Blue and green cone mechanisms in retinitis pigmentosa

Michael A. Sandberg and Eliot L. Berson

Pronounced abnormalities in the increment threshold curves for the blue and green cone mechanisms only 10° above the fovea, and in some cases in the fovea as well, have been found with a 2.5° stimulus in different genetic types of retinitis pigmentosa. Whenever cone thresholds were abnormal, thresholds determined by the blue cone mechanism (\( \pi_r \)) and \( \pi_t \) were more elevated than those determined by the green cone mechanism (\( \tau_r \)). Thresholds determined by the green cone mechanism were consistently more elevated at low background intensities than at intermediate and high background intensities. Threshold elevations for the blue and green cone mechanisms relative to each other in the perifovea in a given patient tested with the 2.5° stimulus could be simulated in normal observers tested with a single small stimulus. These findings support the idea that the summation pools for blue and green cone mechanisms are proportionally reduced below normal in retinitis pigmentosa, at least in the perifovea, and are compatible with the idea that both mechanisms are comparably involved at the photoreceptor level.

Key words: retinitis pigmentosa, cone, rod, tritanomaly, color vision, psychophysics, retina, retinal degeneration, increment threshold, monochromat

The relative involvement of the different cone mechanisms in retinitis pigmentosa is not yet completely known; in particular, a question exists as to whether blue, green, and red cone mechanisms are equally affected in a given retinal area. A tendency to tritanomaly detected by the Farnsworth D-15 Panel and certain pseudoisochromatic plates has been reported in some patients with advanced retinitis pigmentosa. Marre and Hansen have isolated each cone mechanism with chromatic adaptation at a single background intensity in retinitis pigmentosa and have reported that thresholds determined by the blue cone mechanism are preferentially elevated in these diseases.

Color vision tests such as the Farnsworth D-15 Panel as routinely performed provide neither a measure of threshold cone activity nor information about extrafoveal cone function. Chromatic adaptation with a steady background provides an opportunity to study cone mechanisms at threshold in different retinal areas; however, the green (\( \lambda_{\text{max}} \approx 545 \text{ nm} \)) and red (\( \lambda_{\text{max}} \approx 580 \text{ nm} \))...
Fig. 1. Two-channel Maxwellian-view optical system with 1,000 W xenon arc lamp (S1) for test channel and 50 W tungsten-halogen lamp (S2) for background channel. Symbols are as follows: L1, 19 D quartz achromat; L6, 10 D achromat; L15, 15 D achromat; L42, 8 D achromat; L14, 30 D erfe; L10, 14 D double condensor; WB, water bath; M1, first-surface mirrors; F1, heat-absorbing glass; F1, interference or color absorption filter; F1, neutral density filter; F1, cross-rotating balanced neutral density wedges; F1, color absorption filter; F1, circular field stop; F1, crosshair or circular field stop; SH, electronic shutter; AS1, circular aperture stops; BS, cube-type beam splitter; PH, phoropter (to correct for ametropia or aphakia); E, observer's pupil. Hatched line indicates lightproof enclosure for observer.

nm.) cone spectral sensitivity curves overlap so much that it is difficult to isolate one cone mechanism from the other without light adapting both. The blue (λmax ≈ 440 nm.) cone spectral sensitivity curve overlaps to a far less extent with the green and red cone curves; therefore the blue cone mechanism can be isolated from the other two without being light adapted as much. For example, at background intensities adequate to define fully the three cone spectral sensitivity curves in normal observers, thresholds determined by the green and red cone mechanisms were elevated about 2 log units, while thresholds determined by the blue cone mechanism were raised only 1 log unit above the normal dark-adapted cone spectral sensitivity curve.6

This study was done to compare thresholds determined by the blue and green cone mechanisms over a wide range of background intensities in different genetic types of retinitis pigmentosa to see if, in fact, thresholds governed by the blue cone mechanism are preferentially elevated in these diseases. Thresholds were measured in the fovea and in the perifovea in these patients to determine if the relative involvement of the blue and green cone mechanisms was comparable in different retinal areas.

Methods

Psychophysical testing. Stiles' two-color increment threshold technique7 was used to measure thresholds over a wide range of background intensities with a two-channel Maxwellian-view optical system (Fig. 1). Patients and normal observers were presented a test stimulus subtending a visual angle of 2.5° or less centered on a steady 68° background field. Test stimuli, 200 msec. in duration, were either 420 or 500 nm. (10 nm. half-bandwidth) to facilitate identification of blue and green cone mechanisms. Since the blue cone mechanism is about 0.8 log units more sensitive to 420 than 500 nm., while the green cone mechanism is about 1.1 log units more sensitive to 500 than 420 nm.,8 threshold measurements at 420 and 500 nm., relative to each other at any given background intensity, help to identify which
the foveal center or to the perifovea (10° su-

such that it was impossible to exclude a small

tion in the density of macular pigment among

adjusted by the observer to a threshold criterion

tensity. The intensity of the test stimulus was

perior retina) on backgrounds of increasing in-

lus subtending 2.5° was then presented either to

study.

8 Test stimuli were

30 minutes and then asked to fixate on a crosshair

wave stimuli used to measure thresholds in this

anism to ^4 was unlikely in view of the short-

les was done with stimuli less than 2.5° in an

tation. Second, cone increment threshold measure-

observers at low background intensities otherwise

condition, cone thresholds were obtained in normal

from patients with retinitis pigmentosa. Cone in-

from patients with retinitis pigmentosa. Cone in-

cumechanism is governing the response. These

test stimuli were also chosen because the optical
density of macular pigment is the same for both

waves; this avoids the problem of introduc-
ing uncertain correction factors for possible variation
in the density of macular pigment among

patients and normal observers. The background
channel transmitted only the long-wave end of the
spectrum (cut-on at 540 nm); long-wave light
was chosen to adapt maximally the red and to a
lesser extent the green cone mechanisms and
thereby allow separation of the blue cone mech-

anism.

Data obtained were compared with Stiles' \( \tau \)
mechanisms (i.e., \( \tau_r \) for the rod mechanism, \( \tau_b \),
and \( \tau_g \) for the blue cone mechanism, and \( \tau_s \)
for the green cone mechanism). Test stimuli were
such that it was impossible to exclude a small
contribution from the red cone mechanism in \( \tau_r \).
However, a contribution of the red cone mecha-

anism to \( \tau_s \) was unlikely in view of the short-

wave stimuli used to measure thresholds in this

study.

Under the standard condition for measuring
thresholds, observers were first dark adapted for
30 minutes and then asked to fixate on a crosshair
centered in the background field. The test stimu-
lus subtending 2.5° was then presented either to
the foveal center or to the perifovea (10° su-

perior retina) on backgrounds of increasing in-
tensity. The intensity of the test stimulus was
adjusted by the observer to a threshold criterion of
50% seeing.

In addition to the above-mentioned standard
condition, a variation was employed in normal
observers to obtain data for comparison with those

Table I

<table>
<thead>
<tr>
<th>Initials</th>
<th>Sex</th>
<th>Age</th>
<th>Visual acuity</th>
<th>Color vision</th>
<th>Diagnosis</th>
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<tr>
<td>M. S.</td>
<td>M</td>
<td>26</td>
<td>20/20</td>
<td>Normal</td>
<td>Normal observer</td>
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<tr>
<td>M. E.</td>
<td>M</td>
<td>19</td>
<td>20/20</td>
<td>Normal</td>
<td>Normal observer</td>
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<td>20/20</td>
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<td>Oguchi's disease</td>
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<td>20/400</td>
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<tr>
<td>M. L.</td>
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<td>13</td>
<td>20/200</td>
<td>Protan-deutan axis</td>
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<td>20/25</td>
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<td>Normal</td>
<td>Dominant retinitis pigmentosa</td>
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<td>J. L.</td>
<td>M</td>
<td>14</td>
<td>20/70</td>
<td>Normal</td>
<td>Sex-linked retinitis pigmentosa</td>
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Blue-green in retinitis pigmentosa
observers. The congenital rod monochromats had spectral sensitivity curves that matched the standard relative scotopic luminous efficiency function ($\lambda_{\text{max}} \approx 505 \text{ nm}$) under both dark- and light-adapted conditions; the blue cone monochromat had a spectral sensitivity curve that matched the standard relative scotopic luminous efficiency function ($\lambda_{\text{max}} \approx 505 \text{ nm}$) under dark-adapted conditions but had a spectral sensitivity curve that matched that of Stiles' $\pi_3$ mechanism ($\lambda_{\text{max}} \approx 440 \text{ nm}$) under light-adapted conditions. Many patients with retinitis pigmentosa had "bone spicule" pigmentation in the midperiphery, but none had "bone spicule" pigmentation in the fovea or 10° superior retina. All patients with retinitis pigmentosa had steady foveal fixation. All had clear media except P. G., who had minimal posterior subcapsular lens changes; R. B. and D. W. were aphakic. Patients H. W., A. W., and S. F. had dark-adapted spectral sensitivity curves for the 10° superior retina that were above normal dark-adapted cone sensitivity for wavelengths below 620 nm and, as expected, approximated the standard relative scotopic luminous efficiency function ($\lambda_{\text{max}} \approx 505 \text{ nm}$). The remaining patients had dark-adapted spectral sensitivity curves that were below normal dark-adapted cone sensitivity over the entire visible range and, with the exception of C. S., approximated a broad cone spectral sensitivity function ($\lambda_{\text{max}} \approx 560 \text{ nm}$). C. S. showed a biphase curve whose shape approximated the standard relative scotopic luminous efficiency function at short waves and the cone spectral sensitivity function at long waves. All patients with retinitis pigmentosa had very reduced full-field electroretinograms. Families B., W., and F. and patient C. S. have been described previously.

Results
In the fovea after dark adaptation for 30 minutes (Fig. 2), normal observers show rod ($\pi_r$) function at low background intensities (i.e., low background retinal illuminances) and blue cone ($\pi_1$ and $\pi_3$) function at high intensities in response to the 420 nm. stimulus and show rod function at low background intensities, green cone ($\pi_4$) function at intermediate intensities, and blue cone function at high intensities in response to the 500 nm. stimulus. In the perifovea after dark adaptation for 30 minutes (Fig. 2), normal observers demonstrate rod function at low intensities and blue cone function at high intensities in response to the 420 nm. stimulus and rod function at low intensities and blue cone function at high intensities in response to the 500 nm. stimulus. In the fovea and perifovea after cone recovery from short-wave preadaptation (i.e., cone isolation), the blue cone ($\pi_1$) mechanism of normal observers governs thresholds for the 420 nm. stimulus and the green cone ($\pi_3$) mechanism governs thresholds for the 500 nm. stimulus at low background intensities.

After dark adaptation for 30 minutes, thresholds of both rod monochromats in the perifovea (Fig. 2) approximate the normal curve for the rod mechanism; the thresholds of the blue cone monochromat in the perifovea approximate the normal curve for the rod mechanism at low background intensities and the normal curve for the blue cone mechanism at high intensities. The patient with Oguchi's disease shows thresholds that correspond with those from normal observers obtained after cone recovery from short-wave preadaptation (i.e., cone isolation) at low and intermediate background intensities.

Fig. 3 illustrates increment threshold data for younger and older patients with dominant and recessive retinitis pigmentosa. In the fovea the younger patient with dominant disease (S. B.) and the younger patient with recessive disease (S. S.) show normal cone function. The older patient with dominant disease (R. B.) and the older patient with recessive disease (P. G.) have abnormal blue and green cone function. The green cone ($\pi_4$) mechanism governs threshold from low to intermediate background intensities for both 420 and 500 nm. stimuli with thresholds 1.0 to 1.5 log units above normal at low background intensities but approximating normal at intermediate background intensities. The blue cone ($\pi_3$) mechanism governs threshold at high background intensities with thresholds about 2.0 log units above normal; thresholds for Stiles' $\pi_3$ (the high-intensity blue cone mechanism) are elevated 2.7 to 3.0 log units above normal with the 420 nm. stimulus and cannot be detected with the 500 nm. stimulus under these conditions.
test conditions. These two older patients also showed a tritan deficiency on color vision testing (Table I).

In the perifovea (Fig. 3), S. B. shows thresholds for the blue cone (π1 and π3) mechanism that are 2.0 log units above normal over the full range of background intensities (seen with the 420 nm stimulus); thresholds for the green cone (π4) mechanism are 1.5 log units above normal.
Fig. 3. Increment thresholds obtained for S. B. (*) and her father R. B. (▲) with dominant retinitis pigmentosa with complete penetrance and for S. S. (○) and P. G. (△) with autosomal recessive retinitis pigmentosa. Thresholds were determined after 30 minutes of dark adaptation, and data points each represent single measurements (reliable to within ±0.15 log unit as determined by selected repeat measurements). Solid lines represent normal curves for the \( \pi \) mechanism derived from Fig. 2.

at low background intensities but approximate normal thresholds for the green cone mechanism at intermediate background intensities (seen with the 500 nm stimulus). R. B. could not see the test stimulus in the perifovea. S. S. shows nondetectable blue cone function as tested; thresholds for the green cone (\( \pi_1 \)) mechanism (seen with 420 and 500 nm stimuli) are elevated about 2.0 log units above normal at low background intensities but are elevated only 0.7 to 1.0 log units above normal at inter-
mediate background intensities. P. G.'s findings resemble those of S. S. although thresholds are more elevated.

C. B. showed measurements virtually identical to those of his sister S. B. Families W. and F. with dominant disease showed results similar to that of Family B. illustrated in Fig. 3, although some of the younger members (i.e., H. W., A. W., and S. F.) showed normal cone thresholds in the perifovea. C. Sa. and F. S. with autosomal recessive disease showed cone thresholds that fell between those of S. S. and P. G. J. L. and C. S. with sex-linked disease showed cone function that was virtually identical to that seen in S. S. with autosomal recessive disease.

Fig. 4 compares perifoveal cone increment threshold data for normal observers in response to 12' and 4' stimuli to the perifoveal curves for patients with retinitis pigmentosa in response to a 2.5° stimulus. The data for normal observers with the 12' stimulus closely fit the curves for the blue and green cone mechanisms for patients with dominant disease (average of S. B. and C. B.). The data for normal observers with the 4' stimulus closely fit the curves for the green cone mechanism for patients with recessive disease (average of S. S., C. Sa., C. S., and J. L.) for both the 420 and 500 nm. stimuli; with this very small stimulus under these conditions, blue cone function cannot be detected in the data for normal observers even for the 420 nm. stimulus.

**Discussion**

This investigation demonstrates that pronounced abnormalities in the increment threshold curves for the blue and green cone mechanisms exist only 10° from the fovea and, in some cases, in the fovea as well in young patients with different genetic types of retinitis pigmentosa. Whenever cone thresholds were abnormal in the perifovea or fovea, thresholds determined by the blue cone mechanism were more ele-
vated than those determined by the green cone mechanism. Only when foveal cone thresholds were severely elevated in older patients with retinitis pigmentosa was a tendency to tritanomaly revealed by the Farnsworth D-15 Panel and Kalmus Plate.

Previous studies in normal observers have shown that at low background intensities, increment thresholds determined by the green cone mechanism to a small spot are well above those to a large spot, while at high background intensities this disparity is greatly reduced. This illustrates that spatial summation is important in determining cone thresholds, particularly at low background intensities. For patients with retinitis pigmentosa in the present study, thresholds determined by the green cone mechanism were very elevated at low background intensities but approximated normal at intermediate and high background intensities. This preferential elevation at low background intensities raised the possibility that a reduction in the capacity for spatial summation for the green cone mechanism exists in retinitis pigmentosa. This was supported by the finding that increment threshold data for the green cone mechanism from normal observers tested with small stimuli closely approximated in shape and level the increment threshold curves for the green cone mechanism from patients tested with a much larger stimulus.

A previous investigation in normal observers has revealed that increment thresholds determined by the blue cone mechanism for a small spot are well above those for a large spot, regardless of background intensity. This has been explained by the fact that the summation pool for the blue cone mechanism (unlike that for the green) is not much affected by background intensity. The present study showed that thresholds determined by the blue cone mechanism for patients with retinitis pigmentosa are comparably elevated at low and high background intensities in the perifovea; this was found for two young patients, S. B. and C. B., with dominant retinitis pigmentosa with complete penetrance.

Responses of normal observers tested in the perifovea have shown a greater elevation of thresholds determined by the blue cone mechanism relative to those determined by the green cone mechanism when the size of the test stimulus was decreased; a decrease in stimulus size results in a proportional reduction in the number of blue and green cone photoreceptors stimulated and consequently in a reduction in blue and green cone summation pools. In the present study in the perifovea the preferential elevation of thresholds determined by the blue cone mechanism relative to those determined by the green in a given patient with retinitis pigmentosa tested with a large stimulus could be simulated in normal observers tested with a single small stimulus. This finding supports the idea that the summation pools for the blue and green cone mechanisms are proportionally reduced below normal in these diseases, at least in the perifovea. This finding is also compatible with the idea that blue and green cone photoreceptors are comparably involved, at least in the perifovea.

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REFERENCES