ON-Response Deficit in the Electroretinogram of the Cone System in X-Linked Retinoschisis

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PURPOSE. The purpose of this study was to evaluate the hypothesis that the reduced b-wave to a-wave ratio of the brief-flash electroretinogram (ERG) of the cone system typically observed in X-linked retinoschisis (XLRS) represents a relatively greater deficit in the ON response (response to light onset) than the OFF response (response to light offset). A second purpose was to investigate the use of sawtooth flicker as a stimulus for eliciting ERG ON and OFF responses.

METHODS. Light-adapted, full-field ERGs were recorded in six patients with XLRS and six age-similar control subjects in response to 8-Hz rapid-on and rapid-off sawtooth flicker to emphasize ON and OFF responses, respectively. ERG responses were analyzed in terms of the amplitudes and implicit times of the a-wave, b-wave, and d-wave components.

RESULTS. There was no significant difference between the patients with XLRS and the control subjects for either the amplitude of the a-wave of the ON response or the amplitude of the d-wave of the OFF response. However, the amplitude of the b-wave of the ON response was reduced significantly in the patients with XLRS, resulting in a significantly reduced b-wave to d-wave ratio. The patients' implicit times were increased significantly for all waveform components.

CONCLUSIONS. The reduced b-wave to d-wave ratio of the ERG of the cone system in these patients with XLRS is consistent with a relative dysfunction of the cone ON bipolar cell pathway in this disorder. The results show further that sawtooth flicker is a promising stimulus for eliciting well-defined ERG waveforms that can provide a quantitative assessment of the properties of ON and OFF responses in retinal disease. (Invest Ophthalmol Vis Sci. 2001;42:453–459)

X-linked juvenile retinoschisis (XLRS) is an hereditary form of juvenile-onset vitreoretinal degeneration that is characterized by a schisis or intraretinal splitting within the macula, and, in approximately 50% of patients, in the peripheral retina as well. The schisis occurs at the level of the nerve fiber and ganglion cell layers of the retina and has been proposed to be reflective of degenerative Muller cells that are the primary cause. Dysfunction of Muller cells has been thought to account for the fact that patients with XLRS typically show a reduced b-wave to a-wave ratio in the brief-flash electroretinogram (ERG) of both rod and cone systems, such that the a-wave amplitude is normal, or near-normal, but the b-wave amplitude is reduced substantially. This hypothesis is based on the traditional assumption that the ERG b-wave represents the response of Muller cells to bipolar cell activity. However, recent evidence suggests that Muller cells probably make little direct contribution to the ERG response. In addition, the XLRS1 gene that is altered in XLRS is expressed primarily in rod and cone photoreceptors, but not in Muller cells, so that the link between the genetic defect and the relative b-wave attenuation in XLRS is presently uncertain.

The purpose of the present study was to determine whether the reduced b-wave amplitude of the brief-flash ERG of the cone system in XLRS represents a specific abnormality in the ON response, as has been observed in several other retinal disorders that include congenital stationary night blindness (CSNB), acquired night blindness, melanoma-associated retinopathy (MAR), and cone or cone-rod dystrophy. When a long-duration flash is used to separate the ON and OFF responses of the cone system in these disorders, the amplitude of the b-wave of the response to light onset is more reduced than the amplitude of the d-wave of the response to light offset, resulting in a reduced b-wave to d-wave ratio.

A decreased b-wave to d-wave ratio was reported previously in one patient with XLRS, but the amplitudes of the b-wave and d-wave of this patient were within normal limits, so it is not apparent how this finding may generalize to other patients with XLRS. Additional suggestive evidence for an ON-response deficit in XLRS was provided by a recent study that examined the ERG responses of the cone system to sinusoidal flicker. Patients with XLRS showed a relatively greater attenuation of the first of two waveform peaks in the ERG response to 8-Hz sinusoidal flicker, which was interpreted as a predominant impairment in the ON response. However, ON and OFF responses were not assessed directly in that study.

Traditionally, the ON and OFF responses of the ERG of the cone system have been evaluated by recording the responses to the onset and offset of a luminance increment that is 100 msec or longer in duration. However, there can be considerable intersubject variability in the OFF response when measured in this way, more so than for the ON response, due in part to eye movements that tend to obscure the waveform morphology of the OFF response. In fact, we observed such response contamination by eye movements in a pilot study of ERG ON and OFF responses of patients with XLRS in which long-duration flashes were used. This variability in the OFF response makes it difficult to compare the properties of ON and OFF responses quantitatively. The ERG OFF response has also been measured as the response to the onset of a luminance decrement, but this alters the retinal adaptation state relative to incremental stimuli.

In the present study, we used sawtooth flicker as an alternative stimulus for eliciting ERG ON and OFF responses. The sawtooth waveform maintains a constant adaptation state for both increments and decrements, so that quantitative comparisons between ON and OFF responses can be made more readily than with incremental and decremental flashes. In addition, the temporal frequency of sawtooth flicker can be varied to allow an investigation of the temporal properties of ON and OFF responses. Sawtooth flicker has been used to study the response properties of ON and OFF ganglion cells.
and to investigate psychophysical sensitivity to increments and decrements. However, to our knowledge, it has not been applied to the measurement of ERG ON and OFF responses. In the present study, sawtooth flicker was used to test the hypothesis that there is a relative impairment in the ERG ON response in XLRS. Preliminary versions of this work have appeared in abstract form.

**Materials and Methods**

**Subjects**

Six unrelated male patients with XLRS participated in the study. The patients' ages and characteristics of the tested eye (which was the left eye for all subjects) are summarized in Table 1. All patients had the typical signs and symptoms of XLRS. Their chief symptom was reduced central vision. The foveas of all patients had microcystic lesions that had a radial spoke-like appearance. Three (patients 1, 2, and 6) also had peripheral schisis-like changes, predominantly in the inferior temporal quadrant. Peripheral visual field restrictions corresponded to the clinically observed peripheral schisis. One (patient 6) had a sheen-like appearance at the posterior pole, primarily temporal to the macula, similar to that described previously in some patients with XLRS. The ERG responses of all patients had a reduced b-wave to a-wave amplitude ratio that was most apparent for the response of the dark-adapted eye to a maximal white stimulus. Patient 2 was using topical medication for increased intraocular pressure but had no glaucomatous field loss. Although blood samples were obtained from two of the patients with XLRS, molecular genetic information was not available for any of them.

The ERG results from the patients with XLRS were compared with those of six control subjects (two men and four women) with normal vision, whose ages ranged from 24 to 38 years. There was no significant difference between the mean ages of the patients with XLRS and the control subjects (t = -1.58, P = 0.14). The control subjects had best-corrected Snellen visual acuities of 20/20 or better in the tested eye, clear ocular media, and normal-appearing fundi on ophthalmologic examination. The study adhered to the tenets of the Declaration of Helsinki, and it was approved by the institutional review board of the University of Illinois at Chicago. Informed consent was obtained from all subjects after the nature and possible consequences of the study had been explained to them.

**Stimuli and Recording**

The stimulus consisted of full-field flicker that had either a rapid-on or a rapid-off sawtooth temporal waveform and that was presented against a rod-desensitizing adapting field. These two stimulus waveforms are illustrated in Figure 1. Each cycle of rapid-on flicker consisted of an abrupt increase in luminance, to emphasize an ON response, followed by a linear decrease in luminance. Each cycle of rapid-off flicker consisted of an abrupt decrease in luminance, to emphasize an OFF response, followed by a linear increase in luminance. The two waveforms have the same time-average luminance, which is indicated by the dashed lines in the figure. In addition, both waveforms have the same amplitude spectrum, consisting of all even and odd multiples of the fundamental frequency, with the amplitudes of the harmonic components decreasing in proportion to their frequency. The two waveforms differ only in the phases of the harmonics: the frequency components for rapid-off flicker are shifted by 180° from those for rapid-on flicker. That is, rapid-off sawtooth flicker is the inverse of rapid-on flicker.

The stimuli were provided by two optical channels, each with a light source consisting of a 300-W tungsten-halogen bulb (each housed within a projector; Eastman Kodak, Rochester, NY), and each with infrared blocking filters. One channel provided a temporally modulated light for generating the sawtooth flicker. The other channel provided a steady, rod-desensitizing adapting field. The light source for the temporally modulated channel was powered by a custom-built regulated DC power supply. The achromatic stimuli were presented within an integrating sphere (Oriel, Stratford, CT) and the light from the two optical channels was combined with a "y" fiber-optic light guide (Oriel).

Temporal modulation of the test field was controlled by a ferroelectric liquid crystal (FLC) shutter (Displaytech, Longmont, CO) and driver (DR-95; Displaytech). The driver was controlled in turn by a signal processing board (DAS-801; Keithley, Cleveland, OH) housed within a microcomputer. The FLC shutter was driven at a constant temporal frequency of 1000 Hz and was pulse-width modulated under computer control, with the duty cycle controlled by a linearized lookup table. A shutter and driver (Vincent Associates, Rochester, NY) within the second optical channel controlled the adapting field presentation.

Luminances were calibrated with a photometer (LS-110; Minolta, Osaka, Japan). The luminance of the adapting field was 17.4 candelas (cd)/m² (2.94 log troland [td], assuming an 8-mm pupil). The maximum luminance of the sawtooth stimulus was 393 cd/m² (4.30 log td).

**Table 1. Patient Characteristics**

<table>
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<th>Patient</th>
<th>Age</th>
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<td>36</td>
<td>20/40</td>
<td>2B</td>
<td>2B</td>
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Data are from the left eye.

* 1, No peripheral visual field restriction; 2A, peripheral visual field restriction in only one quadrant; 2B, peripheral visual field restriction in two quadrants.

† 1, Foveal schisis only; 2B, peripheral fundus changes present in two quadrants.

**Figure 1.** Illustration of stimulus waveforms for 8-Hz rapid-on (top) and rapid-off (bottom) sawtooth flicker. Dashed lines: Time-average luminance.
and the minimum luminance was 1.4 cd/m² (1.85 log td). In the absence of the adapting field, these luminances produced a modulation of 99%. Against the adapting field, the modulation was 91.2%.

Procedure
The pupil of the tested eye was dilated with 2.5% phenylephrine hydrochloride and 1% tropicamide drops, and the cornea was anesthetized with proparacaine drops. The subject's head was held in position with a chin rest and forehead bar. Subjects were light adapted to room illumination before testing and were then adapted for 2 minutes to the rod-desensitizing adapting field. ERGs were recorded with a Burian-Allen bipolar contact lens electrode, grounded at the earlobe. Responses were acquired with a signal-averaging system (Viking IV; Nicolet, Madison, WI) that was triggered by a transistor–transistor logic (TTL) signal generated by the signal-processing board and synchronized with the onset of the luminance transient of the sawtooth stimulus. Amplifier bandpass settings were 0.5 to 500 Hz.

ERG recordings were made at stimulus frequencies of 4, 8, 16, and 32 Hz, although the responses to the 8 Hz stimulus are the focus of the present study. Each stimulus was presented continuously, and recordings were begun after the subjects had adapted to the waveform for approximately 30 seconds For each condition, two traces of four sweeps each were obtained to determine reproducibility, and then the two traces were averaged off-line, so that each waveform represented the mean of eight 500-msec recordings.

Statistical Analysis
The results from the patients with XLRS and the control subjects were compared using two-tailed t-tests, with a Bonferroni correction for multiple comparisons. Regression coefficients were based on Pearson correlations. P < 0.05 was considered to be statistically significant.

RESULTS
The ERG responses of a representative control subject to sawtooth flicker are illustrated in Figure 2. This figure presents ERG responses to rapid-on (Fig. 2, left) and rapid-off (Fig. 2, right) sawtooth flicker at four temporal frequencies: 4, 8, 16, and 32 Hz. At the three lower temporal frequencies, there were marked asymmetries between the responses to rapid-on and rapid-off flicker. The ERG response to each cycle of rapid-on flicker was biphasic, consisting of an initial negative trough (a-wave) and a subsequent positive peak (b-wave), similar to the ERG response obtained at the onset of a standard luminance increment.19 There was also a linear ramp between the end of the b-wave and the beginning of the response to the next cycle of the stimulus. The ERG response to each cycle of rapid-off flicker was monophasic, with a single positive peak (d-wave), similar to the ERG response to the offset of a luminance increment.19

At temporal frequencies of 32 Hz and higher, it would be expected that the ERG would be dominated by the response to the stimulus fundamental, because the higher harmonics of the stimulus would evoke relatively little response.31 As a consequence, the ERG responses to rapid-on and rapid-off flicker at 32 Hz should be equivalent but phase-shifted by 180°. This was the case, as is shown in Figure 2. At 32 Hz, the ERG responses to rapid-on and rapid-off flicker had a similar appearance, but the response to rapid-off flicker was displaced by one half cycle. The sawtooth nature of the ERG waveforms at 32 Hz is due to the presence of harmonic components that were generated by retinal nonlinearities.31

In the remainder of the study, the focus of the data analysis was on a stimulus frequency of 8 Hz. The ERG waveforms at this temporal frequency contained four responses per 500-msec recording epoch, which allowed an assessment of response consistency. There was also enough temporal separation between the stimulus cycles (125 msec) to provide adequate expression of the response waveform.

Figure 3 presents the ERG waveforms of the patients with XLRS (Fig. 3, left) and the control subjects (Fig. 3, right) in response to 8-Hz rapid-on sawtooth flicker. All subjects

![Figure 2. ERG waveforms of a representative control subject to rapid-on (left) and rapid-off (right) sawtooth flicker at 4, 8, 16, and 32 Hz (top to bottom in each panel). The stimulus waveform is represented below each ERG response. Arrows: Peaks of a-, b-, and d-waves.](Image)

![Figure 3. ERG waveforms of the patients with XLRS (left) and control subjects (right) in response to 8-Hz rapid-on sawtooth flicker. Dashed lines: Time of stimulus onset; stimulus waveform is illustrated on the x-axis. The waveforms are arranged in order of increasing b-wave amplitude. Numbers next to the waveforms in the left panel refer to the patient designations from Table 1.](Image)
showed biphasic responses to the rapid-on sawtooth stimulus, consisting of a series of a-waves and b-waves, as seen in Figure 2. The waveforms in Figure 3 are arranged from top to bottom in order of increasing b-wave amplitude for both the patients with XLRS and the control subjects (the ERG of the control subject whose responses are shown in Fig. 2 is the fourth tracing from the top in Fig. 3). There was a range of overall response amplitudes for both subject groups. However, by comparison with the control subjects, the patients with XLRS showed an attenuation of the b-wave that was greater than that of the a-wave.

Figure 4 illustrates the ERG waveforms of the patients with XLRS (Fig. 4, left) and control subjects (Fig. 4, right) in response to 8-Hz rapid-off sawtooth flicker. The order of the waveforms is the same as in Figure 3. All subjects showed monophasic responses to the rapid-off sawtooth stimulus, consisting of a series of d-waves, as seen in Figure 2. Of note, the responses of each subject were very consistent across cycles of the rapid-off stimulus, without contamination by the eye movement artifacts that can sometimes obscure the OFF response to long-duration flashes. There was a range of overall response amplitudes for both subject groups. However, by comparison with the control subjects, the patients with XLRS showed an attenuation of the b-wave that was greater than that of the a-wave.

Figure 4 presents the mean implicit times for the patients with XLRS (filled bars) and the control subjects (open bars). Compared with the control subjects, the patients with XLRS had significantly increased implicit times for all three waveform components (a-wave, $t = 4.48, P < 0.001$; b-wave, $t = 6.07, P < 0.001$; d-wave, $t = 3.02, P < 0.01$). There was no relationship between the implicit times and response amplitudes of the patients with XLRS for the a-wave ($r = -0.54, P =$ Implicit times were averaged across the four responses in each waveform.

Figure 5A presents the mean a-, b-, and d-wave amplitudes ($\pm$ SEM) of the patients with XLRS (filled bars) and the control subjects (open bars). The patients with XLRS showed slight reductions in the mean amplitudes of the a-waves and d-waves compared with the control subjects, but the differences were not statistically significant (a-wave, $t = 1.07, P = 0.30$; d-wave, $t = 0.93, P = 0.37$). Only one (patient 6) had an a-wave amplitude that was less than the b-wave of the control subjects, and only two (patients 4 and 6) had d-wave amplitudes that were less than those of the control subjects. However, there was a significant reduction in the mean b-wave amplitude of the patients with XLRS compared with the control subjects ($t = 4.18, P < 0.001$). Four (patients 2, 4, 5, and 6) had b-wave amplitudes that were less than those of the control subjects.

Figure 5B presents the mean explicit times for the patients with XLRS (filled bars) and the control subjects (open bars). Compared with the control subjects, the patients with XLRS had significantly increased explicit times for all three waveform components (a-wave, $t = 4.48, P < 0.001$; b-wave, $t = 6.07, P < 0.001$; d-wave, $t = 3.02, P < 0.01$). There was no relationship between the explicit times and response amplitudes of the patients with XLRS for the a-wave ($r = -0.54, P =$

![Figure 4](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/932898/ on 06/24/2017)

**Figure 4.** ERG waveforms of the patients with XLRS (left) and control subjects (right) in response to 8-Hz rapid-off sawtooth flicker. Designations are as in Figure 3.

![Figure 5](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/932898/ on 06/24/2017)

**Figure 5.** Mean amplitudes (A) and implicit times (B) of the a-, b-, and d-waves of the patients with XLRS and control subjects. Error bars, SEM. *Statistically significant differences ($P < 0.05$).
0.27), b-wave ($r = -0.13$, $P = 0.81$), or d-wave ($r = -0.52$, $P = 0.29$).

A comparison between the b-wave amplitude of the ON response and the d-wave amplitude of the OFF response for each subject is presented in Figure 6. This figure plots log b-wave amplitude as a function of log d-wave amplitude for the individual patients with XLRS (filled symbols) and the control subjects (open symbols). Log amplitudes were used so that proportional changes in amplitude could be evaluated more easily. The patients with XLRS showed a range of response amplitudes. Two (patients 1 and 3) had b-wave and d-wave amplitudes that were within 2 SDs of the mean amplitude of the control subjects (indicated by the dashed lines). The other four (patients 2, 4, 5, and 6) had d-wave amplitudes that were within 2 SDs of the mean amplitude of the control subjects but b-wave amplitudes that were more than 2 SDs below the control mean.

There was a significant correlation between b-wave and d-wave amplitude in both the patients with XLRS ($r = 0.96$, $P < 0.01$) and the control subjects ($r = 0.88$, $P < 0.01$). However, the nature of that relationship differed between the two groups. In the control subjects, the slope of the regression line was less than 1.0, indicating that d-waves were proportionally smaller than b-waves in those control subjects with the smaller overall ERG amplitudes. In the patients with XLRS, however, the slope of the regression line was greater than 1.0, so that the b-wave amplitude was substantially smaller than the d-wave amplitude in those patients with the smaller overall ERG responses.

As a consequence, the b-wave to d-wave amplitude ratio was significantly lower in the patients with XLRS than in the control subjects ($t = 6.16$, $P < 0.001$). This is illustrated in Figure 7, which plots the b-wave to d-wave amplitude ratio in each subject. The b-wave to d-wave ratios of the patients with XLRS were more than 2 SDs below the mean of the control subjects, and there was no overlap between the two groups. In the patients with XLRS, the ratios were all less than 1.0 (indicated by the dashed line), whereas in the control subjects, the ratios were above this value. It is notable that even the patients who had b-wave and d-wave amplitudes that were within the normal range (patients 1 and 5) had reduced b-wave to d-wave ratios.

**DISCUSSION**

The purpose of this study was to determine whether the ON response of the ERG of the cone system is reduced differentially relative to the OFF response in XLRS. The patients with XLRS who were included in this study represented a relatively broad range of b-wave amplitudes of the ON response, from response amplitudes that were within normal limits to amplitudes that were markedly attenuated (Fig. 6). Regardless of the extent of b-wave attenuation, however, all the patients with XLRS showed a reduction in the b-wave to d-wave ratio compared with the control subjects (Fig. 7). The reduced b-wave to d-wave ratios demonstrate that there is a greater deficit in the ON response than in the OFF response of the cone system in XLRS.

For the primate cone system, the initial portion of the b-wave of the ON response represents primarily the activity of depolarizing bipolar cells (DBCs), with the later portion of the b-wave modulated by the response of hyperpolarizing bipolar cells (HBCs). Intravitreal administration of 2-amino-4-phosphonobutyric acid (APB), which blocks the DBC light response, virtually eliminates the b-wave. Therefore, the significantly reduced b-wave to d-wave ratio of the cone system that we observed in these patients with XLRS likely represents a predominant response attenuation within the DBC pathway.
Of note, these patients with XLRS did not show an enhancement of the d-wave that is frequently observed in other forms of retinal disease in which there is a differentially reduced ON response.19 The initial portion of the d-wave of the OFF response represents the activity of HBCs together with the offset of the cone photoreceptor response.32 However, the waveform characteristics are also modulated by the activity of DBCs,32 so that a reduced DBC response would be expected to enhance the amplitude of the d-wave. The absence of an enhanced d-wave, together with the slightly reduced d-wave amplitude observed in two of these patients with XLRS (Fig. 6), suggests that there may be some impairment within the HBC pathway as well as within the DBC pathway.

In addition to an ON-response defect, the patients with XLRS in this study had significantly increased implicit times for all ERG waveform components (Fig. 5B). Increased implicit times of the a-wave and b-wave of the cone system have been noted before in XLRS,9,10 and an increased implicit time of the d-wave was reported recently.34 Based on a recent study,35 it is likely that the increased ERG implicit times of patients with XLRS result from a “sluggish” cone photoreceptor response. According to that study, the frequency-response function of an early linear filter (presumed to represent the cone photoreceptor response) showed a lower corner frequency in patients with XLRS than in control subjects. A lower corner frequency corresponds to a broadened impulse–response function, with a delayed response peak.36 Such a delayed cone photoreceptor response could account not only for the increased implicit time of the a-wave, which represents primarily cone photoreceptor activity,37 but also the prolonged implicit times of the other ERG components that depend on the cone photoreceptor response.

The precise explanation for the ON-pathway defect that we observed in the ERG of the cone system in XLRS remains to be resolved. It is possible that the attenuated b-wave amplitude of the ON response directly reflects dysfunctional DBCs, given current evidence that the b-wave represents the summed activity of DBCs.11,12 An alternative possibility is that the reduced ON response is a consequence of the abnormal cone photoreceptor response described above. Although there are no apparent differences in the response gains of DBCs and HBCs, there are systematic differences in their temporal response properties, as well as differences in their signal transduction mechanisms.38 Therefore, it is conceivable that an abnormal cone photoreceptor input could have a differential effect on the response properties of the two bipolar cell types, so that there is an apparently greater response deficit within the DBC pathway.

It is also possible that the ON-response deficit in XLRS is a secondary effect of Müller cell dysfunction on the DBC pathway. As noted in the Introduction, histologic studies have reported evidence of abnormal Müller cells in XLRS.22–4 Müller cells have an important role in maintaining the homeostasis of extracellular glutamate and potassium levels (reviewed by Reference 39). It has been proposed that the golden-white fundus sheen that has been observed in some patients with XLRS,28,29 and was apparent in one of our patients (patient 6), results from an abnormal accumulation of extracellular potassium.39 Changes in extracellular potassium levels can influence neuronal responses, and high levels of glutamate are potentially toxic to neural elements.39 Therefore, the relatively greater attenuation of the b-wave of the ON response in XLRS may represent a greater susceptibility of DBCs to abnormalities in the extracellular environment, in which Müller cell dysfunction may play a role.

The relationship between the abnormal ON response of the ERG of the cone system in XLRS and mutations in the XLRS1 gene remains to be identified. As noted in the Introduction, the XLRS1 gene is expressed primarily in photoreceptor cells.13–15 The gene product is a protein (retinoschisin) that is secreted by the photoreceptors and is involved in cell–cell interactions, particularly within the inner retina and probably including Müller cells.15 This protein has also been reported to be associated with photoreceptor and cone bipolar cell membranes.14 Thus, there are a number of candidate mechanisms by which mutations in a gene that is expressed in photoreceptors could affect the ON response of the cone system ERG in XLRS.

An ON-response defect of the cone system has been observed in several other forms of retinal disorders in which, as in XLRS, the brief-flash ERG of both rod and cone systems shows a reduced b-wave to a-wave ratio.16–19 It has been proposed that an overall impairment in the response properties of DBCs could account not only for the relative attenuation of the b-wave of the cone system in these disorders, but also for the b-wave attenuation of the rod system,17,18,21 because the primary rod pathway involves signal transmission through rod bipolar cells, which are of the depolarizing type.40 A similar explanation may account for the relative attenuation of the b-wave that has been observed for both rod and cone systems in XLRS.5–10 However, there are important differences between XLRS and these other disorders that show an ON-response deficit. For example, the b-wave attenuation of rod and cone systems is not as severe in patients with XLRS as it is in patients with other disorders, such as CSNB and MAR.18 Further, in contrast to patients with these other disorders, patients with XLRS typically have normal or near-normal rod-mediated absolute thresholds,6,8 despite the moderately attenuated rod b-wave amplitude and a markedly reduced scotopic threshold response.6 Therefore, the relationship between the abnormal ERG responses of the rod system and the ON-response deficit of the cone system in XLRS requires further clarification.

Sawtooth flicker was used as a stimulus for eliciting ERG ON and OFF responses in the present study, with the goal of minimizing the potential eye movement artifacts that can particularly affect the ERG OFF response to long-duration flashes.21,22 The sawtooth stimulus was successful in this regard. The ON and OFF responses elicited by sawtooth flicker showed good intrasubject consistency across stimulus cycles. This stimulus also has several properties that are potentially useful in assessing the characteristics of the ERG ON and OFF responses. For example, sawtooth flicker has the same time-average luminance for both increments and decrements, so that an equivalent adaptation state is maintained for each. The temporal frequency of the stimulus can be varied to assess the frequency–response characteristics of ON and OFF responses. The two waveforms are inversely related but otherwise identical, so that differences in the ERG responses to the two stimuli can be used to investigate retinal nonlinearities. Thus, sawtooth flicker may be of value in quantitative studies of ERG ON and OFF responses in various forms of retinal disease.

In summary, the patients with XLRS in this study showed an attenuation of the b-wave of the ON response of the cone system that was greater than the attenuation of the d-wave of the OFF response, regardless of overall ERG amplitude. This finding indicates that there is a relatively greater impairment within the DBC pathway than within the HBC pathway. The precise explanations for the attenuated ON response in XLRS and the relationship to mutations in the XLRS1 gene remain to be determined.

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References


