ELSEVIER

The a-Wave Latency in Control Subjects and Patients with Retinal Diseases

D. I. Hamasaki*, Mu Liu*, Hui Qiu†, Eriko Fujiwara‡ and Byron L. Lam*

*Bascom Palmer Eye Institute, University of Miami, School of Medicine, Miami, FL, USA;
†Department of Ophthalmology, Hamamatsu University Medical School, Hamamatsu, Japan;
‡Department of Ophthalmology, Fukuoka University School of Medicine, Fukuoka, Japan

Purpose: To determine the a-wave latency of the electroretinograms (ERGs) recorded from control subjects and patients with retinal diseases.

Methods: The a-wave latency and implicit time (IT) were measured retrospectively from the ERGs of 40 control subjects and 99 patients. The patients included 9 with complete congenital stationary night blindness (cCSNB), 13 with achromatopsia or cone dystrophy, 5 with supernormal and delayed rod ERG syndrome, and 72 with retinitis pigmentosa (RP). To assess whether latency measurements can be obtained reliably by different observers from patients with smaller a-wave amplitudes and noisier baselines, the a-wave latency and IT of the ERG of the right eye of 10 control subjects and 10 patients with RP were measured by three observers.

Results: The mean a-wave latency measured for the same 10 control ERGs by three observers differed by less than 1 millisecond while the mean IT differed by 1.7 milliseconds. For 10 ERGs from RP patients, the mean for the a-wave latency measured by the three observers differed by less than 2.0 milliseconds and by 1.1 millisecond for the IT. The coefficient of variation varied from 24.8% to 36.7% for the latency and from 11.5% to 16.0% for the IT. The a-wave latencies elicited by the 0-dB stimulus under scotopic and photopic conditions from the 40 control subjects were not statistically different. The a-wave latency in patients with cCSNB did not differ significantly from that in control subjects. The longer a-wave latency in patients with achromatopsia suggested that the rods have a longer latency than cones. The scotopic and photopic a-wave latencies were significantly longer in RP patients. The longer latency in RP patients was not due to smaller a- or b-wave amplitudes.

Conclusions: The a-wave latency can be measured as reliably as the IT in control subjects but the reliability is not as good for the latency as for the IT in RP patients. The larger coefficients of variation in RP patients were most likely due to the measurements being made from RP patients at different stages of their disease. Our results suggest that the a-wave latency in control subjects is determined by cones under both scotopic and photopic conditions. The longer a-wave latency in RP patients suggests that the rods and cones are altered over a significant area of the retina. **Jpn J Ophthalmol 2002;46:433–442**

Key Words: Achromatopsia, a-wave latency, complete congenital stationary night blindness, implicit time, retinitis pigmentosa.

Introduction

The implicit times (ITs) of the a- and b-waves of the electroretinogram (ERG) are used to evaluate the time course of the ERG in humans and laboratory animals. The IT is defined as the time between stimulus onset and the peak of the response. Because of the confounding effects of the a- and b-waves, the physiological significance of the IT is not known.[1]

Historically, the time course of the ERG was assessed by measuring the latency of the a-wave where the latency is defined as the time between stimulus onset to the beginning, as opposed to the peak, of

Received: July 23, 2001
Correspondence and reprint requests to: D. I. HAMASAKI, PhD, Bascom Palmer Eye Institute, University of Miami, School of Medicine, Miami, FL 33136, USA

Published by Elsevier Science Inc.
0021-5155/02/$–see front matter
PII S0021-5155(02)00504-X

Jpn J Ophthalmol
Vol 46: 433–442, 2002

the response.[2] The selection of the latency of the a-wave was based on similar neurophysiological measurements of the latency of a response, eg, the compound nerve action potentials, muscular contractions, and other evoked potential changes.[3]

Although the latency was measured and used in the early ERG studies on animals,[2] only the IT has been used from the very early days of clinical electroretinography. Thus, Karpe, in his 1945 monograph on clinical electroretinography, reported measurements of the IT (although he called it the latency, his Figure 11 clearly shows that he measured the IT) in a large number of control subjects.[4] However, he had great difficulties as about one-half of the ERGs did not show an a-wave, and the resolution of his recording system was ± 10 milliseconds. Jacobson in 1961[5] and Krill in 1971[1] stated that it was important to measure the time course of the ERG and recommended that the IT be measured. However, Krill did caution the clinician about the confounding effects of the a- and b-waves on the IT. In the most recent textbook of clinical electroretinography,[6] the latency of the a-wave is not mentioned at all.

The reason for the switch from the latency to the IT has not been stated. However, one reason put forth is that more reliable measurements of the IT can be made because the peak of a response is easier to select than the slower potential changes at the beginning of a response. Whether more reliable measurements can be made of the IT than of the latency has not been tested.

The purpose of this study was to determine whether the a-wave latency can be determined reliably from the ERGs of control subjects and patients with reduced a-wave amplitudes. We also determined whether the a-wave latency provides additional information on the pathophysiology of retinal diseases.

Materials and Methods

Control Subjects

The latency and IT of the a- and b-waves were measured retrospectively from the ERGs recorded from both eyes of 40 subjects who did not have any ophthalmological or neurological diseases. There were 20 men and 20 women, and their ages ranged from 15–65 years with a mean ± SD of 34.2 ± 12.3 years. All of the subjects had a visual acuity of 20/20 or better. A signed informed consent was obtained from all these control subjects after an explanation of the purpose of the study. The ERGs were stored in a computer file and were recalled to make the measurements off-line. These ERG findings were compared to the ERG findings in the 20 normal subjects reported by Jacobi et al,[7] who also used the LKC system for their recordings, as we did.

Patients

The ERGs of 99 patients with different types of retinal diseases were examined retrospectively. The diagnosis for the retinal diseases was made from the clinical findings and the ERGs. The number and types of retinal diseases will be presented with the results.

ERG Recordings

The ERGs were recorded simultaneously from both eyes with bipolar Burian-Allen contact lens electrodes. The ground electrode was placed on the right earlobe. The LKC 2000 system (LKC Technologies, Gaithersburg, MD, USA) was used to deliver and control the stimulus intensity and to record the ERGs. The bandpass of the recording system was set from 0.3–500 Hz. A sampling rate of 2000 samples/s with an analysis time of 250 milliseconds was used. The luminance of the stimulus was 2.35 cd/m^2 per second, and the stroboscopic flash was presented as a Ganzfeld stimulus. The recordings and stimulus intensities conformed to the standards recommended by the International Society of Clinical Electrophysiology of Vision (ISCEV).[8]

The dark-adapted 24-dB rod response, the dark-adapted mixed rod-cone response (0 dB), and the light-adapted single flash cone response (0 dB) and 30-Hz flicker responses presented on a 29.2 cd/m^2 background were recorded from all controls and patients.

The procedure for each control/patient was; pupillary dilation with topical 1% tropicamide and 2.5% phenylephrine HCl, 30 minutes of dark-adaptation, insertion of the contact lenses under dim red illumination, recording of the dark-adapted ERGs. Then the eyes were light-adapted for 10 minutes at 29.2 cd/m^2, and the cone single flash responses and 30-Hz flicker responses were recorded.

Measurement of a-Wave Latencies and Implicit Times

All analyses were done off-line. The ERGs were recalled and displayed on the computer monitor with a time base of 5 ms/division (Figure 1). In the LKC system, the stroboscopic flash is marked on the response by a vertical line (#1). To mark the latency and IT, the cursor was either slowly dragged along the response until the beginning of a negative-going

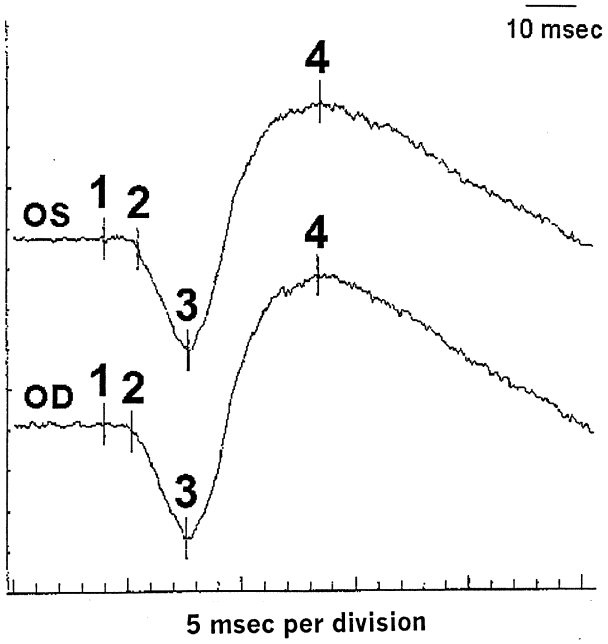

Figure 1. Scotopic mixed rod-cone electroretinograms (ERGs) demonstrating how measurements of the latency and implicit time were made. #1: stimulus onset, #2: beginning of the a-wave, #3: peak of the a-wave, and #4: peak of the b-wave. a-wave latency: time between #1 and #2, a-wave implicit time: time between #1 and #3, and b-wave implicit time: time between #1 and #4.

wave was noted, or with experience, the mouse arrow was pointed at the beginning of the response (the latency) and the mouse was clicked to place a marker (#2). In similar fashion, a second mark was placed at the trough of the a-wave to mark the IT of the a-wave (#3), and another cursor was placed at the peak of the b-wave (#4) to mark the IT of the b-wave. The time between the cursors was calculated by the computer, and the digital values for the a-wave latency and IT, and that for the b-wave IT were printed out.

Statistical Analyses

All of the data were collected in Excel tables, and the Student unpaired *t*-test was used to determine whether differences in the values were statistically significant. The Pearson product moment was used to calculate the coefficients of correlation. A P value of $< .05$ was considered significant.

Results

Reliability of the a-Wave Latency Measurements

We showed that the measurements of the a-wave latency could be made as reliably as those of the IT for the ERGs recorded from anesthetized rats,[9] and the question arose whether similar reliability of the latency measurements can be obtained from control subjects and patients with smaller a-wave amplitudes and noisier baselines.

To examine this, the a-wave latency and IT were measured by three observers from the ERGs of the right eye of 10 control subjects and from 10 patients with RP. The ERGs selected for the measurements were the scotopic mixed rod-cone ERGs elicited by the 0-dB stimulus. The first observer was an experienced electrophysiologist and the one who recorded all of the ERGs (M.L.); the second was an experienced laboratory neurophysiologist (D.I.H.); and the third was an inexperienced bioengineering student (I.P.) who had done the comparable measurements in the rats.

The mean ± SD of the a-wave latencies for the 10 ERGs from the control subjects were 4.2 ± 0.49 for M.L., 4.7 ± 0.59 for D.I.H., and 4.0 ± 0.64 for I.P. (Table 1). None of these differences was significant. The mean ± SD of the IT for the same ERGs were 18.1 ± 3.16 for M.L., 16.5 ± 0.72 for D.I.H., and

Table 1. Reliability of Measurements of a-Wave Latency and Implicit Time by Three Observers

	Controls*				RP Patients†			
	a-Wave Latency		Implicit Time		a-Wave Latency		Implicit Time	
Observer	Mean ± SD (ms)	CV (%)‡	Mean ± SD (ms)	CV (%)‡	Mean ± SD (ms)	CV (%)‡	Mean ± SD (ms)	CV (%)‡
M.L.	4.2 ± 0.47	11.4	18.1 ± 3.16	17.4	6.9 ± 2.53	36.7	24.4 ± 3.91	16.0
D.L.H.	4.7 ± 0.59	12.5	16.5 ± 0.72	4.4	8.8 ± 2.18	24.8	23.3 ± 2.69	11.5
I.P.	4.0 ± 0.64	16.3	18.2 ± 2.18	11.9	6.8 ± 2.45	35.8	23.5 ± 3.04	13.0

* n = 10.
† RP: retinitis pigmentosa. n = 10.
‡ CV: coefficient of variation (SD/mean %).

Jpn J Ophthalmol
Vol 46: 433–442, 2002

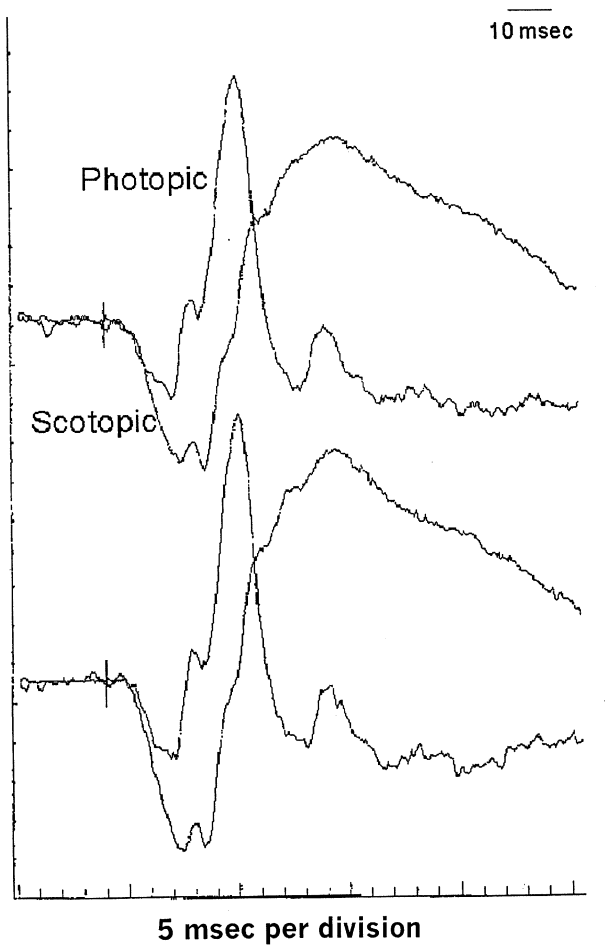

Figure 2. Scotopic and photopic electroretinograms recorded from the right and left eyes of a control subject.

18.2 ± 2.18 for I.P. (Table 1). The coefficients of variation (SD/mean) for the a-wave latency were 11.4% for M.L., 12.5% for D.I.H., and 16.3% for I.P.; and for the IT, they were 17.4% for M.L., 4.4% for D.I.H., and 11.9% for I.P.

For the 10 patients with RP, the mean ± SD of the a-wave latency were 6.9 ± 2.53 for M.L., 8.8 ± 2.18 for D.I.H., and 6.8 ± 2.45 for I.P. (Table 1); and for the IT for the same ERGs, they were 24.4 ± 3.91 for M.L., 23.3 ± 2.69 for D.I.H., and 23.5 ± 3.04 for I.P. (Table 1). The coefficients of variation for the a-wave latency were 36.7% for ML, 24.8% for DIH, and 35.8% for IP; and for the IT, the coefficients of variation were 16.0% for M.L., 11.5% for D.I.H., and 13.0% for I.P.

a-Wave Latency in Control Subjects

A scotopic mixed rod-cone ERG and a photopic cone ERG elicited by the 0-dB stimulus from the right (upper) and left (lower) eyes of a control subject are shown in Figure 2. The baseline and stimulus onset have been aligned to demonstrate the time course of the a-waves under scotopic and photopic conditions. Under both conditions, the beginning of the a-waves (ie, latency) was identical. However, the amplitude of the a-wave was smaller and the IT was shorter for the photopic ERGs.

From ERGs such as these, the a-wave latencies (milliseconds), ITs (milliseconds), and amplitudes (a-Amp; μV), and the b-wave ITs (b-IT; milliseconds) and amplitudes (b-Amp; μV) were measured for the ERGs recorded from the right and left eyes of the 40 control subjects. The mean ± SD for these waves are shown in Table 2 for the scotopic mixed rod-cone ERGs (upper) and for the photopic single flash cone ERGs (lower) elicited by the 0-dB stimulus.

The mean ± SD of the scotopic a-wave latency was 4.4 ± 0.8 milliseconds for the right eyes and 4.3 ± 0.7 milliseconds for the left eyes, and under photopic conditions, the a-wave latency was 4.1 ± 1.2 milliseconds for the right eyes and 4.2 ± 1.2 milliseconds for the left eyes. The differences between the right and left eyes, and the differences between the scotopic

Table 2. Data from Both Eyes of 40 Control Subjects (Mean ± SD)

	a-Lat* (ms)	a-IT† (ms)	a-Amp‡ (μV)	b-Amp§ (μV)	b-IT‖ (ms)
Scotopic					
Right	4.4 ± 0.8	18.5 ± 3.2	256.3 ± 48.3	479.4 ± 97.5	50.8 ± 3.2
Left	4.3 ± 0.7	18.4 ± 3.2	242.3 ± 43.0	472.1 ± 95.9	50.6 ± 3.5
Photopic					
Right	4.1 ± 1.2	15.1 ± 0.6	49.4 ± 13.0	165.6 ± 51.9	30.5 ± 1.2
Left	4.2 ± 1.2	14.9 ± 0.8	45.3 ± 11.7	159.7 ± 44.2	30.4 ± 1.2

* a-Lat: a-wave latency.
† a-IT: a-wave implicit time.
‡ a-Amp: a-wave amplitude.
§ b-Amp: b-wave amplitude.
‖ b-IT: b-wave implicit time.

Table 3. Coefficient of Correlation for Values Measured in Both Eyes of 40 Control Subjects

a-Wave Latency vs:*	Coefficient of Correlation			
	Scotopic		Photopic	
	Right	Left	Right	Left
a-wave IT	0.253	0.288	0.060	0.073
P	.115	.072	.711	.656
a-wave Amp	−0.272	−0.300	−0.118	−0.164
P	.090	.060	.501	.312
b-wave IT	0.360‡	0.288	−0.151	−0.303
P	.022	.071	.352	.057
b-wave Amp	0.031	0.086	−0.179	−0.399‡
P	.850	.598	.268	.011

* IT: implicit time, Amp: amplitude.
† n = 40.
‡ Correlation significant at .05 level (two-tailed).

and photopic conditions were not statistically significant.

For all of the other parameters, the differences between the right and left eyes were also not statistically significant (Table 2).

Coefficients of Correlation

To determine whether the a-wave latency can be predicted by knowing the values of the other parameters, eg, the IT, of the ERG, we calculated the coefficient of correlation between the a-wave latency and the a-wave IT, the a-wave amplitude, the b-wave IT, and the b-wave amplitude for the 40 control subjects (Table 3, upper).

All of the correlations were weak and only two values were significant: for the right eye under scotopic conditions, $r = 0.310$ between the a-wave latency and the b-wave IT; and for the left eye under photopic conditions, $r = 0.399$ between the a-wave latency and b-wave amplitude.

Patients with Different Types of Retinal Diseases

The question then arose whether the a-wave latency can provide additional information on the pathophysiology of patients with various types of retinal diseases. The a-wave latency and IT, and the b-wave IT for 9 patients with the complete type of congenital stationary night blindness (cCSNB), 13 patients diagnosed with achromotopsia or cone dystrophy, and 5 patients with supernormal b-waves are shown in Table 4. The *P* values (*t*-test vs control) and the number of eyes are also shown.

Congenital Stationary Night Blindness. The first set of patients selected to be analyzed were those diagnosed with cCSNB because the best evidence suggests that the photoreceptors are normal in cCSNB patients and that the pathology is in the synapses between the photoreceptors and second order neurons.[10,11] We thus predicted that the a-wave latency would not be altered in cCSNB patients.

A scotopic mixed rod-cone ERG recorded from a cCSNB patient and an ERG recorded from a control

Table 4. Comparison of Data from Both Eyes of Patients with Complete Congenital Stationary Night Blindness (CSNB), Achromatopsia, or Supernormal b-Waves with Data from Control Subjects (Mean ± SD)

	Scotopic				Photopic			
	a-Wave Latency (ms)		a-Wave IT (ms)		a-Wave Latency (ms)		a-Wave IT (ms)	
	Right	Left	Right	Left	Right	Left	Right	Left
Control subjects	4.4 ± 0.8	4.3 ± 0.7	18.5 ± 3.2	18.4 ± 3.2	4.1 ± 1.2	4.2 ± 1.2	15.1 ± 0.6	14.9 ± 0.8
CSNB								
Mean	4.1 ± 0.9	3.8 ± 1.0	19.6 ± 0.8	19.2 ± 0.9	4.1 ± 1.3	3.9 ± 0.9	18.4 ± 2.3	18.2 ± 2.2
*P**	.532	.098	.108	.195	.94	.53	.0001	.0001
n†	9	7	9	7	9	7	9	7
Achromats								
Mean	5.2 ± 0.8	6.0 ± 1.9	19.4 ± 2.4	21.3 ± 4.6	8.5 ± 5.1	11.7 ± 6.7	24.1 ± 5.4	19.5 ± 1.4
*P**	.004	.0001	.413	.253	.0001	.0001	.0001	.0001
n†	13	9	13	9	6	2	6	2
Supernorm								
Mean	5.7 ± 1.0	5.7 ± 0.8	28.3 ± 1.2	28.8 ± 1.8	5.8 ± 1.8	6.2 ± 2.0	18.0 ± 1.8	17.9 ± 1.3
*P**	.002	.001	.0001	.0001	.0001	.0016	.0001	.0001
n†	5	5	5	5	5	5	5	5

* *t*-test, vs control data.
† n = number of eyes.

Jpn J Ophthalmol
Vol 46: 433–442, 2002

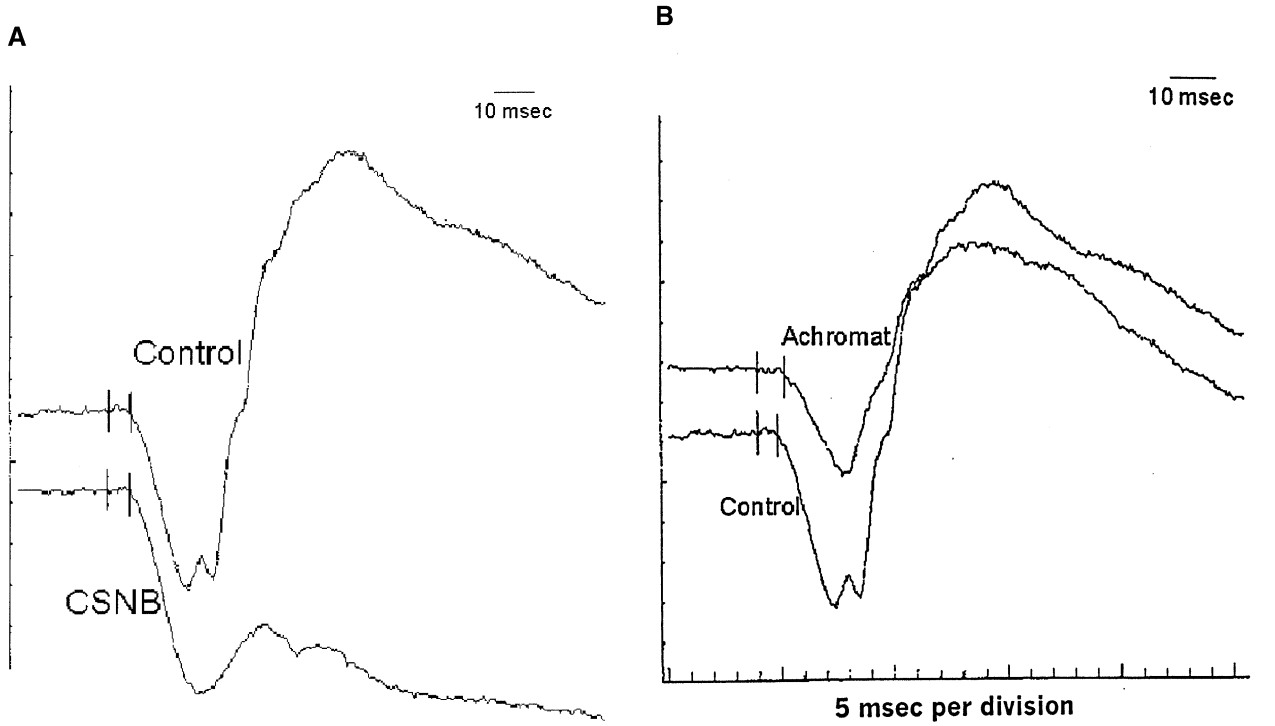

Figure 3. (**A**) Comparison of the scotopic mixed rod-cone electroretinograms (ERGs) recorded from a patient with complete congenital stationary night blindness (CSNB) and a control subject. (**B**) Comparison of the scotopic mixed rod-cone ERGs recorded from a patient with achromatopsia and a control subject.

subject are compared in Figure 3A. The characteristic negative-type ERG can be seen in this cCSNB patient, and the a-wave latencies of the two ERGs do not differ.

For the 9 cCSNB patients, the mean ± SD of the a-wave latency under scotopic conditions was 4.1 ± 0.9 milliseconds for the right eyes and 3.8 ± 0.1 milliseconds for the left eyes (Table 4). Under photopic conditions, the mean a-wave latency was 4.1 ± 1.3 milliseconds for the right eyes and 3.9 ± 0.90 milliseconds for the left eyes. The differences between the two eyes and between the scotopic and photopic conditions were not statistically significant. Most importantly, the a-wave latency of the cCSNB patients did not differ significantly from those in control subjects.

The scotopic a-wave IT in cCSNB patients also did not differ from those in control subjects but it was significantly longer under photopic conditions.

Achromatopsia. The second group of patients analyzed were those with achromatopsia or cone dystrophy. These patients are characterized by having normal scotopic ERGs and by an absence of photopic ERGs. Thus in achromats, there is widespread dysfunction of the cones, and the ERGs are generated only by the rods.

A scotopic mixed rod-cone ERG recorded from a patient diagnosed with achromatopsia is shown in Figure 3B along with the ERG from a control subject. A comparison of the ERGs showed that the a-wave latency of the achromatopic eye was slightly longer than that of the control eye. In the 13 patients, the mean a-wave latency was 5.2 ± 0.8 milliseconds for the right eyes (n = 13) and 6.0 ± 1.9 milliseconds for the left eyes (n = 9) under scotopic conditions. Both values were significantly longer than the a-wave latency of the corresponding right and left control eyes. In 6 of the 13 patients, a small a- and b-wave (mean b-wave amplitude = 20.8 μV) was elicited from the right eye under photopic conditions, and the mean a-wave latency was 8.5 ± 5.1 milliseconds. This value was also significantly longer than that in the control eyes.

Supernormal and delayed rod ERG syndrome. The third group of patients analyzed were those diagnosed as having the supernormal and delayed rod ERG syndrome. The ERGs of these patients are characterized by having higher scotopic thresholds, significantly larger b-wave amplitudes than control subjects, a delayed b-wave IT, and weak photopic responses.[12] The mean ± SD of the a-wave latency for

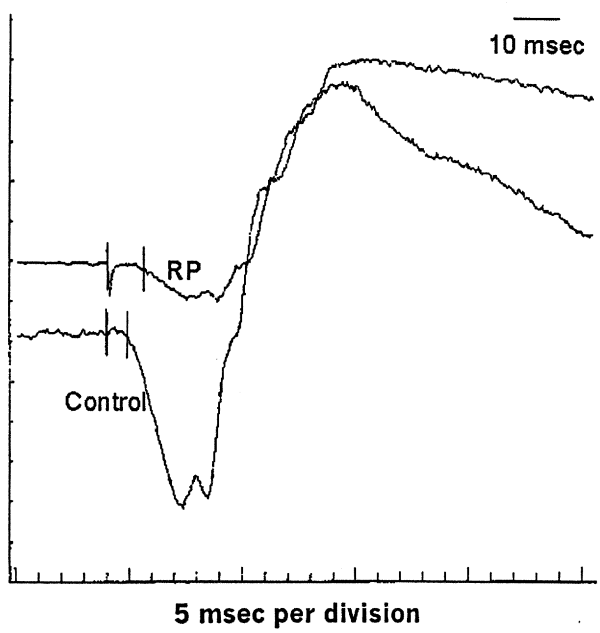

Figure 4. Comparison of the scotopic mixed rod-cone electroretinograms (ERGs) recorded from a patient with retinitis pigmentosa (RP) and a control subject.

the 5 patients diagnosed as having supernormal ERGs was 5.7 ± 1.0 for the right eyes and 5.7 ± 0.8 milliseconds for the left eyes under scotopic conditions, and 5.8 ± 1.8 milliseconds for the right eyes and 6.2 ± 2.0 milliseconds for the left eyes under photopic conditions. The differences between the 2 eyes and between the scotopic and photopic conditions were not statistically significant. However, the latencies for these patients were significantly longer than the corresponding latencies for control eyes.

Patients with Retinitis Pigmentosa

A scotopic mixed rod-cone ERG recorded from 1 retinitis pigmentosa (RP) patient is compared to the corresponding ERG recorded from a control subject in Figure 4. The decreased a- and b-wave amplitudes can be clearly seen in the ERG recorded from the RP patient. Relevant to this study, a prolongation of the a-wave latency and IT can also be seen.

The a-wave latencies, ITs, and amplitudes, and the b-wave ITs and amplitudes were measured from the ERGs elicited by the 0-dB stimulus under scotopic and photopic conditions for 72 patients diagnosed with RP (Table 5). These values are compared with the corresponding values for the 40 control subjects.

As expected, the a- and b-wave amplitudes were significantly smaller in the RP patients than in the control subjects under both scotopic and photopic conditions. The mean ± SD of the a-wave latencies for the scotopic mixed rod-cone ERGs was 7.3 ± 2.6 milliseconds for the right eyes and 7.6 ± 2.8 milliseconds for the left eyes. The difference between the 2 eyes of the RP patients was not significant, but both were significantly longer than the mean latencies of

Table 5. Data from Patients with Retinitis Pigmentosa (RP) and Controls (C) Recorded under Scotopic and Photopic Conditions*

	a-Lat† (ms)	a-IT‡ (ms)	a-Amp§ (μV)	b-AmP‖ (μV)	b-IT¶ (ms)
Scotopic					
Right eye					
C	4.4 ± 0.8	18.5 ± 3.2	256.3 ± 48.3	479.4 ± 97.5	50.8 ± 3.2
RP	7.3 ± 2.6	24.6 ± 7.7	51.4 ± 48.7	93.8 ± 99.4	56.7 ± 11.4
Left eye					
C	4.3 ± 0.7	18.4 ± 3.2	242.3 ± 43.0	472.1 ± 95.9	50.6 ± 3.5
RP	7.7 ± 2.7	24.8 ± 7.8	50.1 ± 44.1	95.7 ± 98.2	63.3 ± 63.2
Photopic					
Right eye					
C	4.1 ± 1.2	15.1 ± 0.6	49.4 ± 13.0	165.6 ± 51.9	30.5 ± 1.2
RP	7.8 ± 3.0	20.6 ± 6.2	15.1 ± 9.0	39.80 ± 36.8	39.7 ± 8.2
Left eye					
C	4.2 ± 1.2	14.9 ± 0.8	45.2 ± 11.7	159.7 ± 44.2	30.4 ± 1.2
RP	8.6 ± 6.2	20.5 ± 6.4	15.6 ± 9.5	42.7 ± 37.5	39.3 ± 8.1

*Values are mean ± SD.
†a-Lat: a-wave latency.
‡a-IT: a-wave implicit time.
§a-Amp: a-wave amplitude.
‖b-Amp: b-wave amplitude.
¶b-IT: b-wave implicit time.

Jpn J Ophthalmol
Vol 46: 433–442, 2002

the corresponding control eyes ($P < .0001$). The ITs for both the a- and b-waves were also significantly longer for the 2 eyes of the RP patients compared to the 2 eyes of control subjects.

Under photopic conditions, the mean ± SD of the a-wave latency was 8.5 ± 5.0 milliseconds for the right eyes and 8.5 ± 6.3 milliseconds for the left eyes of the RP patients. Both of these a-wave latencies were also significantly longer than those for the control eyes. The ITs of the photopic a- and b-wave were also significantly longer than those of control subjects.

Effect of a- and b-Wave Amplitudes on a-Wave Latencies

The question arose whether the longer a-wave latencies were related to the lower a- and b-wave amplitudes in the RP patients. To answer this question, we first segregated and analyzed the ERGs of RP patients into those with scotopic a-wave amplitude greater than 70 μV and those with photopic a-wave amplitude greater than 20 μV (Table 5, upper). Under scotopic conditions, the mean ± SD of the a-wave latencies was 6.2 ± 1.69 milliseconds for the right eyes and 5.8 ± 1.27 milliseconds for the left eyes. Both values were significantly longer than the latency for the control eyes. Under photopic conditions, the mean ± SD of the a-wave latency for the right eyes was 6.8 ± 1.63 milliseconds and 5.9 ± 1.81 milliseconds for the left eyes. Both values were also significantly longer than the latency for the control eyes.

The eyes were then segregated for ERGs that had scotopic b-wave amplitudes that were greater than 100 μV and photopic b-wave amplitudes that were greater than 60 μV (Table 6). Under scotopic conditions, the mean ± SD of the a-wave latency for the right eyes was 6.2 ± 1.69 milliseconds and 5.8 ± 1.27 milliseconds for the left eyes. Both values were significantly longer than the mean latency for the control eyes. Under photopic conditions, the mean ± SD of the a-wave latency for the right eyes was 6.3 ± 1.39 milliseconds and 5.7 ± 1.93 milliseconds for the left eyes. Both values were also significantly longer than the mean latency for the control eyes.

Coefficient of Correlation

Another way of examining the relationship between the a-wave latency and the other parameters of the ERG was to calculate the coefficient of correlation between the a-wave latency and the a-wave IT, the a-wave amplitude, the b-wave IT and the b-wave amplitude (Table 7). The strongest coefficient of correlation was that between the a-wave latency and the a-wave IT for the photopic ERGs of the left eye ($r = 0.722$). However, the coefficient of correlation for the right eye under the same conditions was $r = 0.291$. In general, shorter a-wave latencies were correlated with larger a- and b-wave amplitudes, but the correlations were generally weak even though a few were significant.

Discussion

Reliability of a-Wave Measurements

The mean a-wave latency measured by three observers for 10 control ERGs differed by less than 1 millisecond while the mean IT differed by 1.7 milliseconds. The standard deviations for the a-wave latencies were relatively small and comparable for the three observers. The coefficients of variation varied from 11.4% to 16.3% for the latency and from 4.4% to 17.4% for the IT. We can conclude from these findings that measurements of the a-wave latency can be made as reliably as those of the IT in control subjects.

The comparable measurements of the ERGs from eyes with RP showed that they were not as reliable for both the latency and the IT as they were in the

Table 6. Mean ± SD of the a-Wave Latencies (Lat) and a- and b-Wave Amplitudes (Amp) for Electroretinograms Recorded from Retinitis Pigmentosa Patients

	Scotopic		Photopic	
	Right (n = 20)	Left (n = 18)	Right (n = 19)	Left (n = 19)
a-Wave Amp*	116.9 ± 42.6	114.1 ± 32.7	26.7 ± 7.1	28.0 ± 7.30
a-Wave Lat	6.2 ± 1.69	5.8 ± 1.27	6.8 ± 1.63	5.9 ± 1.81
	Right (n = 21)	Left (n = 26)	Right (n = 13)	Left (n = 17)
b-Wave Amp†	216.4 ± 103.4	199.1 ± 95.9	100.0 ± 44.8	94.8 ± 38.5
b-Wave Lat	6.2 ± 1.96	6.3 ± 1.61	6.3 ± 1.39	5.7 ± 1.93

*Scotopic a-wave >100 μV and photopic a-wave >20 μV.
†Scotopic b-waves >100 μV and photopic b-waves >60 μV.

Table 7. Coefficient of Correlation for Values Measured in Both Eyes of Retinitis Pigmentosa Patients

a-Wave Latency vs:	Coefficient of Correlation			
	Scotopic		Photopic	
	Right (n = 72)	Left (n = 68)	Right (n = 67)	Right (n = 65)
a-wave IT	.255†	.092	.291†	.722‡
P	.031	.453	.017	.0001
a-wave Amp	−.398‡	−.539‡	−.294†	−.360‡
P	.001	.0001	.016	.003
b-wave IT	.190	.012	.140	.558‡
P	.110	.920	.258	.0001
b-wave Amp	−.236†	−.342‡	−.278†	−.272†
P	.046	.004	.023	.028

IT: implicit time, Amp: amplitude.
† Correlation significant at .05 level (two-tailed).
‡ Correlation significant at .01 level (two-tailed).

control eyes. Although the mean of the a-wave latencies measured by the three observers differed by less than 2.0 milliseconds and by less than 1.1 milliseconds for the ITs, the coefficients of variation varied from 24.8% to 36.7% for the latencies and from 11.5% to 16.0% for the ITs. The larger coefficients of variation were a reflection of the larger SDs. These findings indicate that the measurements of the latency and IT were not as reliable in the RP patients as in the control subjects, and that the reliability was better for the IT than for the latency.

The larger SD for both the latency and IT in the RP patients was not too surprising because the measurements were made on the ERGs of RP patients at different stages of their disease process. Thus, unlike the measurements of control subjects that came from one population, the RP patients included patients of different ages and with different inheritance patterns. Future analysis on RP patients of the same genetic background and at comparable stages of their disease should improve the reliability of the latency measurements.

a-Wave Latency in Control Subjects

A comparison of our data to those presented by Jacobi et al for 20 control eyes showed that our findings were very similar and were well within the 95% confidence limits of their means.[7] (Unfortunately, they did not measure the a-wave latency.) This good agreement confirmed that our stimulating and recording conditions met the standards recommended by the ISCEV Committee on Standardization.[8] More importantly, we can conclude that the values of the a-wave latency, as well as the other parameters, were obtained from a normal population. However, because the a-wave latency is greatly affected by the stimulus intensity, the normal a-wave latency should be determined for each laboratory.

Of special interest in the control subjects was the finding that the a-wave latencies obtained from the ERGs elicited under scotopic and photopic conditions were not statistically different. This would suggest either that the rods and cones have the same a-wave latencies or that the latency recorded under scotopic conditions is being determined by cones. Because the mean a-wave latency of the dark-adapted ERGs recorded from patients with achromatopsia or cone dystrophy was significantly longer than the control a-wave latency, we conclude that the rods have a small but significantly longer latency than the cones. This then indicates that the a-wave latency of the dark-adapted ERGs elicited by the 0-dB stimulus under scotopic conditions is being determined by the cones.

a-Wave Latency in Retinal Diseases

The results from our experiments on rats strongly supported the idea that the a-wave latency is determined exclusively by photoreceptor activity.[13] We thus predicted that the a-wave latency in patients with cCSNB would not be significantly different from the a-wave latency of control subjects. Our findings agreed with our prediction, and support the earlier conclusion that the photoreceptors are normal in cCSNB patients and the defect is in the synapses. It will be interesting to measure the a-wave latency in patients with the incomplete type of CSNB, as their mutation alters the L-type calcium channel-subunit gene.[14,15]

The delayed a-wave latency in the patients with supernormal and delayed rod ERGs indicated that the photoreceptors were abnormal, agreeing with the higher thresholds in these patients. However, the delay in the a-wave latency was not sufficient to account for all of the delay in the b-wave IT.

a-Wave Latency in Patients with RP

The reduced a- and b-wave amplitudes and the delayed IT of the scotopic and photopic ERGs in RP patients are in good agreement with data in the literature. On the other hand, the significantly longer a-wave latency in RP patients has not been reported, and interestingly, the delay was noted under both scotopic and photopic conditions. Because we showed that the a-wave latency of the mixed rod-cone response elicited by the 0-dB stimulus under scotopic conditions was not significantly different from the mean a-wave latency elicited by the same stimulus

Jpn J Ophthalmol
Vol 46: 433–442, 2002

under photopic conditions, we conclude that the a-wave latency was determined by cones under both scotopic and photopic conditions. Then the delayed latency in patients with RP indicates that the cones also have altered phototransduction processes. This is in support of evidence in the literature that both rods and cones are affected in patients with RP.[16]

The delayed a-wave latency was found even in RP patients with relatively large a- and b-waves. This indicates that the delays were not due to the difficulty in making the latency measurements even though the overall reliability was not as good for the latency.

In our laboratory experiments, we showed that focal retinal changes did not alter the a-wave latency but that a large area of the photoreceptors had to be damaged to increase the a-wave latency.[13] Thus, the marked delay in the a-wave latency in RP patients suggests that both the rods and cones are altered over a large area of the retina.

Latency and Implicit Time

The time course of the a-wave has been of clinical interest from the earliest studies of human ERGs. However, because of the limitations of equipment, it was not possible to obtain accurate time measurements in the early clinical studies. For example, Karpe in 1945 reported a resolution of about ± 10 milliseconds. Nevertheless, it was not all due to the limitations of the equipment because even as late as 1991, when digital computers with high sampling rates were available, the implicit time was still considered to characterize the time course of the ERGs.

More recently, the time course of the a-wave has been described by fitting a set of Gaussian time curves to the initial part of the a-waves.[17] RP patients have been analyzed with this technique but reports of a delay of the a-wave latency have not been published. We cannot explain why a delay was not noted in any of the RP patients, because our findings showed that the delays were quite significant.

The main advantage of using the latency is that it is determined exclusively by photoreceptor activity. Even though the reliability of a-wave latency measurements was not as good in RP patients, the mean delay in RP patients was large enough to be statistically significant. We can conclude that this delay indicates that there is an alteration of the phototransduction process of both rods and cones over a large area of the retina in RP patients.

In conclusion, we have shown that the measurements of the latency were as reliable as those for the IT in control subjects with normal amplitude a-waves. However, the reliability of the a-wave latency was not as good as for the IT in RP patients because measurements were made from patients at different stages of their disease process. Nevertheless, we recommend that the latency and not the IT be used to evaluate the time course of the ERG because the origin of the a-wave latency is known.

This study was supported in part by the William and Norma Horvitz Retinal Degeneration Endowment. The authors thank Mr. Indushekhar Persaud for making the measurements of the a-wave latency and implicit time.

References

1. Krill, AE. Hereditary retinal and choroidal diseases. Volume i. Evaluation. Hagerstown, MD: Harper & Row, 1972.
2. Granit R. Sensory mechanism of the retina. London: Oxford University Press, 1947.
3. Ruch TC, Fulton JF. Medical physiology and biophysics. Philadelphia, PA: Saunders, 1960.
4. Karpe, G. The basis of clinical electroretinography. Acta Ophthalmol (Scand) 1945;24(Suppl):1–118.
5. Jacobson, JH. Clinical electroretinography. Springfield, MO: Charles C Thomas, 1961.
6. Heckenlively JR, Arden GA. Principles and practice of clinical electrophysiology of vision. St Louis, MO: Mosby-Year Book, 1991.
7. Jacobi PC, Miliczek KD, Zrenner E. Experiences with the international standard for clinical electroretinography: normative values for clinical practice, interindividual and intraindividual variations and possible extensions. Doc Ophthalmol 1993;85:95–114.
8. Marmor MF, Zrenner E. Standard for clinical electroretinography (1999 update). Doc Ophthalmol 1999;97:143–156.
9. Fujiwara E, Qiu H, Liu M, et al. Reliability and significance of measurements of a-wave latency in rats. Jpn J Ophthalmol 2002;46:419–425.
10. Carr RE, Ripps H, Siegel IM, Weale RA. Rhodopsin and the electrical activity of the retina in congenital night blindness. Invest Ophthalmol 1966;5:497–507.
11. Miyake Y, Yagasaki K, Horiguchi M, Kawase Y, Kanda T. Congenital stationary night blindness with negative electroretinogram. A new classification. Arch Ophthalmol 1986;104:1013–1020.
12. Alexander K, Fishman, G. Supercontrol scotopic ERG in cone dystrophy. Br J Ophthalmol 1984;68:69–78.
13. Qiu H, Fujiwara E, Liu M, Lam BL, Hamasaki DI. Evidence that a-wave latency of the electroretinogram is determined solely by photoreceptors. Jpn J Ophthalmol 2002;46:426–432.
14. Strom TM, Nyakatura G, Apfelstedt-Sylla E, et al. An L-type calcium-channel gene mutated in incomplete X-linked congenital stationary night blindness. Nat Genet 1998; 19: 260–263.
15. Bech-Hansen NT, Naylor MJ, Maybaum TA, et al. Loss-of-function mutations in a calcium-channel alpha1-subunit gene in Xp11.23 cause incomplete X-linked congenital stationary night blindness. Nat Genet 1998;19:264–267.
16. Bird AC. Retinal photoreceptor dystrophies. Edward Jackson Memorial Lecture. Am J Ophthalmol 1995;119:543–562.
17. Hood DC, Birch DG. Rod phototransduction in retinitis pigmentosa: estimation and interpretation of parameters derived from the rod a-wave. Invest Ophthalmol Vis Sci 1994;35: 2948–2961.