those agents are suggested to have therapeutic potential, the degree of anatomic rescue of photoreceptors is variable among agents. Further studies are warranted to assess survival-promoting agents for the preservation of retinal function, whereby recording of ERG responses provides a relatively simple, fast, reliable test.

Key Words

basic fibroblast growth factor (bFGF), electroretinographic response, light damage, midkine, rat, retinal degeneration

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Clinical Evaluation of Multifocal Electroretinogram

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Purpose. To compare the multifocal electroretinogram (ERG) system to conventional gan/feld and focal ERGs obtained from patients with known retinal diseases to assess its clinical applicability.

Methods. A multi-input system analysis was used to explore the field topography of ERG responses to local luminance modulation in patients with retinitis pigmentosa, pericentral pigmentary retinal dystrophy, branch retinal arterial occlusion, or idiopathic macular hole.

Results. The dysfunctional areas measured by multifocal ERG were compatible with those assumed by combined findings of gan/feld and focal ERGs. However, the wave shapes of multifocal ERG in the retina with arterial occlusion differed from those of conventional focal ERG, suggesting that the negative and positive deflections shown in the first-order kernel of multifocal ERG may not correspond to conventional a- and b-waves of ERG.


Although many authors have applied focal electroretinogram (ERG) to detect focal retinal abnormalities, the averaging technique used to improve the signal-to-noise ratio permits testing of a single local
Recently, Sutter et al\(^3\) introduced a "multifocal ERG system" that can stimulate multiple retinal areas simultaneously and detect each response independently by applying the multi-input system analysis technique.\(^6\) Using this system, they have succeeded in constructing an "ERG topography" of fine resolution. The technique, however, is in a preliminary stage, and few studies have evaluated the system for clinical application.\(^7\) It is important to determine whether this system may be clinically applicable. The authors have compared the results obtained by multifocal ERG to those acquired by ganzfeld and focal ERGs\(^8\) from patients with known retinal diseases.

SUBJECTS AND METHODS. Methods. The system used for recording multifocal ERG has been described by Sutter et al.\(^5\) The stimulus matrix consisted of 103 hexagonal elements displayed on a CRT color monitor (Sony [Tokyo, Japan] GDM 2038) driven at a 75-Hz frame rate. These hexagons were scaled with eccentricity to elicit approximately equal signal amplitude at all locations (Fig. 1A). At a viewing distance of 27 cm, the radius of stimulus array subtended approximately 25° high and 30° wide. Each hexagon was independently alternated between black and white according to a pseudorandom sequence called binary m-sequence\(^5\) at a rate of 75 Hz. This stimulation technique allowed extraction of the response from each stimulus element. The high luminance was 138.0 cd/m\(^2\), and the low luminance was 3.5 cd/m\(^2\), resulting in a mean screen luminance of approximately 70.8 cd/m\(^2\). A small red fixation spot was placed at the center of the stimulus matrix. A Burian-Allen bipolar contact lens electrode was used for signal derivation, and a ground electrode was attached to the carlobe. Subjects' pupils were fully dilated with a combination of 0.5% tropicamide and 0.5% phenylephrine hydrochloride. The opposite eye was occluded. After subjects were optically corrected to their best visual acuities, they were asked to look at the fixation spot. The signal amplification was 50,000, and the filter setting was bandpass 6 Hz to 100 Hz (Nihon Koden [Tokyo, Japan] AB-620G). An artifact rejection technique was used.\(^9\) The total recording took 4 minutes and were divided into eight segments. Local responses were extracted from the raw data by computing cross-correlation between the m-sequence and the response cycle.\(^5\) The amplitude of each local response was estimated as the dot product between the normalized response template and each local response (scalar product method).\(^5\) Electroretinographic topographies were constructed to visualize the retinal response density (amplitude per unit retinal area). The array of local responses and ERG topography were plotted in the same manner as the visual field.

Our system for recording the focal ERG has been described.\(^8\) Briefly, the subject's pupils were fully dilated; an infrared television camera was positioned to monitor the exact locus of stimulation on the fundus during recordings, and a Burian-Allen bipolar contact lens electrode permitted clear observation of the fundus on the television monitor. The intensity of the white stimulus light (4°, 5°, 10°, 15° diameter) and the background light were 3.2 and 2.2 scotopic trolands (log), respectively. The ERG was recorded with 5-Hz rectangular stimuli for 100 msec with the light on and 100 msec with the light off. A total of 512 responses were averaged by a signal processor.

Ganzfeld ERGs were recorded according to a previously described method.\(^8\) After 30 minutes of dark adaptation, a rod (scotopic) ERG was recorded with a blue light at an intensity of \(5.2 \times 10^{-3} \text{ cd} \cdot \text{m}^{-2} \cdot \text{sec}^{-1}\).
A cone-rod mixed single bright-flash (bright white) ERG was recorded with a white stimulus at an intensity of 44.2 cd m\(^{-2}\) sec\(^{-1}\). A cone (photopic) ERG and a 30-Hz flicker ERG were recorded with a white stimulus intensity of 4 cd m\(^{-2}\) sec\(^{-1}\) and 0.9 cd m\(^{-2}\) sec\(^{-1}\), respectively, under a background illumination of 21 foot-lamberts. Four responses and 16 responses were averaged to record cone ERG and 30-Hz flicker ERG, respectively.

Subjects. Fifteen normal subjects (ranging in age from 21 to 63 years) and four patients with either retinitis pigmentosa, pericentral pigmentary retinal dystrophy, branch retinal arterial occlusion, or idiopathic macular hole were examined. The research followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects and patients after the nature and possible consequences of the study were explained.

RESULTS. Normal Subjects. An array of 103 local responses of multifocal ERG and ERG topography obtained from the left eye of a normal subject (24-year-old woman) are shown on Figures 1B and 1C, respectively. A small response was seen at the blind spot (arrow), and this residual response can be explained by the fact that the element size of the hexagon at the blind spot is larger than the blind spot.

Ten continuous recordings of multifocal ERG were obtained from a normal subject to investigate the reproducibility of this technique. Mean response densities (±1 SD) at two areas of central hexagon and 15° temporal field hexagon (including the blind spot) were 11.4 ± 1.7 nV/deg·deg and 1.4 ± 0.3 nV/deg·deg, respectively, suggesting fine reproducibility. Intersubject variability of multifocal ERG was investigated in 15 normal subjects at the same two areas mentioned. Mean response densities (±1 SD) were 12.2 ± 2.7 nV/deg·deg and 1.7 ± 0.5 nV/deg·deg, respectively.

Patients. Retinitis pigmentosa. A 39-year-old woman had a 2-year history of peripheral visual disturbance. Visual acuity was 1.5 in both eyes. Goldmann perimetry revealed constriction of the visual field (Fig. 2, top), and the fundus examination disclosed attenuated arteries, scattered pigmentary changes, and a pale disc. Although ganzfeld ERG was nondetectable in rod and cone components (Fig. 3A), focal ERG with 5°-, 10°-, and 15°-diameter spots at the fovea was well preserved (Fig. 3B). The result of multifocal ERG revealed reduced responses in the peripheral field but relatively preserved responses in the central field (Fig. 4).

Pericentral pigmentary retinal dystrophy. A 47-year-old woman had a 3-year history of bilateral paracentral visual loss. Visual acuity was 1.0 in both eyes. Goldmann perimetry showed annular scotoma (Fig. 2, middle), and the fundus examination disclosed depigmented spots along the vascular arcade. There were neither attenuated arteries nor pigmentary changes. Focal macular ERG within 15° was preserved (Fig. 3B), but ganzfeld ERG was moderately decreased in core and rod components (Fig. 3A). Multifocal ERG revealed reduced responses in the area approximately corresponding to the annular scotoma presented by Goldmann perimetry (Fig. 4).

Branch retinal artery occlusion. A 51-year-old man noticed sudden visual loss in the upper visual field of the left eye. Visual acuity was 1.5 in both eyes. Goldmann perimetry revealed a small superior scotoma in the left eye (Fig. 2, bottom), and the fundus examination disclosed a branch occlusion in the inferotemporal artery of the left eye. Whitening retinal edema was seen along the artery. Ganzfeld ERG was normal.
Ganzfeld ERG

A

Normal

Case 1

Case 2

Case 3

Scotopic

Bright White

Photopic

30 Hz Flicker

Focal ERG

B

Normal

Case 1

Case 2

Case 3

Upper

(Nonusal)

Lower

(Involved)

FIGURE 3. (A) Ganzfeld electroretinograms (ERGs) in a normal subject, patient 1, patient 2, and patient 3. Rod (scotopic), cone (photopic and 30-Hz flicker), and cone-rod mixed (bright white) ERG are shown. (B) Focal macular ERGs in a normal subject, patient 1, and patient 2. Three different sizes of stimulus spot (5°, 10°, and 15° in diameter) were used. (C) Focal ERGs in the left eye of patient 3 recorded with a 10°-diameter spot in the retina at normal upper area and lower arterial occlusion.

(Fig. 3A), but focal ERG recorded with a 10°-diameter spot in the retina with arterial occlusion showed a markedly reduced response with a negative configuration, compared with a response recorded at the opposite normal upper area (Fig. 3C). Multifocal ERG demonstrated decreased responses corresponding to the ischemic inferotemporal area but did not show a negative wave configuration in the presumed affected area, and both negative and positive deflections had smaller amplitudes than the other ERGs (Fig. 4).

Idiopathic macular hole. A 59-year-old woman with a 1-year history of reduced central vision in the right eye was referred for treatment. Visual acuity was 0.2 (OD) and 1.0 (OS). A full-thickness macular hole measuring approximately one third of a disc diameter surrounded by an elevated halo was observed in the right eye. Focal macular ERG recorded with a 4°-diameter spot at the fovea of the right eye was decreased approximately one half in amplitude compared with that in the left eye. Multifocal ERG demonstrated low amplitude at the central area corresponding to a macular hole but normal responses at other areas, resulting in a volcano-like topography (Fig. 4).

DISCUSSION. The multifocal ERG system, designed by Sutter et al., was reported to be a promising tool to detect the spatial extent of retinal dysfunction. It is essential, nevertheless, to evaluate the possible correlations between results obtained from this technique and those from conventional ganzfeld and focal ERGs in known retinal diseases. Thus, we studied four patients with known retinal diseases, as follows: only the central retina functioned normally (retinitis pigmentosa); only the paracentral retinal area was dysfunctional (pericentral pigmented retinal dystrophy); only the inferior retina was dysfunctional (branch retinal arterial occlusion); and only the macula was impaired (idiopathic macular hole). The dysfunctional areas measured by multifocal ERG were compatible

FIGURE 4. (A) One hundred three local responses of multifocal electroretinogram and (B) electroretinogram topographies obtained from the left eye of patient 1, patient 2, and patient 3, and the right eye of patient 4.
with those assumed by combined findings of ganzfeld and focal ERGs.

The technique also offered high-resolution mapping of the retina in a very short time, which had never been achieved by conventional averaging ERG techniques. Some problems must be considered, however, when mapping the retina. The intersubject variability of multifocal ERG may limit its sensitivity in detecting slightly impaired lesions. Therefore, an age-matched normal control is needed to evaluate the amplitude because a significant inverse correlation between amplitude of local ERG response and age has been reported.\(^5\) Another problem is that steady eye fixation may be difficult to achieve in a patient with poor visual acuity because of the inability to see the central fixating point and eye movement may result in considerable noise. For such patients, Sutter (personal communication) has suggested various fixation aids to be displayed on the television monitor (for example, a small cross placed at the center or eccentric spokes).

A final problem is the analysis of each wave shape recorded simultaneously from multiple retinal locations using a high-frequency random stimulus. The multifocal ERG discussed in this report (first-order kernel) can be considered as the mean response to a local flash. As presented in a normal subject (Fig. 1B), it consists of a negative deflection followed by a positive deflection, with a shape similar to that of conventional a- and b-waves. However, whether these deflections have the same retinal origins as the a- and b-waves remains controversial. Because the physiological substrate of kernels is not well understood,\(^6,10\) comparing the wave shape of conventional focal ERG to that of multifocal ERG is important. For example, in a patient with branch retinal arterial occlusion (patient 3), conventional focal ERG showed a negative configuration in the impaired retina. Although the a-wave was preserved, the b-wave and oscillatory potentials were essentially absent when compared with ERG obtained from the upper normal retina (Fig. 3C). This finding is reasonable because the retinal artery supplies the areas at the origin of the b-wave and oscillatory potentials, but the photoreceptors—the origin of the a-wave—are supplied by choroidal circulation. On the other hand, multifocal ERG in the presumably affected area did not show a negative configuration, and both negative and positive deflections showed smaller amplitudes than the other ERGs. This result suggests that the negative and positive deflections shown in the first-order kernel of multifocal ERG may not correspond to conventional a- and b-waves of ERG. Therefore, further studies are needed to identify the origin of each component of multifocal ERG.

**Key Words**

electroretinogram, focal, ganzfeld, multifocal, topography

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