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Amplitude Decrease of Photopic ERG b-Wave at Higher Stimulus Intensities in Humans

Mineo Kondo, Chang-Hua Piao, Atsuhiro Tanikawa, Masayuki Horiguchi, Hiroko Terasaki and Yozo Miyake

Department of Ophthalmology, Nagoya University School of Medicine, Nagoya, Japan

Purpose: The b-wave of the human photopic electroretinogram (ERG) elicited by a short-flash increases in amplitude with increasing stimulus intensities at lower stimulus levels, but then decreases at higher stimulus intensities. The purpose of the present study was to explore this phenomenon in more detail, using short- and long-flash stimuli.

Methods: The intensity-response functions of the b-wave elicited by short- and long-flashes were compared from threshold to higher stimulus intensities in 5 normal subjects. Short- and long-flash ERGs were elicited under rod-saturating background levels using white light-emitting diodes built into a contact lens electrode.

Results: Whereas the amplitude of the short-flash b-wave decreased at higher intensities, the amplitude of the long-flash ERG b-wave did not decrease but plateaued. The long-flash ERG d-wave or OFF-response decreased at higher stimulus levels as did the short-flash elicited b-wave.

Conclusions: Because it is widely accepted that the b-wave and the OFF-response d-wave interact to produce a single positive response, our results suggest that the decrease in the b-wave amplitude at high stimulus intensity is caused by the decrease of the d-wave at the higher stimulus intensities. **Jpn J Ophthalmol 2000;44:20–28** © 2000 Japanese Ophthalmological Society

Key Words: D-wave, electroretinogram, light-emitting diode, off-response, photopic hill.

Introduction

The photopic b-wave of the electroretinogram (ERG), elicited by a short-flash stimulus under rod-saturating background illumination, is used clinically to assess the human cone system. It has been reported that the amplitude of the photopic b-wave increases according to a log tanh function, or the Naka-Rushton equation, at the lower stimulus intensity levels.[1,2] At still higher stimulus intensities, the amplitude of the photopic b-wave does not continue to increase but instead decreases. This unusual property of the human photopic b-wave was first described briefly by Peachey et al,[2] and confirmed by Wali and Leguire.[3] The latter used a high-intensity photographic flash unit and reported that the photopic b-wave amplitude increased at lower stimulus levels. At higher luminance levels (>0.8 cd-s/m^2), the b-wave decreased as described by Peachey et al.[1,2] At still higher intensities, the amplitude of the b-wave plateaued at the lower values. Because a plot of the b-wave amplitude as a function of the stimulus intensity has an inverted "U" shape, this phenomenon has been named the "photopic hill." After these descriptions, there have been no further reports about this phenomenon and the exact mechanism for this unusual function has not been determined.

In the present study, we examined two aspects of this phenomenon. First, we tested to see if other ERG components demonstrate an amplitude decrease at higher stimulus intensities, because previous studies have focused only on the b-wave. Second, we explored this phenomenon using not only short-flashes, but also long-flash stimuli to separate the ON- and OFF-responses. The earlier studies used only short-flash stimuli, and the ON-response and the

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Correspondence and reprint requests to: Mineo KONDO, MD, Department of Ophthalmology, Nagoya University School of Medicine, 65 Tsuruma-cho, Showa-ku, Nagoya 466, Japan

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OFF-response could not be analyzed separately.[4–8] Photopic ERGs, elicited by short- and long-duration stimuli, were recorded from 5 normal subjects. We shall show that this "photopic hill" phenomenon was obtained with the short-flash stimuli but not with the long-flash stimuli. In addition, we shall show that reducing the duration of the long-flash stimulus leads to the "summation" of the b- and d-waves at the short stimulus durations. We suggest that the increase in the b-wave amplitude elicited by the short-flash of high stimulus intensities results from the summation of the b- and d-waves, and that the decrease of the b-wave at very high stimulus intensities is due to the decrease in the d-wave amplitude (rapid OFF-response) at these higher stimulus levels.

Materials and Methods

Subjects

Five healthy Japanese men aged 27 to 34 served as subjects. Except for refractive errors of −1.00 to −5.00 diopters, no ophthalmologic or neurologic abnormalities were present. Informed consent was obtained after a full explanation of the procedures. All procedures were conducted in accordance with the principles embodied in the Declaration of Helsinki.

Stimulus

To obtain high stimulus intensities not only for short-flash stimuli but also for long-flash stimuli, we used a contact lens electrode with built-in light-emitting diodes (LEDs). We have previously reported on the clinical application of red and blue LED built-in contact lens electrodes for recording full-field ERGs.[9–11] In the present study, a newly developed, high-intensity, white LED (Nichia, Tokushima) was used. Three of the white LEDs were incorporated into the contact lens electrode and they served as the source for the stimulus and the background. Stimulus duration, stimulus intensity, and background intensity were controlled by the electrical current delivered to the LEDs by a specially designed LED-driver (Tomey, Nagoya). The electrode contained a white diffuser beneath the LEDs, which produced a homogeneous stimulus and background illumination. Maximal stimulus intensities were 3.9 and 3.5 log cd/m^2 at the cornea for a stimulus duration of 5 ms (short-flash) and a stimulus duration of 250 ms (long-flash), respectively. The stimulus intensity was increased in steps of 0.3–0.5 log units. The luminance of the background light was 40 cd/m^2, which has been reported to be sufficient to desensitize rods.[12]

Recording and Analysis

The pupil of the test eye was fully dilated with a combination of 0.5% tropicamide and 0.5% phenylephrine hydrochloride. The cornea was anesthetized by topical 0.4% oxybuprocaine hydrochloride before the contact lens electrode was inserted. The reference and ground electrodes were attached to the forehead and earlobe, respectively. The signals were amplified with a bandpass between 1.5 and 300 Hz (MEG-1200; Nihon Kohden, Tokyo). To minimize the adaptational effect of the stimulus, a minimum number of responses (two to eight) were averaged with a relatively long interstimulus interval of 2 to 10 seconds (Mac Lab; AD Instruments, Castle Hill, Australia).

Results

Representative photopic ERGs elicited by a short-flash (5 milliseconds, Figure 1A) and a long-flash (250 milliseconds, Figure 1B) of 2.7 log cd/m^2 under a constant background of 40 cd/m^2 are shown in Figure 1. The a-wave was measured from the baseline to

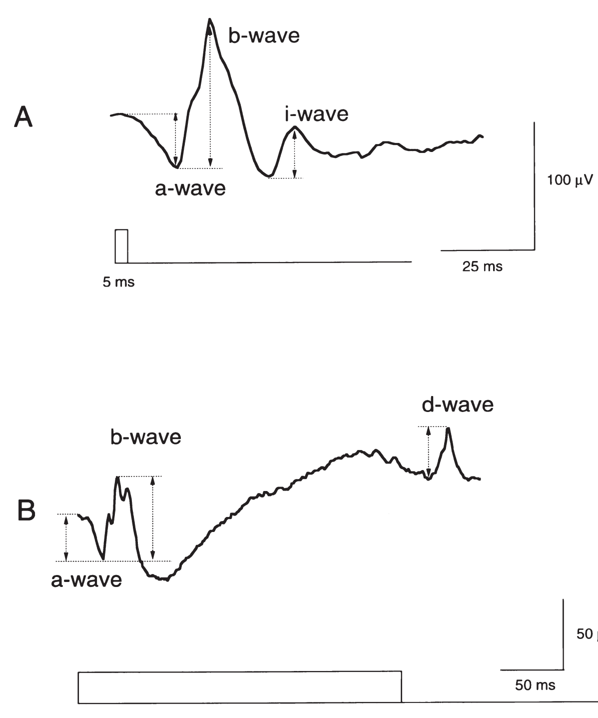

Figure 1. Photopic electroretinograms recorded in response to short-flash (stimulus duration 5 milliseconds, **A**) and long-flash (stimulus duration 250 milliseconds, **B**) stimuli of 2.7 log cd/m^2 under constant background illumination of 40 cd/m^2. Vertical lines with arrowheads indicate where amplitudes of a-, b-, i-, and d-waves were measured.

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maximum initial negativity, the b-wave was measured from the first trough to the positive peak, and the i-wave was measured from the negative trough following the b-wave to the next positive peak. The d-wave was measured from the potential level just before the rapid positive peak.

Short-Flash Stimuli

Initially, we examined the photopic hill phenomenon using short-flash stimuli. Figure 2 shows the photopic, short-flash (stimulus duration = 5 milliseconds) ERGs elicited by increasing stimulus intensities and recorded from one of the normal subjects. At the lower stimulus levels, the amplitude of the short-flash b-wave increased with increasing stimulus intensities until it reached a maximum at a stimulus intensity of 3.0 log cd/m^2 (=0.70 log cd-s/m^2). Further increases in the stimulus intensity led to a progressive decrease in the amplitude of the b-wave. These findings agree with past reports,[2,3] and the stimulus intensity, which elicited the maximal b-wave amplitude, 3.0 log cd/m^2 (=0.70 log cd-s/m^2) was approximately the same as the value reported earlier.[3] The b-wave amplitude did not decrease and reached a plateau as described by Wali and Leguire[3] presumably because the maximum stimulus intensity in our system (1.6 log cd-s/m^2) was approximately 1.7 log units lower than their maximum intensity (3.3 log cd-s/m^2).

The mean ± standard error of the mean (SEM) of each component obtained from the 5 subjects is plotted in Figures 3A and 3B. As noted in the ERGs in Figure 2, the mean b-wave increased at the lower stimulus intensities, reached a maximum, and then decreased as the stimulus intensity was increased. The implicit times for the photopic b-wave remained unchanged from threshold to 1.9 log cd/m^2, and then increased (Figures 2 and 3B), confirming the results of the earlier studies.[2,3,7,13] The vertical dashed line in Figure 2 is drawn at 32 milliseconds and is helpful in illustrating how the implicit time varies with the stimulus intensity.

The i-wave of the short-flash ERG also showed a photopic hill. The amplitude of the wave increased up to a stimulus intensity of 2.7 log cd/m^2 (=0.40 log cd-s/m^2), nearly the same intensity as that for the b-wave, and then decreased at higher stimulus intensities. The implicit time of the i-wave also increased with increasing stimulus intensity as did the implicit time of the b-wave (Figure 3B).

The amplitude of the short-flash a-wave did not show the photopic hill phenomenon and continued to increase with increasing stimulus intensity up to the maximal stimulus intensity (Figure 3A). The implicit time of the a-wave, unlike the b-wave, decreased with increasing stimulus intensity up to the maximal stimulus intensity.

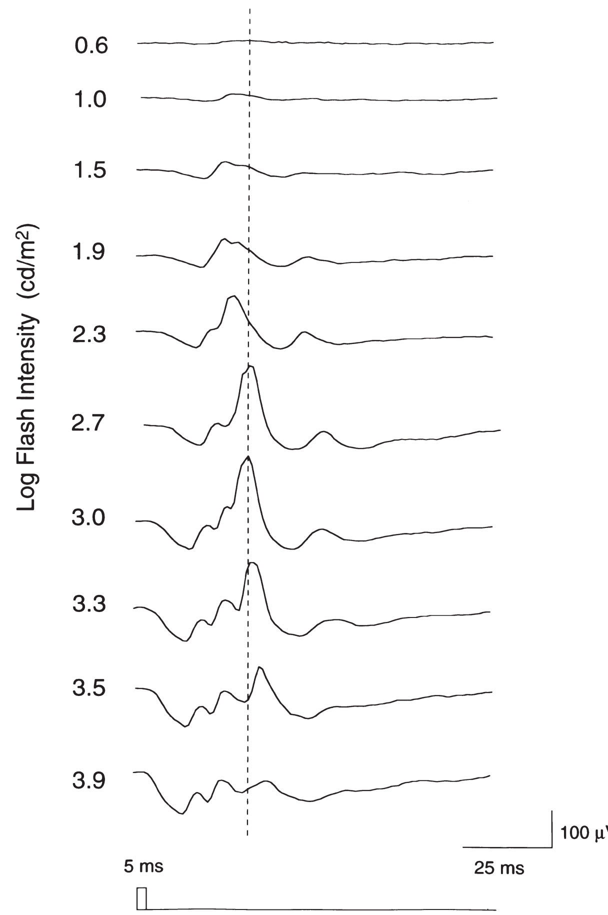

Figure 2. Photopic short-flash electroretinograms elicited from normal subjects by different stimulus intensities. Stimulus duration was 5 milliseconds and constant background illumination was 40 cd/m^2. Vertical dashed line indicates 32 milliseconds.

Long-Flash Stimuli

After the short-flash series, we studied this phenomenon using long-flash stimuli. Because the amplitude of the d-wave or rapid OFF-response is important for our analysis, we selected a stimulus duration that would elicit a large d-wave. It has been reported that the amplitude of the d-wave becomes larger as the flash duration becomes longer and reaches a maximum amplitude at approximately 150–200 milliseconds. Even longer stimulus dura-

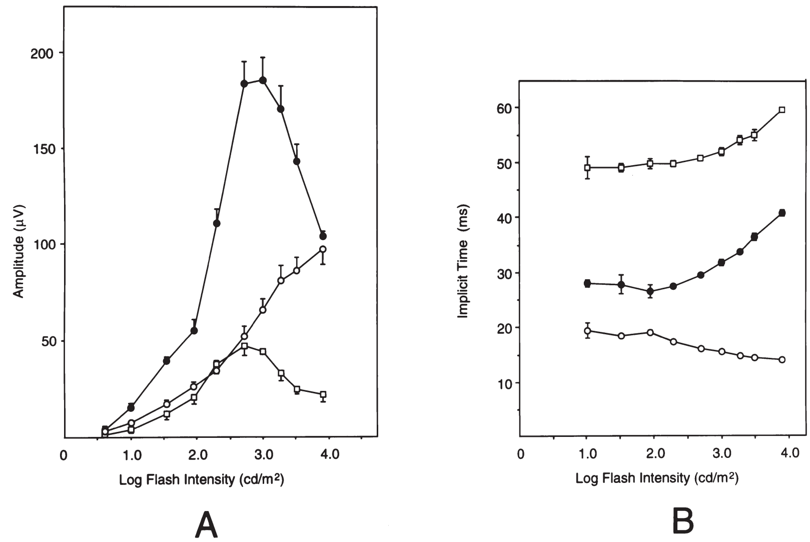

Figure 3. Intensity-amplitude (**A**) and intensity-timing (**B**) curves for the a-, b-, and i-waves in response to short-flash of 5 milliseconds under constant background illumination of 40 cd/m^2. Data points represent mean ± SEM for 5 subjects. ○, a-wave; ●, b-wave; □, i-wave.

tions do not increase the amplitude of the d-wave significantly.[14,15] We, therefore, selected a stimulus duration of 250 milliseconds for our long-flash stimuli.

Figure 4 shows an intensity-response series for photopic long-flash ERGs recorded from the same subject whose ERGs are shown in Figure 2. As with the b-wave elicited by the short-flash stimuli, the amplitude of the long flash b-waves increased with increasing stimulus intensities up to 2.7 log cd/m^2. With further increases in intensity, the b-wave did not decrease as significantly as the b-wave elicited by short-flash stimuli but remained at approximately the same amplitude, ie, the b-wave amplitude plateaued. The i-wave was not observed with the long-duration stimuli.

Figures 5A and 5B show the intensity-amplitude and intensity-timing function for the a-wave, b-wave, and d-wave elicited by 250-millisecond-duration stimuli. The mean ± SEM of the amplitude for each component obtained from the 5 subjects is plotted in Figure 5A. As observed in the individual ERGs, the mean amplitude of the long-flash b-wave increased with increasing stimulus intensities up to 2.7 log cd/m^2; with further increasing stimulus intensity, the b-wave did not decrease but plateaued. Thus, the photopic hill was not observed in the long-flash b-waves. The implicit time of the long-flash b-wave did not change significantly with increasing stimulus intensity, which is also different from the short-flash ERG b-wave.

In contrast to the b-wave, the d-wave (= rapid OFF-response) decreased at higher stimulus levels (Figure 5A). The stimulus intensity that elicited the maximal d-wave amplitude was 2.7 log cd/m^2. This is approximately the same intensity that elicited maximal b- and i-waves with the short-flash stimuli. The implicit time for the d-wave increased with increasing stimulus intensities at the higher stimulus levels as did the b-wave implicit times elicited by short-flash stimuli. At the higher stimulus intensities, the amplitude of the d-wave decreased and another slow positive component (Figure 4, asterisks) appeared and increased gradually in amplitude and timing, and dominated the OFF-response.

The long-flash a-wave showed a pattern similar to that of the short-flash ERG a-wave; the amplitude of the a-wave continued to increase for the full intensity range, and the implicit time decreased for the full range of stimuli.

Effect of Stimulus Duration on Photopic Hill

We shall argue that the photopic hill seen in the short-flash ERGs results from the “summation” of the b-wave and the d-wave. If this is correct, we should be able to show the development of the photopic hill by reducing a long-duration stimulus to a short-duration stimulus in fixed steps. The ERGs elicited by three different stimulus intensities whose duration was reduced from 250 to 5 milliseconds in six steps are shown in Figure 6. At 2.7 log cd/m^2, the ERGs elicited by the 250-millisecond duration stimulus consisted of a small b-wave and a large positive d-wave (see also Figure 4). As the stimulus duration was shortened, the d-wave moved progressively closer to the b-wave and was seen as a separate wave with the 50-millisecond duration stimulus. Over this range of durations, the amplitude of the b-wave amplitude did not change significantly. Reducing the

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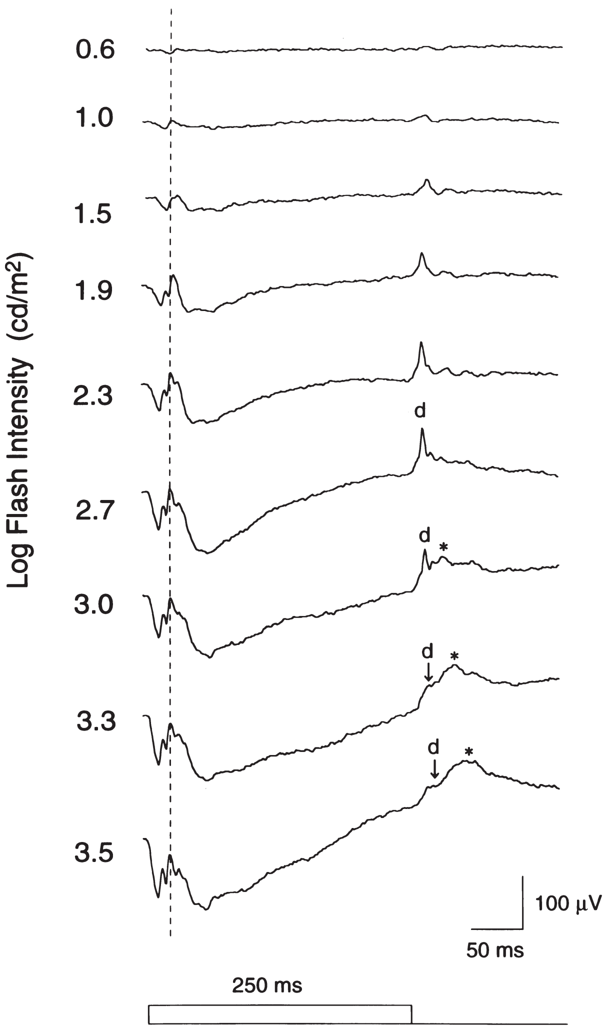

Figure 4. Photopic long-flash electroretinogram (ERG) elicited by different stimulus intensities and recorded from the same subject whose ERGs are shown in Figure 2. Stimulus duration was 250 milliseconds and background illumination was 40 cd/m^2. Vertical dashed line indicates 30 milliseconds. At the higher stimulus intensities, the amplitude of the d-wave decreased and another slow positive component (asterisks) dominated the OFF-response.

duration from 25 to 10 milliseconds led to a 2.7-fold increase in the amplitude of the b-wave, and a further decrease to 5 milliseconds increased the amplitude of the b-wave another step. The i-wave was not present in the ERGs until the stimulus duration was 10 and 5 milliseconds.

With a weaker stimulus (1.9 log cd/m^2), the d-wave was still present but significantly smaller. As with the higher stimulus intensity, reducing the stimulus duration moved the d-wave closer to the b-wave, and at 10 milliseconds, there was a sudden 1.6-fold increase in the amplitude of the b-wave. Thus, the same pattern of change was seen in the amplitude of the b-wave at this stimulus intensity. With the higher stimulus intensity (3.5 log cd/m^2), a small d-wave was elicited with the 250-millisecond stimulus. The same pattern of changes was also observed at this intensity but the enhancement did not occur until the stimulus duration was 5 milliseconds. The increase was only 1.9-fold.

Reading horizontally across Figure 6, as stimulus intensities increase, the b-wave amplitude is maximal at 2.7 cd/m^2 for the 5- and 10-millisecond-duration stimuli, and is less for the lower and higher stimulus intensities, ie, a photopic hill is present. With longer stimulus durations, the photopic hill was not present.

Computer-Constructed Photopic Hill

The question then arises whether this photopic hill phenomenon represents a simple algebraic summation of the b-wave and the d-wave. To answer this question, we took the ERGs elicited by the 250-millisecond-duration stimulus for different stimulus intensities as shown in Figure 4 and "cut off" the d-wave at stimulus offset. This segment was then "pasted" into another file with the beginning of the segments (light offset) placed 5 milliseconds after light onset. The computer was then instructed to add these two files, ie, the ON-response and the OFF-response, with the OFF-response delayed by 5 milliseconds.

The results of this procedure are shown in Figure 7. For comparison, the actual flash-produced short-flash ERGs are shown by dashed lines (see also Figure 2). As in the actual flash-produced short-flash ERGs, there was an increase in the b-wave with increasing stimulus intensities until 2.7–3.0 log cd/m^2, in the constructed ERGs. With still higher stimulus intensities there was a decrease in the b-wave as also noted with the flash-produced ERGs. Thus, these constructed short-flash ERGs showed the photopic hill with the largest b-wave elicited by 2.7–3.0 cd/m^2. However, a careful examination of the shapes of the ERGs and a comparison with the ERGs shown in Figure 2 show that there are differences in their shape and that the constructed ERG b-wave was consistently smaller in amplitude than the flash produced short-flash b-wave.

Discussion

Our results clearly demonstrated that there is a different intensity-amplitude function for short-flash and long-flash b-waves, especially at the higher stimulus level; the short-flash b-wave decreased at higher

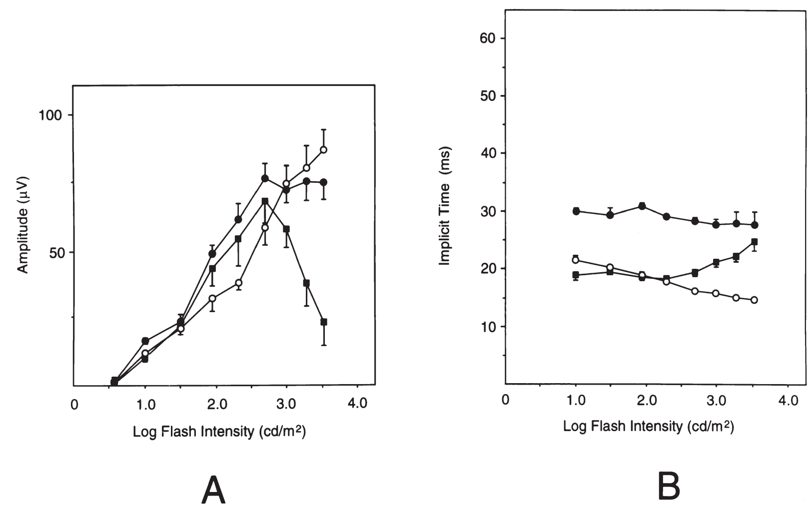

Figure 5. Intensity-amplitude (**A**) and intensity-timing (**B**) curves for the a-, b-, and d-waves in response to long-flash of 250-millisecond duration under constant background illumination of 40 cd/m^2. Data points represent mean ± SEM for 5 subjects. ○, a-wave; ●, b-wave; □, d-wave.

stimulus intensities showing a photopic hill, whereas the long-flash ERG b-wave did not decrease but plateaued. The d-wave of the long-flash ERGs, on the other hand, also demonstrated a distinct photopic hill. There is good evidence that with short flash stimuli, the ON- and OFF-response components interact to produce a single response, which is called the b-wave.[4–8] Our results with different stimulus durations (Figure 6) provide further evidence that this occurs. We showed that the enhancement of the b-wave was proportional to the amplitude of the d-wave elicited by a long duration stimulus. However, the summation was not a simple algebraic addition as shown in Figure 7, where the computer was used to summate the ON b-wave and the OFF d-wave. While these constructed short-flash ERGs showed a photopic hill, the shape of the constructed ERGs differed from the flash-produced short-flash ERGs. In addition, the constructed ERG b-wave was consistently smaller in amplitude than the light evoked short-flash b-wave. Similar results have been reported by Seiple and Holopigian.[15] We can conclude that, as a first approximation, the photopic hill phenomenon results from the summation of the ON b-wave and the OFF d-wave, but there are probably other components that are determining the final shape and amplitude of the short-flash ERG.

Our results also demonstrated that there was a different intensity-timing function for short-flash and long-flash ERG b-waves especially at the higher

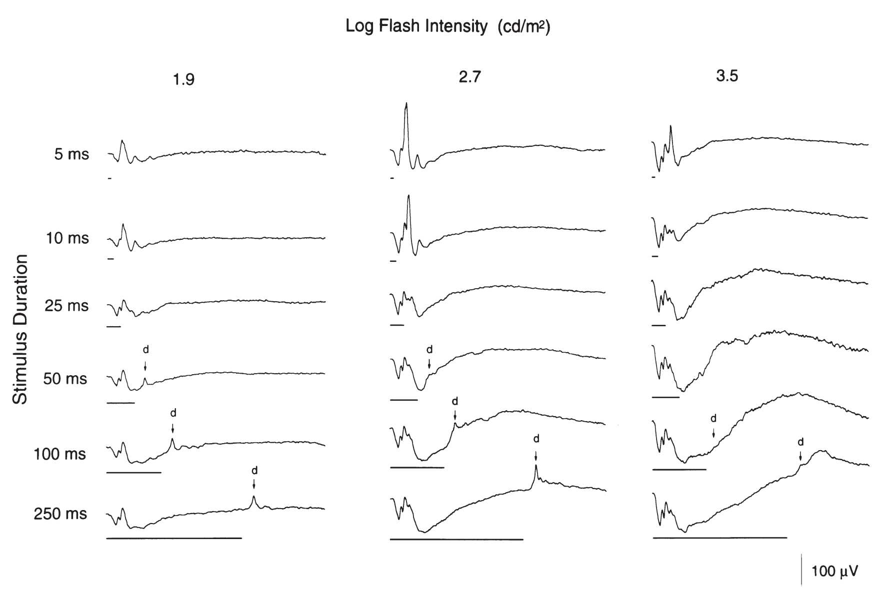

Figure 6. Photopic electroretinograms (ERGs) elicited by three stimulus intensities for different stimulus durations. Numbers above each column represent stimulus intensity. Horizontal line beneath each ERG is the stimulus marker.

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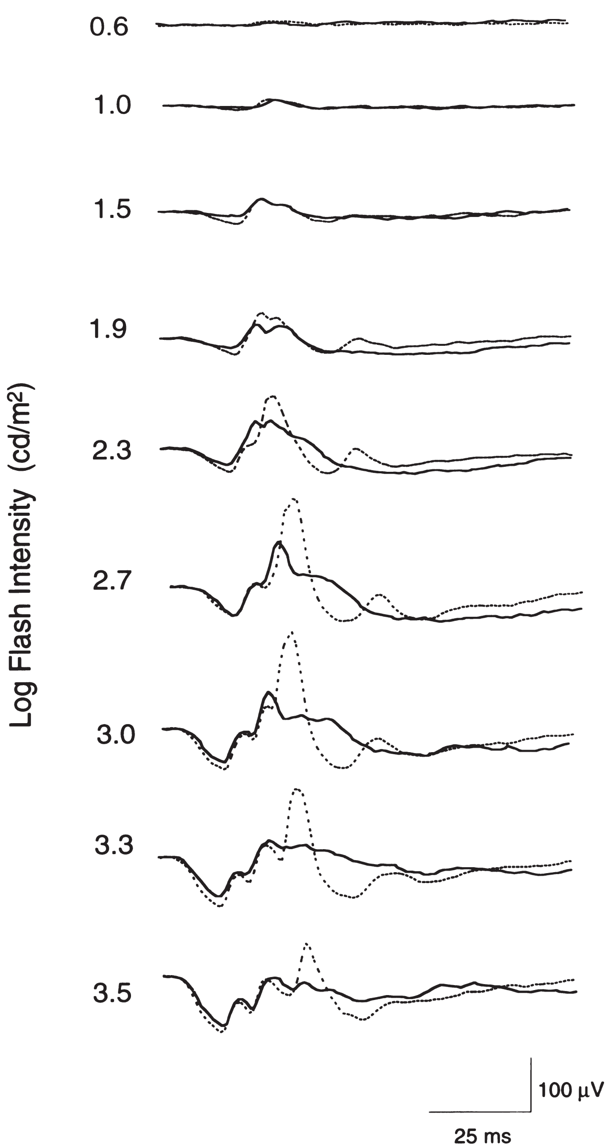

Figure 7. Computer-constructed short-flash electroretinograms (ERGs). From ERGs elicited by 250-millisecond duration stimulus of different intensities (as in Figure 4), OFF d-wave was "cut" at light offset. This segment was then "pasted" into another file with beginning of segments (light offset) placed 5 milliseconds after light onset. The computer was then instructed to add these two files. For comparison, flash-produced short-flash ERGs are shown by dotted lines (see also Figure 2).

stimulus levels; the implicit times for the short-flash b-waves increased with increasing stimulus intensity, confirming earlier results,[2,3,7,13] while that of long flash b-waves did not change significantly. The implicit times for the long-flash d-waves, on the other hand, increased with increasing stimulus intensity, which is similar to that of the short-flash b-waves. Taken together, these results support the previously presented suggestion that the d-wave plays a major role in shaping the main positive peak of the short-flash ERGs.[7,8,16]

The question then arises as to why the amplitude of the long-flash d-wave decreases at the higher stimulus intensities. The exact mechanism responsible for this phenomenon is not easy to determine because the cellular origin of the primate d-wave is not well-understood. Intraretinal analysis of the monkey d-wave,[17] and the subsequent studies by Yonemura and Kawasaki[18] indicated that the d-wave is produced mainly by the rapid offset (or decay) of the cone late receptor potential. However, recent reports using pharmacological agents have produced evidence that the primate d-wave does not have a single cellular origin but has contributions from multiple sources. The positive deflection of the primate d-wave appears to be shaped mainly by the cone photoreceptors and the hyperpolarizing OFF-bipolar cells.[19] Additionally, the depolarizing ON-bipolar cells can limit the amplitude of the d-wave.[14,20] One possible explanation for the d-wave decrease at higher stimulus levels is, therefore, a change in the relative balance of electrical activities from these different components. To determine the exact mechanism for the decrease will require further studies of the intensity-response function of the d-wave at higher stimulus intensities in the primate retina treated with various pharmacological agents. One might also speculate that the high-intensity and long-duration flashes used in our study can change the adaptational level considerably, thereby causing a decrease of the d-wave. This possibility, however, is thought to be small because it is well-known that light adaptation leads to an increase of amplitude in the d-wave.[5,15]

We have also noted another slow positive component (Figure 4, asterisk) following the rapid d-wave that appeared at the higher stimulus levels. At the higher stimulus intensities, the rapid d-wave decreased and this slow positive wave dominated the OFF-response. This slow component partly resembles the "slow component of the OFF-response" described by Brown[17] and Kawasaki et al,[21] although the time course of their "slow component of the OFF-response" is considerably slower than our "slow OFF-response." Whereas they concluded that the "slow component of OFF-response" represented a decay in the late receptor potential of rod photoreceptors, our results show that a similar component was recorded under rod desensitizing conditions. To date, we cannot determine whether our "slow OFF-response" elicited by higher stimulus levels is the same as their "slow decay of the OFF-response."

Our results also revealed that the i-wave recorded with short-flash stimuli also decreased at higher stimulus intensities. As shown in Figures 2 and 3, both intensity-amplitude and intensity-timing functions of the i-wave were very similar to those of the d-wave. These findings support the hypothesis that the i-wave of the short-flash ERG represents part of the d-wave (rapid OFF-response). Nagata,[6] who first described this component, stated that the i-wave is a remnant of the OFF-response. Subsequent studies[2,22] also supported this suggestion although this interpretation still remains controversial.[23]

Finally, our results provide useful information concerning optimum recording conditions for photopic long-flash ERGs. Long-duration stimuli have been reported to be suitable for dissecting the contribution of the cone photoreceptors and the cone ON- and OFF-pathways of the primate photopic ERG.[14,19,20] Clinical application of the long-duration stimuli for some retinal diseases has also been reported.[14,24–27] However, the stimulus conditions have not been standardized. The present results showed that too strong stimuli may not be suitable for clinical photopic long-flash ERG because the d-wave amplitude decreases. The optimum stimulus intensity for photopic long-flash ERG, therefore, should be between 1.5–3.0 log cd/m^2.

In conclusion, our results indicated that the photopic hill phenomenon of the short-flash ERG b-wave was related to the amplitude decrease of the d-wave at higher stimulus levels. Although the exact mechanism of d-wave amplitude decrease at higher stimulus levels still remains obscure, our results have contributed to the understanding of this unique phenomenon. In addition, our results suggest that very strong stimuli may not be suitable for clinical photopic long-flash ERG recordings.

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