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Relationships between the electroretinogram a-wave, b-wave and oscillatory potentials and their application to clinical diagnosis

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Abstract. The electroretinogram is the electrical response of the retina to a light stimulus. The amplitude and temporal pattern of its components, the a-wave, the b-wave and the oscillatory potentials, depend on the functional integrity of the retina, on the intensity of test flash reaching the retina and on the ambient illumination. The latter contributions to the normal variability in the electroretinogram can be circumvented by constructing the relationships between the different electroretinogram waves. The electroretinogram responses were recorded from 18 dark-adapted subjects with normal vision. The slope of the a-wave and the amplitude of the b-waves were measured in the time domain. The oscillatory potentials were isolated by a digital filter and were transformed to the frequency domain for quantitative measurement. The relationship between each pair of variables could be fitted by linear segments. Our findings suggest that this mode of electroretinogram analysis can be useful in localizing the site of action of retinal disorders and that the relationship between the a-wave slope and the power density of the oscillatory potentials is a useful index for identifying disorders of the inner retina.

Introduction

The electroretinogram (ERG) is a complex electrical signal that is recorded from the retina in response to a light stimulus. It is composed of several distinct waves that originate in different retinal structures [1, 2]. The a-wave is the leading edge of the fast P-III (late receptor potential), which reflects the photocurrent generated by light absorption in the outer segments of the photoreceptors. The b-wave reflects changes in the membrane potential of Müller (glia) cells that are induced by changes in the extracellular concentration of potassium ions. Since the extracellular potassium ion level depends on neuronal activity in the inner nuclear layer, the b-wave is considered a reliable index of retinal function. The oscillatory potentials are small-amplitude wavelets superimposed on the ascending limb of the b-wave. They are generated in the inner retina, probably by local neural networks involving bipolar, amacrine and ganglion cells. The ERG oscilla-

tory potentials are considered to be sensitive to disturbances in the retinal circulation [3, 4]. Therefore, they are used to evaluate the severity of diabetic retinopathy [5, 6], to assess the chances of it developing into a proliferative stage [7, 8] and to evaluate the effects of central retinal vein occlusion [9–11].

In patients, the corneally recorded ERG responses may be significantly reduced in size and exhibit an abnormal pattern. Such findings may reflect trivial causes, such as reduction in the light intensity reaching the retina or changes in the electrical resistance of extraretinal tissues [12–14]. Under these conditions, all of the ERG components are expected to be similarly affected. Therefore, the dependency of each ERG component on log flash intensity may appear subnormal, but the relationships between the ERG waves will be within the normal range [15]. When retinal malfunction occurs, the ERG components may be selectively affected, causing the relationships between them to change. These changes can be used to localize the site of the disorder.

This study was designed to derive the normal relationships between the different components of the corneal ERG over a wide range of flash intensity to characterize the entire dynamic range of the eye. A similar approach has been applied for the relationship between the oscillatory potentials and the b-wave amplitude [16] and more recently for the relationship between the oscillatory potentials and the a-wave slope [11]. In the present study, the three ERG components, a-wave, b-wave and oscillatory potentials, are related to each other to examine the properties of signal transmission between the different retinal structures that generate these ERG components and to test their usefulness for electrodiagnosis.

Subjects and methods

Eighteen volunteer students (20–30 years old) with no visual complaint participated in this study. Informed consent was obtained from each subject.

The ERG responses were recorded between a corneal electrode (Medical Workshop, the Netherlands) and a reference cup electrode placed on the forehead above the eye. An ear clip served as the ground electrode. The ERG signal was amplified ($\times 10\,000$) and filtered (0.1–1000 Hz) by a differential amplifier (Grass P511). The output of the amplifier was digitized at a rate of 2 KHz (Labmaster A/D interface) and stored in a hard disk of a personal computer (IBM XT compatible).

The photostimulation system consisted of an electronic camera flash that was triggered by the computer on command by the experimenter. The intensity and color content of the light stimuli were controlled by a set of 'neutral'-density and broad-band colored optical filters. The active corneal electrode contained a −100-diopter lens to produce a quasi-Ganzfeld illumination.

Complete mydriasis was achieved with 0.5% cyclopentolate hydrochloride and 0.5% phenylephrine hydrochloride. After local anesthetic (0.4% benoxinate hydrochloride) was applied, the corneal electrodes were placed with 2.5% methylcellulose. The ERG responses were first recorded in the light-adapted state with background illumination of 11 foot-lamberts. The room light was then turned off and the subject was allowed to dark adapt for 30 minutes. With the subject in the dark-adapted state, a series of ERG responses was recorded with white-light stimuli of different intensities to characterize the entire dynamic range of the eye. For each test light intensity, four stimuli were applied at 20-s intervals. This interstimulus interval was chosen as an optimum one for obtaining large-amplitude oscillatory potentials [17, 18] without affecting the a- and b-waves.

The ERG analysis was done off-line with a 386-SX personal computer. Time-domain analysis included measurements of the a-wave slope as an indicator of photoreceptor activity [19, 20] and of the b-wave amplitude as an index for retinal function [21]. These variables were determined by the computer with a specially designed program that first smoothed the ERG response with a gaussian (low-pass) function. The first minimum point was then identified and the maximum point was determined within the following 50 ms. The a-wave slope was measured between the a-wave onset and the first major negative peak (or deflection) [11]. The a-wave onset was defined by the first poststimulus time at which the potential differed by more than 2 standard deviations from the mean of the baseline. The latter was calculated for the prestimulus interval of 30 ms. The b-wave amplitude was measured from the trough of the a-wave to the peak of the b-wave.

The oscillatory potentials were isolated from the ERG signal by applying to the raw data a computer algorithm based on a five-pole analogue Butterworth filter [22, 23]. This procedure selectively attenuated all of the components of the ERG that were slower than 100 Hz or faster than 200 Hz, thereby leaving the oscillatory potentials. The power density spectrum of the ERG oscillatory potentials was then derived by a fast Fourier transform. The filtered signal was multiplied by a square window of a duration selected by the computer from the trough of the a-wave to the peak of the b-wave. This window was used to eliminate artifacts due to rapid eye movements that appeared in the later portions of the ERG [11]. Zeros were added to the ERG signal (in the time domain) to achieve 1.9-Hz resolution in the power density spectrum, regardless of the segment length specified for analysis. The power density was computed with the assumption that the ERG voltages were measured across a hypothetical 1-ohm resistor [24].

Results

Figure 1 shows a series of ERG responses recorded from one eye of a dark-adapted volunteer with normal vision. These responses were elicited

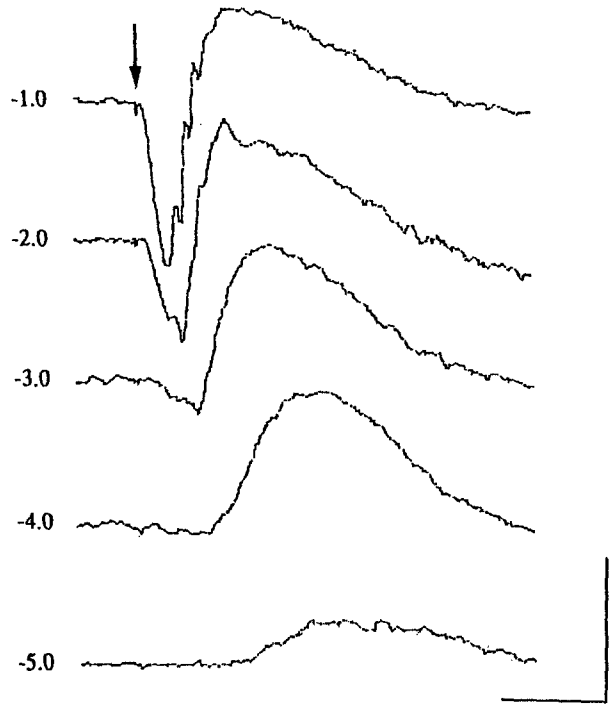

Fig. 1. Representative ERG responses recorded from one eye of a subject with normal vision. The intensity of each white flash is given in log relative units to the left of each trace. Flash onset is marked by the arrow. Calibration bars denote 400 μV (vertical) and 25 ms (horizontal).

with white-light stimuli attenuated by 'neutral'-density filters. The log relative intensity is indicated to the left of each trace. The b-wave threshold was below −5.0 log relative intensity, while the a-wave threshold was higher by about 2 log units (around −3.0 log relative intensity). The oscillatory potentials became apparent on the ascending limb of the b-wave only when brighter (log relative intensity of −2.0) stimuli were used. Therefore, most previous studies on the properties of the oscillatory potentials used only bright light stimuli [17, 18, 22, 25, 26].

Figure 2 shows a typical ERG response elicited in the dark-adapted state by a bright (log relative intensity of −1.0) white-light stimulus. The oscillatory potentials appear as small perturbations on the ascending limb of the large-amplitude b-wave and therefore cannot be measured (A). After application of the digital filter, the a- and b-waves are selectively attenuated and the oscillatory potentials can be easily identified (B). It should be noted that the digital filter differentiated the early part of the a-wave to produce oscillations that were excluded from the analysis. The ERG oscillatory potentials are designated by small arrows in Fig. 2B. The power density spectrum of the oscillatory potentials (C) is characterized by a high-

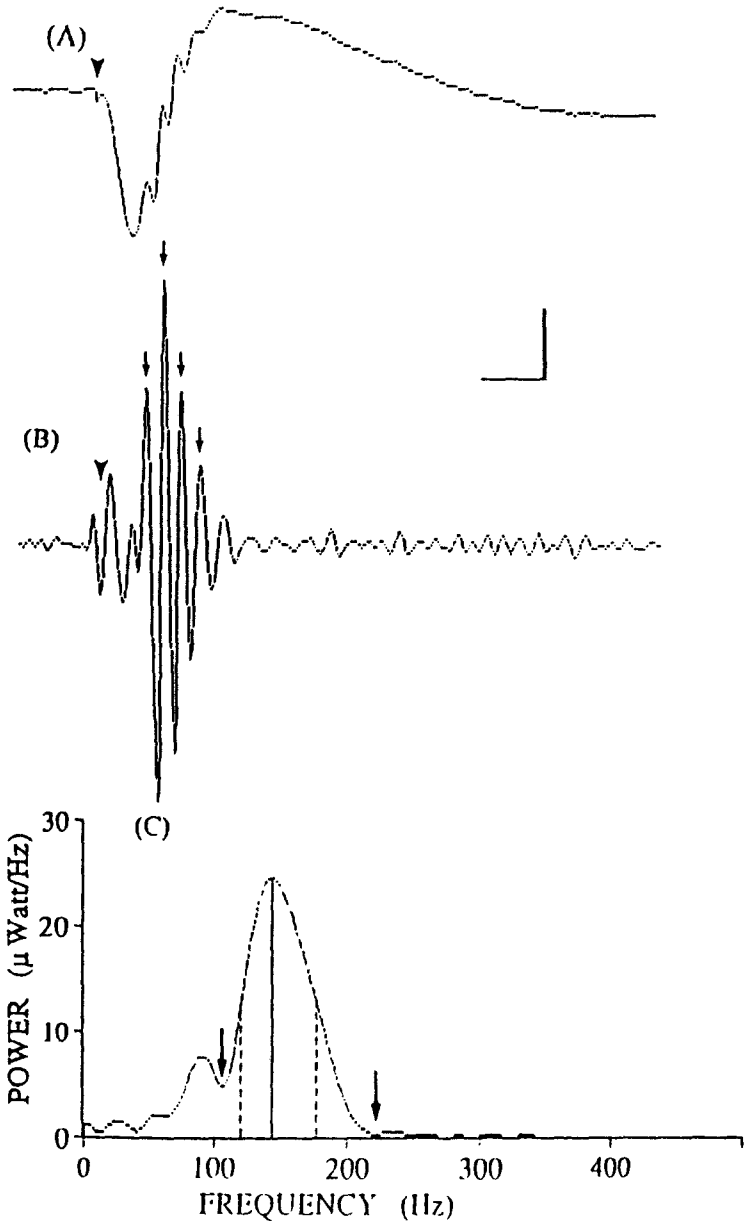

Fig. 2. The photoresponse elicited by a bright (log relative intensity of −1.0) white-light stimulus from a dark-adapted subject with normal vision before (A) and after (B) the application of the digital filter. The isolated oscillatory potentials are designated by small arrows. The power density spectrum of the oscillatory potentials (C) was measured at the dominant frequency (continuous line) to derive the peak power density. Half-band area was defined between the frequencies (dashed lines) at which the power density was half that of the peak. Band area was measured by integrating the power density spectrum curve between the minima (arrows) on both sides of the band. Vertical bar denotes 200 μV (A) and 20 μV (B). Horizontal bar represents 20 ms.

frequency band that peaks at 144 Hz. Three different variables were used to describe the magnitude of the oscillatory potentials in the frequency domain [24, 26–28]. The methods of computing these variables are illustrated in Fig. 2C. The peak power density was measured at the dominant frequency (continuous line). The half-band area was defined by the area under the power density spectrum curve, which was bound by the frequencies (dashed lines) where the power/Hz was half that measured at the dominant frequency. The band area was calculated by integrating the power density spectrum between the minima on both sides of the high-frequency band (arrows).

To choose the most reliable variable that represented the magnitude of the oscillatory potentials, we tested the variability of all four variables between different subjects. The dark-adapted ERG responses were recorded from 18 volunteers with no visual complaints, and the oscillatory potentials were isolated as described above. For each light stimulus intensity, the peak power density, half-band area, and band area were calculated from the power density spectrum of the isolated oscillatory potentials. In addition, the sum of amplitudes was calculated in the time domain [5–7]. These data are summarized in Table 1 as mean and standard deviation. From this information, the coefficient of variation (standard deviation/mean) was calculated for each variable to assess its variability among the normal subjects. In general, the variability of all the variables increased when the test flash intensity was reduced. Among the four variables, the

Table 1. Normal range of four variables measured in the time and frequency domains that can be used to assess the magnitude of the ERG oscillatory potentials

Log relative intensity	Variable	Mean	Standard deviation	Coefficient of variation
−1.0	Summed amplitude (μV)	310.5	71.7	0.231
	Peak power density (μW/Hz)	20.0	4.4	0.220
	Band area (μW)	1038.9	386.2	0.372
	Half-band area (μW)	856.2	282.5	0.330
−2.0	Summed amplitude (μV)	145.4	54.9	0.378
	Peak power density (μW/Hz)	9.6	3.5	0.365
	Band area (μW)	492.7	244.5	0.496
	Half-band area (μW)	437.2	173.8	0.398
−2.6	Summed amplitude (μV)	86.4	37.5	0.434
	Peak power density (μW/Hz)	5.7	2.3	0.404
	Band area (μW)	274.2	122.7	0.447
	Half-band area (μW)	260.9	84.6	0.324
−3.0	Summed amplitude (μV)	65.0	28.7	0.442
	Peak power density (μW/Hz)	4.3	1.9	0.442
	Band area (μW)	178.9	83.9	0.469
	Half-band area (μW)	161.2	67.5	0.419

coefficient of variation tended to be smallest for the peak power density. Since it was also the easiest to define and to measure, we used it to describe the magnitude of the oscillatory potentials.

Figure 3 shows the dependency of the a-wave slope (A), the b-wave amplitude (B) and the peak power density of the oscillatory potentials (C) on the log relative intensity of the white-light stimulus. Each data point represents the mean ± standard deviation of values obtained from 18 individuals with normal vision. The data shown in this figure clearly indicate that the a-wave slope and the peak power density of the oscillatory potentials exhibit similar dependency on the intensity of the light stimulus. Both are characterized by similar threshold. They are linearly related to the log light intensity for dim stimuli and increase nonlinearly for bright stimuli (Figs. 3A and 3C). The b-wave is characterized by considerably lower threshold (about 2 log units) and exhibits a saturation-type dependency on log stimulus intensity.

The normal group of subjects exhibits a large degree of variability in every ERG variable, as can be seen from the standard deviations shown in Fig. 3. Some of this variability can be attributed to nonretinal factors, such as pupil size, ocular pigmentation and electrical resistance of extraretinal tissues. These contributions can be circumvented by comparing the different components of the ERG, as shown in Fig. 4. Each data point describes an individual ERG response from one eye of one subject. The b-wave exhibits a complex dependency on the a-wave (Fig. 4A). For very small a-wave slopes, the b-wave amplitude increases at a high rate, suggesting a high degree of amplification between the generators of these two ERG components. For bright light stimuli that elicit large-amplitude ERGs, the b-wave exhibits a linear relationship to the a-wave slope but at a very small gain. The data points relating the peak power density of the oscillatory potentials to the a-wave slope exhibit large spread but seem to follow a linear pattern (Fig. 4B). The dependency of the oscillatory potentials on the b-wave amplitude is characterized by a complex pattern, with a small gain for small-amplitude responses and a large one for large ERGs (Fig. 4B).

The data in Fig. 4 were obtained with light stimuli of different intensities from different individuals. Therefore, two variables contribute to the spread of the data points: the light intensity and the intersubject differences. To examine only the intersubject variability, we derived for each individual the relationships between the different ERG variables with the use of the ERG responses recorded from both eyes. For every subject, the a-wave and oscillatory potentials were characterized by similar threshold and were linearly related (R^2 ranged from 0.86 to 0.98). The b-wave was characterized by considerably lower threshold than either the a-wave or the oscillatory potentials, and, therefore, its relationships to these components were more complex. For simplicity, only ERG responses elicited by light stimuli brighter than the a-wave threshold were used to construct the relationships

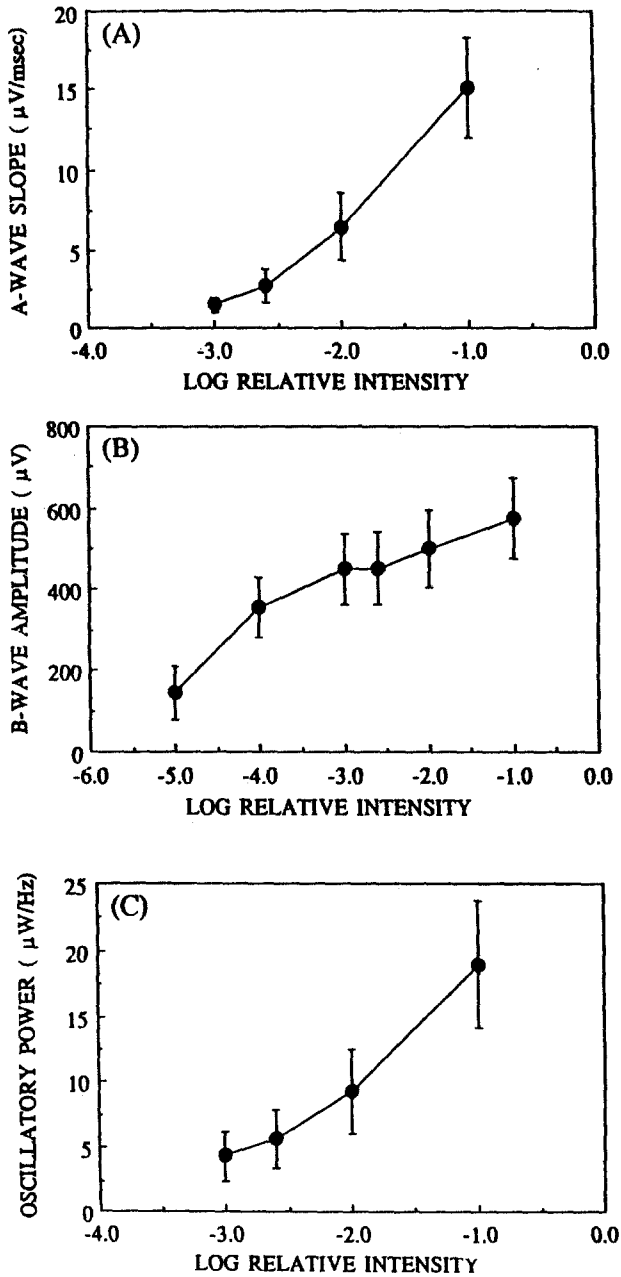

Fig. 3. The dependency of the a-wave slope (A), b-wave amplitude (B) and peak power density of the oscillatory potentials (C) on the log relative stimulus intensity. The data points represent mean ±1 standard deviation of the values measured in both eyes of 18 subjects with normal vision.

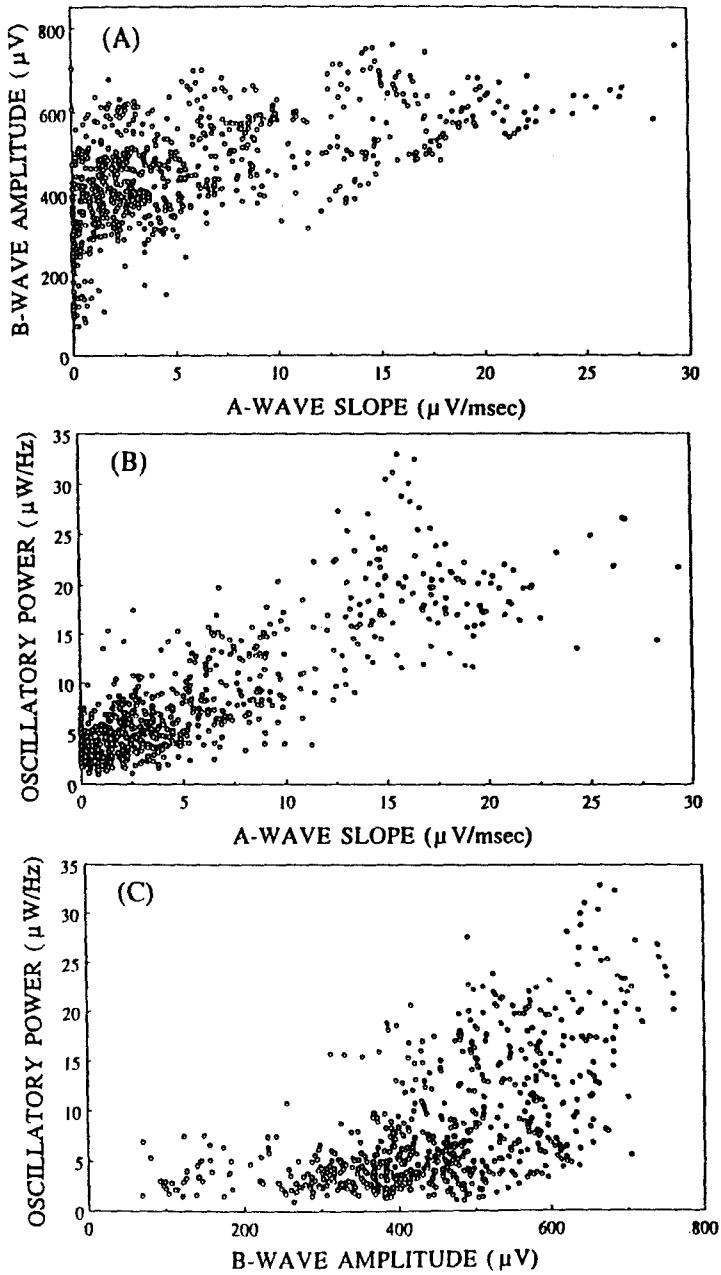

Fig. 4. The relationships between the b-wave amplitude and a-wave slope (A), the peak power density of the oscillatory potentials and the a-wave slope (B) and the peak power density of the oscillatory potentials and the b-wave amplitude (C). Each data point represents one ERG response from one eye of one subject. The ERGs of 18 subjects were used to construct the above relationships.

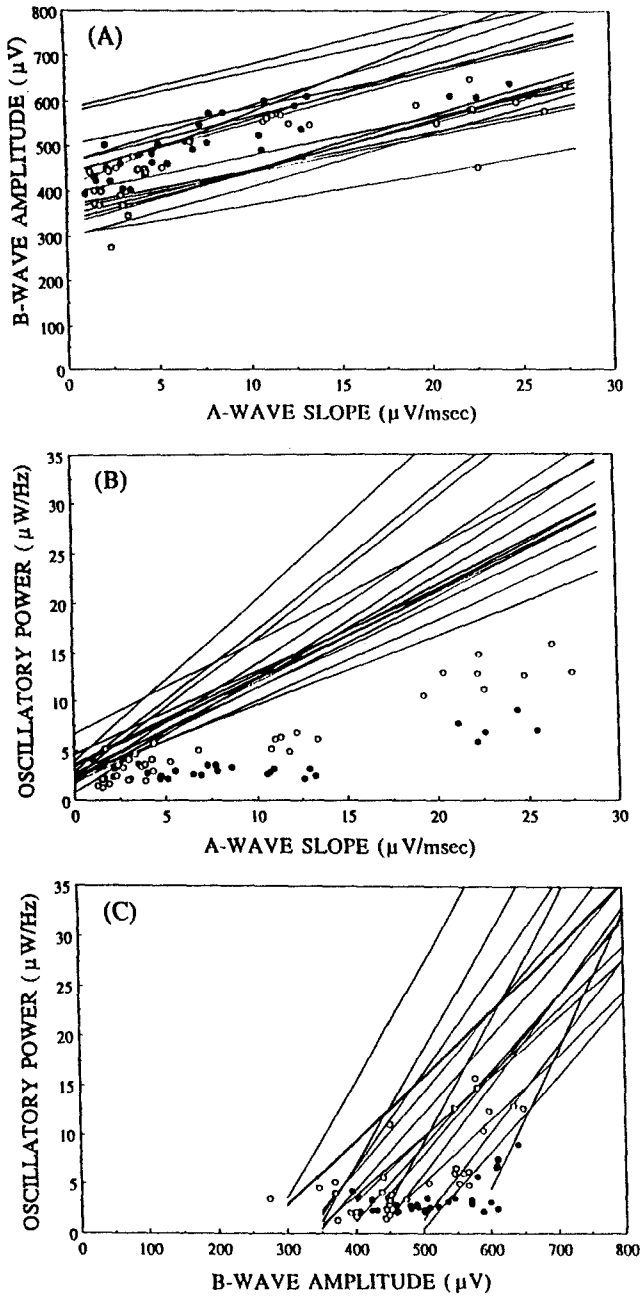

Fig. 5. Linear function for each subject for the b-wave to a-wave relationship (A), oscillatory potentials to a-wave (B) and oscillatory potentials to b-wave (C). Only ERG responses elicited by light stimuli brighter than the a-wave threshold were considered for these relationships. Data from two patients with background diabetic retinopathy are shown as solid and open circles.

Table 2. Normal range of the slope and intercept that describe the linear relationships between a-wave slope, b-wave amplitude and peak power density of oscillatory potentials

Function	Slope		Intercept	
	Mean	Standard deviation	Mean	Standard deviation
B-wave amplitude to a-wave slope	10.57	2.15	405	83
Oscillatory potentials to a-wave slope	0.96	0.3	2.76	1.27
Oscillatory potentials to b-wave amplitude	0.088	0.022	367	89

between the b-wave amplitude and a-wave slope and between the peak power density of the oscillatory potentials and the b-wave amplitude. These functions exhibited weaker linearity than the one relating to the oscillatory potentials to the a-wave (R^2 ranged from 0.65 to 0.85). The mean ($\pm$ standard deviation) values of the slope and intercept of these fitted functions are summarized in Table 2.

Figure 5 shows the linear functions relating the different ERG variables that were fitted for all 18 individuals with normal vision. Data points from two patients with background diabetic retinopathy are shown as solid and open circles. The relationships between the b-wave amplitude and the a-wave slope for both patients are well within the normal range (Fig. 5A), consistent with normal visual information processing from the photoreceptor layer to the inner nuclear layer. The relationships between the peak power density of the oscillatory potentials and the slope of the a-wave differ significantly from the normal group (Fig. 5B). For a given a-wave slope, the oscillatory potentials of both patients are considerably reduced in size. When a linear function is fitted to the patients' data, the intercepts are within the normal range but the slopes are considerably smaller than the normal: 0.13 and 0.46 (solid and open circles, respectively). The peak power density of the oscillatory potentials is smaller than expected from the b-wave amplitude, and the slopes of the lines relating these two variables for both patients, 0.032 and 0.045, are significantly smaller than the normal range. However, the data points are found within the normal range (Fig. 5C).

Discussion

The corneal ERG is a complex electrical signal composed of several waves originating in different retinal structures. Each of these components is differently affected by the experimental conditions and by the functional integrity of the retina. Therefore, the corneal ERG must be used cautiously for interpretation of physiologic processes within the retina. Despite these

limitations, the ERG analysis, discussed here for dark-adapted retinas, provides some insights into retinal physiology and pathology. It should be stressed that the type of ERG analysis described here was not extended to light-adapted retinas because under these conditions, the dynamic range, at least in our electrophysiologic system, was too narrow to allow meaningful comparisons between the different ERG components.

It was previously argued that intersubject and intrasubject variability in the ERGs and differences between different laboratories could be partially circumvented by constructing the relationship between the b- and a-waves [15, 29]. This mode of ERG analysis has been expanded here to include the oscillatory potentials. Our data from a group of volunteers with normal vision demonstrated linear relationship between the peak power density of the oscillatory potentials and the slope of the a-wave (Figs. 4B and 5B). The relationships between the peak power density of the oscillatory potentials and b-wave amplitude (Figs. 4C and 5C) and between the b-wave amplitude and the a-wave slope (Figs. 4A and 5A) were characterized by a complex, nonlinear pattern. These relationships are similar to those previously reported [11] and suggest that disorders in the inner retina, such as those occurring during diabetic retinopathy and central vein occlusion, can be best identified by the oscillatory potentials to a-wave relationship. Affected patients may exhibit normal or slightly reduced values for the power density of the oscillatory potentials, but they are significantly reduced when compared to the a-wave slopes (Fig. 5).

The ERG components, a-wave, b-wave and oscillatory potentials, reflect the electrical activities in different, partially identified, retinal structures. Knowledge of the flow of visual information between these structures may help in localizing the site of retinal disorders. Several models can be hypothesized to describe the interactions between the retinal generators of the different ERG components. The simplest one assumes a hierarchic model arranged in series. The a-wave that originates in the photoreceptors constitutes the input to the inner nuclear layer, which contains the retinal cells whose electrical activity is reflected in the b-wave. The oscillatory potentials are assumed to be generated at more proximal sites, the inner plexiform layer, and therefore they probably depend on the activity in b-wave generators. According to this possibility, any factor that reduces one of the early ERG components (a- or b-waves) is expected to affect proportionally those generated in more proximal sites. An alternative model assumes that the a-wave generators, the photoreceptors, supply two parallel inputs to the neural retina, one leading to the b-wave generators and the other to those of the oscillatory potentials. In addition, a small interaction may exist between the b-wave and the oscillatory potentials. This model is based on the observation that the b-wave mainly depends on the activity in the on-bipolar cells [30], while the oscillatory potentials, which are assumed

to be generated by neural interactions in the inner plexiform layer, probably depend on off- as well as on-bipolar cells. Therefore, the oscillatory potentials reflect, at least partially, visual information that is not transmitted to the b-wave generators.

Electrophysiologic and pharmacologic studies supported one or both of the above schemes. γ-Aminobutyric acid and glycine-related drugs selectively reduced the oscillatory potentials [31, 32]. This observation is consistent with both models because these drugs supposedly act directly on the site of generation of the oscillatory potentials. In the rabbit, a linear relationship was found between the b-wave and the oscillatory potentials before and after administration of iodoacetic acid [33]. This finding supports the first model assuming a serial flow of information between the generators of the ERG components. On the other hand, when the rabbit retina was exposed to 2-amino-4-phosphonobutyric acid, a glutamate analogue that specifically blocks the on-bipolar cells [34], the b-wave was abolished while the oscillatory potentials were selectively preserved and the a-wave grew in amplitude [35]. These results support the second model of parallel processing.

The relationships between the ERG components shown in Figs. 4 and 5 can also be used to decide between the above alternatives. The b-wave to a-wave relationship is characterized by a complex nonlinear pattern (Fig. 4A). This relationship is consistent with the presence of a powerful amplifier between the generators of these two ERG components for dim-light stimuli that saturate when the flash intensity is increased. The peak power density of the oscillatory potentials, on the other hand, is linearly related to the a-wave slope (Figs. 4B and 5B). These findings can be compatible with the serial model only if the relationship between the oscillatory potentials and the b-wave is nonlinear in a manner that exactly compensates for the nonlinearity in the first stage of the model. Furthermore, the ERG data from the two patients with background diabetic retinopathy indicate a situation in which the pathways between the a-wave generators and those of the oscillatory potentials are selectively affected, while the b-wave to a-wave relationship is unaffected and oscillatory potentials to b-wave relationship is only slightly reduced (Fig. 5). This observation is more compatible with the model, suggesting parallel information transmission from the photoreceptors to the b-wave and oscillatory potential generators. This hypothesis can be further examined by applying the mode of ERG analysis suggested here to patients with known retinal disorders.

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