Sequential recording of photic and nonphotic electro-oculogram responses in patients with extensive extramacular drusen

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Abstract. At present, no clinical electrophysiologic test defines dysfunction of the retinal pigment epithelium. We studied four electrophysiologic responses of the retinal pigment epithelium to compare results from three normal subjects with those from three patients with a diffuse retinal pigment epithelial disorder, extramacular drusen. We recorded the fast oscillation, hyperosmolarity response, acetazolamide response, and light peak by means of a clinical protocol in which these could be elicited consecutively. We found no significant differences between the normal subjects and patients with drusen for any of the four responses. These results suggest that retinal pigment epithelial electrophysiologic function is well maintained despite the widespread physical abnormalities of the retinal pigment epithelium in extramacular drusen. This combined test was well tolerated and may prove useful in characterizing other diseases involving the retinal pigment epithelium.

Abbreviation: RPE-retinal pigment epithelium

Introduction

There is no clinical electrophysiologic test that specifically defines retinal pigment epithelial (RPE) function in disease [1]. The c-wave depends on retinal photoreception and resultant changes in extracellular potassium concentration to stimulate the apical RPE membrane [2, 3]. The fast oscillation is also initiated by light and retinal ionic activity [4]. The light response of the standing potential requires photoreception and is severely abnormal (in the absence of retinal damage) only in Best's vitelliform dystrophy, in which there is no known functional abnormality of the RPE [1, 4]. The nonphotic responses to acetazolamide [5, 6], hyperosmolarity [7, 8] and bicarbonate [9], are generated specifically across the basal membrane of the RPE but have not shown diagnostic correlation with RPE disease or dysfunction.

To facilitate investigation of RPE responses, we previously developed a clinical protocol for recording sequentially, in one session, the light response and two nonphotic responses (acetazolamide and hyperosmolarity) [10]. For this study, we expanded this protocol to include the fast oscillation, and we address two questions: Is this protocol well tolerated and applicable to clinical
use? Do these tests show any abnormalities in patients with the diffuse RPE disorder of extramacular drusen?

**Subjects and methods**

The four-test protocol is an extension of a three-test procedure previously described [10]. We recorded the standing potential by the conventional electro-oculographic technique, with silver saucer electrodes placed at each canthus and a ground electrode on the forehead. The examinee generates horizontal saccades by alternately viewing two red light-emitting diodes situated at a visual angle of 30° within a full-field stimulating dome.

Subjects were not preadapted other than room lighting, and the pupils were not dilated. The session began by recording the fast oscillation for about 10 min. Dark and light periods (stimulus intensity, 150 cd/m²) were alternated every 70–80 seconds. Next, room lights were turned off and the subject was dark adapted for 30 min. This was followed by an intravenous injection of mannitol (50 mL of 25% solution over 5 min) with recording for 25–30 min, and then by an injection of acetazolamide (500 mg over 2 to 3 min) with recording for 25–30 min. Finally, the eyes were light adapted for 10–15 min to generate a light peak (stimulus intensity, 150 cd/m²). This stimulus intensity is lower than recommended for undilated pupils in the published standard for clinical electro-oculography [11] but these experiments were begun before the development of the standard, and we did not want to change recording conditions between patients. Total test time was 100–110 min. The standing potential was measured continuously throughout the fast oscillations (with saccades every 1.5 seconds) and thereafter for the first 15 seconds of every minute (with saccades every 1.0 second) beginning 5 min before the end of dark adaptation.

We calculated the magnitude of the nonphotic responses by the formula of (Vo – Vmin) / Vo × 100, where Vo is the baseline electro-oculogram amplitude in the dark and Vmin is the trough value after injection of the drugs. The fast oscillation is expressed as peak/trough amplitude ratio. For the light peak, we calculated the Arden ratio (light peak/dark trough amplitude) and measured peak latency.

We studied both eyes of three normal subjects (age range, 25–51 years; two men and one woman) and three patients with extensive extramacular drusen (age range, 35–51 years; two men and one woman). Best corrected vision in the normal subjects ranged from 20/15 to 20/20, and fundoscopy showed no retinal abnormalities. Best corrected vision in the patient group ranged from 20/15 to 20/25. Fundoscopy and fluorescein angiography disclosed extensive hard drusen not only in the posterior pole, but beyond the arcades and nasal to the disc as well (Fig. 1). Amsler grid testing showed either minimal or no
Fig. 1. Fluorescein angiograms from a patient show diffuse drusen extending beyond the arcades and nasal to the disc, indicative of widespread retinal pigment epitheliopathy.

metamorphopsia. All three of our patients denied a family history of drusen or other hereditary eye diseases, but we did not examine parents or siblings. Exclusion criteria for our protocol included pregnancy or the presence of
significant cardiopulmonary disease. These studies were approved by our institutional Human Studies Committee, and informed consent was obtained before each recording session.

Results

The combined series of electrophysiologic tests was well tolerated by all examinees, and there were no untoward effects from the agents other than occasional local burning or transient paresthesias associated with the injection of acetazolamide. Figure 2 shows a representative record of the standing potential changes from a control subject and a patient with extensive drusen.

The averaged values for each pair of normal and patient eyes, respectively, for the four responses are shown in Fig. 3. There was no clear difference in any of these tests between patients and normal subjects.

Discussion

We found that a four-part combined photic and nonphotic RPE test is clinically feasible and well tolerated. This comprehensive RPE electrophysiologic evaluation may help in classifying and understanding RPE disease. Since a standard for clinical electro-oculography has now been published [11], we recommend that recording conditions for the fast oscillation and light peak components of our combined test be adjusted to conform.

All four of these RPE responses are generated electrically across the basal membrane of the RPE. The light response represents a depolarization of the basal membrane of the RPE [12], presumably by a ‘light peak substance’ originating from the photoreceptors [13] and diffusing across the subretinal space and into the RPE cell. The fast oscillation is a reflection of delayed hyperpolarization of the basal membrane of the RPE [4], possibly mediated by an intracellular decrease in the potassium concentration and involving a change in chloride conductance. The nonphotic responses represent hyperpolarizations of the basal membrane of the RPE independent of light or the neurosensory retina [6, 8, 14].

These nonphotic responses are of theoretical interest as tests of the RPE because the mechanisms of changes in the standing potential are different from those of the light peak and they do not require a photostimulus. Hence, these tests may reveal the status of the RPE independent of abnormality in the photoreceptors or neural retina. However, little is known about the physiologic role of either the photic or nonphotic RPE voltage changes, or about their correlation with visual function.

In this study, we examined patients with widespread drusen, a diffuse pigment epitheliopathy wherein some functional abnormality of the RPE might
Fig. 2. Representative recordings of the four RPE responses from a normal subject (top) and from a patient with extensive drusen (bottom). The fast oscillation is on the left (showing smoothed as well as raw curves), followed by electro-oculogram recording of the hyperosmolarity, acetazolamide and light responses. The vertical calibration bars in each section indicate 200μV amplitude; the darkened points show cursor locations for calculation of trough and peak amplitudes.
Fig. 3. Comparison of data between normal and patient eyes for the four tests. Each point represents the averaged binocular value from a normal subject (closed circle) or a patient (open circle). Dotted lines show the mean for each group of points. There is no substantial difference between patient and control values for any of the responses.

be expected. We thought we might find an abnormality in one or more of the four RPE responses and possibly correlate the amount of electrophysiologic dysfunction with the extent or location of the disease. However, no clear abnormality was demonstrable for any of the tests in the patients with extensive drusen.

These results show that anatomic disturbance of the RPE is not necessarily correlated or commensurate with electrophysiologic abnormality. Alternatively, electrical responses of the basal membrane may simply not be affected by many functional abnormalities of the RPE. Further work is still needed to understand the pathophysiologic and functional implications of these tests, and to determine whether they have diagnostic value.

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References


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