also evaluated a possible relationship between rod loss (rod log R_max) and cone sensitivity (cone log S). There was a weak relationship between rod log R_max and cone log S in normal subjects (Fig. 3E; \( R^2 = 0.03 \)) and in patients with RP (Fig. 3F; \( R^2 = 0.08 \)).

DISCUSSION

Retinitis pigmentosa is invariably associated with morphologic and functional changes in rod and, to a lesser extent, cone photoreceptors. Despite the fact that many of these changes include molecules and structures participating in the phototransduction process, the precise mechanism of action for the mutations in most cases is still unknown. The leading edge of the a-wave provides a noninvasive method for determining the degree to which the disease process affects phototransduction parameters in RP.

TABLE 2. Percentage of Abnormal Values for Rod and Cone R_max and S for the Different Modes of Inheritance and for the Patient Sample as a Whole

<table>
<thead>
<tr>
<th>Mode</th>
<th>adRP</th>
<th>arRP</th>
<th>XIRP</th>
<th>Isolated</th>
<th>RP Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cones (%)</td>
<td>71</td>
<td>83</td>
<td>90</td>
<td>92</td>
<td>84</td>
</tr>
<tr>
<td>Log S</td>
<td>67</td>
<td>75</td>
<td>97</td>
<td>77</td>
<td>78</td>
</tr>
<tr>
<td>Rods (%)</td>
<td>92</td>
<td>92</td>
<td>100</td>
<td>100</td>
<td>96</td>
</tr>
<tr>
<td>Log S</td>
<td>58</td>
<td>39</td>
<td>90</td>
<td>61</td>
<td>62</td>
</tr>
</tbody>
</table>
Availability of Measurable Cone Photoreceptor Responses in RP

These results suggest that analyzable cone a-waves are obtainable in approximately one third of patients with RP. The proportion of analyzable cone a-waves was different among the different groups, but the groups were also different in average age. Among groups of comparable average age, analyzable cone a-waves were present in 38% of the patients with adRP compared with 17% of the patients with arRP. These percentages and the distribution of the total number of RP patients...
tested are different from other estimates of the prevalence of each subtype$^{22-25}$ and are related more to disease severity, age, and the research focus of our laboratory.

Cone Phototransduction Abnormality in RP

Cone degeneration is well documented in different genetic forms of RP.$^{26,27}$ The mechanism is unknown but may involve a variety of pathologic processes, including accumulation of toxic byproducts from rod cell degeneration and loss of trophic factors in the cones.$^{28,29}$ The degeneration of the cones typically leads to a measurable functional cone deficit, such as a delay in cone b-wave implicit time$^{30}$ and a delay in cone pigment regeneration.$^{31,32}$

Despite our progress in understanding the nature of the cone functional deficit in RP, little is known about the extent to which rod degeneration is related to cone malfunction. The results obtained in this study related to the cone photoreceptor abnormalities confirm previous reports of affected cone function in RP patients with different modes of inheritance$^{20,33-35}$ and in animal models of RP.$^{56}$ However, previous studies in-

![Figure 3. Correlation of the different a-wave parameters collapsed across genetic types. Solid line: linear regression model applied to the data and extended to the borders of the graph. Insets: correlation coefficient ($R^2$) and its significance. (A) Cone $R_{\text{max}}$ versus rod $R_{\text{max}}$ in normal subjects. (B) Cone $R_{\text{max}}$ versus rod $R_{\text{max}}$ in patients with RP. Cone $S$ versus rod $S$ in (C) normal subjects and (D) patients with RP. Cone $S$ versus rod $R_{\text{max}}$ in (E) normal subjects and (F) in patients with RP.](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/932921/ on 03/04/2018)
cluded a limited number of patients, estimated cone function indirectly from a single measure of the photopic b-wave ERG amplitude, and/or did not analyze the cone deficit in all modes of inheritance. In a previous study\textsuperscript{20} using a technique similar to the one used in the current study, we reported cone function in 21 patients (mostly adRP) and found a high percentage of reduced maximum cone response (\textasciitilde 70\%) and an even higher percentage of reduced cone S values (\textasciitilde 90\%). The present results, based on a larger sample, provide a more complex picture in this respect. Although we found a proportion of abnormal cone \( R_{\text{max}} \) values similar to that reported previously, it appears that cone S values are outside the normal range in a smaller fraction of patients with adRP (\textasciitilde 67\%), perhaps because age-corrected normative values were used in the present study. In contrast, Cideciyan et al.\textsuperscript{57} found reduced cone amplitude in 5 of 19 patients with adRP and reduced cone sensitivity in only 1 patient,\textsuperscript{57} possibly because their sample was limited to patients with rhodopsin mutations.

It is important to assess the level of cone function with objective methods, because the degree of preservation greatly influences the quality of life. Although previous studies have indicated abnormal cone function in RP, the high incidence (more than four fifths of the patients) of abnormally low cone S values in all genetic forms of RP found in the present study seems surprising. There are numerous reports of cytological and biochemical abnormalities in cone photoreceptors of patients with RP. It has been shown, for example, that the disease process affects cone maturation in an animal model of a rhodopsin mutation.\textsuperscript{56} A common morphologic finding is that axons of peripheral cones are abnormally elongated and branched in R\textsuperscript{P}\textsuperscript{77}\textsuperscript{-58} and/or make ectopic synapses with rod bipolar cells.\textsuperscript{59} In addition, it has been shown that \( \gamma \)-aminobutyric acid (GABA)-reactive and glycine-reactive processes from amacrine cells extend through the outer plexiform and outer nuclear layers as far as the external limiting membrane.\textsuperscript{40} It has been demonstrated recently that horizontal cells contain vesicles that accumulate GABA and glycine, possibly for vesicular release.\textsuperscript{41,42} Thus, it may be possible that even minimal sustained release of both neurotransmitters from the processes of the amacrine cells changes the neurotransmitter balance in the outer retina, which can affect cone function through the feedback (gating of chloride conductance) from the horizontal cells to the cones.\textsuperscript{53,54} Moreover, studies have shown that calbindin and other cytoplasmic proteins (7G6, X-arrestin, and recoverin) are markedly decreased in the cone cytoplasm of some patients with RP, although otherwise the cones were unremarkable cytologically.\textsuperscript{40,45} Although the relationship between the proteins calbindin and 7G6 with phototransduction is not clear at this time, both X-arrestin\textsuperscript{46} and recoverin\textsuperscript{47} have an established role in the phototransduction process. Müller cells also respond to photoreceptor degeneration by upregulated expression of glial fibrillary acidic protein in areas where cones show loss of cytoplasmic proteins and ectopic nuclei.\textsuperscript{29,45} An important mitochondria-specific enzyme, cytochrome c oxidase, was also decreased in the inner segments of RP cones.\textsuperscript{45,47} Taken together, all these findings suggest that several pathologic changes in the outer retina (abnormal synaptogenesis, downregulation of several cone protein expressions, decrease in mitochondrial cone activity, and changes in the neighboring Müller cells) could alter the cone function and exert a measurable effect on the high-energy a-wave parameters.

One additional factor that may contribute to a smeared condition for cone phototransduction in RP is reduced blood flow. It has been shown that choroidal\textsuperscript{48,49} and retinal\textsuperscript{50,51} blood flow is reduced in many patients with RP, and therefore the overall metabolic rate of the RP retina is probably decreased. This may affect cone phototransduction more than rod phototransduction in the areas of the retina where relatively preserved patches of photoreceptors are found. Further research is necessary to determine whether the blood flow reduction is an early change in RP that accelerates photoreceptor dysfunction or is a secondary phenomenon that is related to the already decreased metabolic demand. However, even as a secondary effect, it cannot be ruled out as a factor that exacerbates the adverse conditions for phototransduction.

### Rod Phototransduction Abnormality in RP

The present results are consistent with previous studies showing that RP invariably leads to a decrease in the maximum rod response, because the rods die whereas the efficiency of rod phototransduction may be either normal or reduced.\textsuperscript{6,12,52,55} One possible way for rod sensitivity to be affected is through a mutation (i.e., certain rhodopsin mutations)\textsuperscript{60} that directly affects the phototransduction cascade. Such a mutation may have an adverse effect on amplification (reflected by a lower than normal S values), which remains relatively constant until the rods die. That would lead to gradually decreasing rod \( R_{\text{max}} \) and stable, but reduced, rod S. In some rhodopsin mutations (e.g., Pro23His), it is likely that the activation phase of the rod phototransduction is abnormal from birth.\textsuperscript{52}

### Effect of Age on Cone and Rod Photoreceptor Sensitivity Parameters

Studies have demonstrated that normal aging is accompanied by a gradual loss of photoreceptors (mostly rods).\textsuperscript{72} However, cone loss is only minimal\textsuperscript{44-50} and does not result in a measurable decrease of cone \( R_{\text{max}} \) with age.\textsuperscript{17} In contrast to cone \( R_{\text{max}} \), log cone S in normal subjects decreases with age,\textsuperscript{17} which is consistent with the decrease in ERG b-wave amplitude with age.\textsuperscript{57-58} Although the cone S values were decreased below normal in all patients with RP at all ages in the current study, we did not find a decrease in cone S with age in RP. In part, this could be because declining \( R_{\text{max}} \) with age often precludes measurement of S in older patients. The lack of progression in S with age must also be interpreted with caution, because cross-sectional data such as these often show slower rates of progression than longitudinal data. Thus, patients with less-affected photoreceptor function may have cone sensitivity closer to the normal range during their initial testing. In contrast, the sensitivity parameter seems to be a reflection of the specific mutation in a given patient. In longitudinal measures, for example, \( S \) did not vary significantly over a 4-year interval in a cohort of patients with XIRP.\textsuperscript{17}

Although log S for rods also decreases with age in normal subjects,\textsuperscript{17} we found no decrease with age in patients with RP. The arRP subgroup was the only one that showed a linear decrease in log S with age. However, this result should be interpreted with caution, because it was influenced by the presence of a low log S in one 70-year-old patient. As for the cone S values, this stability with age should be viewed with caution because of the limitations of any cross-sectional analysis. Accurate measures of age-related changes in patients will only become available through longitudinal measures of cone and rod photoreceptor sensitivity parameters.

### Linear Correlations among High-Energy a-Wave Parameters

There was a weak linear correlation between rod and cone \( R_{\text{max}} \) in normal subjects. This is not surprising, because \( R_{\text{max}} \) reflects the number of functioning photoreceptors in the retina, and the range of values among normal subjects is limited. In fact, the results shown in Figure 3A suggest a total range in ratios of less than 0.4 log unit, consistent with measures of the ratios of cones to rods among individuals. Topographical studies of human retina have demonstrated that the numbers of cones and rods can vary among individuals by 24\% to 30\% and

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27% to 35%, respectively, suggesting that the variability in the ratios of the different types of photoreceptors cannot be more than 50%. The highly significant linear correlation between log rod S and log cone S in normal subjects is presumably due to the age dependence of sensitivity parameters for both cone and rod phototransduction processes.

Our results show that, in most of the RP cases, a decrease in rod R max was related to a proportional decrease in cone R max. No such correlation was found, however, between rod log S versus cone log S in patients with RP, possibly because of differences in the impact on the efficiency of the rod and cone phototransduction depending on the mutation and/or the severity of the disease. A slightly higher correlation was found between log cone S and log rod R max, suggesting that cone sensitivity in RP is somewhat dependent on the number of viable rod photoreceptors. 19, 20

Photoreceptor Activity and Mode of Inheritance in RP

The results presented herein extend previous studies in demonstrating differences in the severity of RP among different modes of inheritance. The X-linked form of RP is the most severe form of the disease demonstrating the highest rate of progression. At present, five different loci on the X-chromosome have been related to the disease: RP2, -3, -6, -23, and -24. In our sample, we found decreased log S from the cone photoreceptors in most patients with XIRP. Because log cone S reflects the efficiency of the phototransduction process, the low log S in patients with XIRP, including children, suggests that the gain of the cones is affected early in the course of the disease. The arRP and isolated cases have an intermediate place in terms of severity of photoreceptor dysfunction between the more severe XIRP cases and the less-severe adRP cases. Still, both the maximum amplitude and log S of rod and cone responses were significantly lower than normal. The significant decreases in both log R max and log S for cones in all subtypes of RP serves to emphasize the importance of cone photoreceptor abnormalities in the RP disease process.

Conclusions

In summary, the results of this study suggest that it is possible to record and analyze rod and cone a-wave responses in approximately one third of patients with RP. Besides providing direct measures of abnormal photoreceptor function, rod and cone a-wave recordings may provide a useful outcome measure for future clinical trials in RP.

References