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Evaluation of inner retinal function in myopia using oscillatory potentials of the multifocal electroretinogram

Jennifer C. Chen *,[1], Brian Brown [1], Katrina L. Schmid [1]

School of Optometry and Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia

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Abstract

Purpose: Oscillatory potentials have been suggested to arise from the inner retina at the level of amacrine cells and inner plexiform layer and they are thought to provide a non-invasive assessment of inner retinal function. We sought to investigate the response dynamics of the inner retina of adult emmetropes and myopes by analysing the oscillatory potentials of the multifocal electroretinogram (mfERG) in these groups.

Methods: Eleven emmetropes and 18 myopes underwent mfERG testing using VERIS 5.1.5X. Myopes were further separated based on whether their myopia was stable ($n = 9$) or progressing ($n = 9$). Oscillatory potentials were recorded using a modified mfERG stimulation technique, the slow flash paradigm, and they were extracted using band-pass filtering from 100 to 300 Hz. The slow flash mfERG stimulus array consisted of 103-scaled hexagons and flickered according to a pseudorandom binary *m*-sequence (2^{13}–1). Amplitudes and implicit times of the first-order oscillatory potentials were analysed.

Results: There were significant differences in the implicit time of the oscillatory potentials of the emmetropes, stable myopes and progressing myopes ($F_{2,25} = 3.663$, $p = 0.043$). Progressing myopes had significantly shorter implicit times compared to emmetropes ($p = 0.026$ by 1.0–4.7 ms) and stable myopes ($p = 0.043$ by 0.8–1.3 ms), whereas implicit times of stable myopes and emmetropes were similar. There were no statistically significant differences in amplitude of the oscillatory potentials between the groups ($F_{2,25} = 0.890$, $p = 0.426$).

Conclusions: Significant differences in multifocal oscillatory potentials between stable and progressing myopes were found. This finding is further evidence of an inner retinal involvement in human myopia progression and may suggest an underlying alteration to dopaminergic or GABAergic retinal systems.

Keywords: Myopia; Multifocal electroretinogram; mfERG; Oscillatory potentials; Slow flash mfERG; Refractive error

1. Introduction

Oscillatory potentials (OPs) of the conventional full-field electroretinogram (ERG) are high frequency components that are superimposed on the ascending phase of the b-wave (Karwoski & Kawasaki, 1991; Wachtmeister, 1998). These small amplitude, rhythmic wavelets are believed to be generated by contributions from the inner retina and it has been suggested that their assessment can provide a non-invasive, *in vivo* evaluation of inner retinal function (Wachtmeister, 1998). While their exact cellular origins have not been elucidated, studies using pharmacological agents and cases of inner retinal disease have led to a better understanding of the retinal mechanisms that underlie the generation of OPs. Based on the current theory, OPs are thought to arise from the inner retina at the level of amacrine cells and/or the inner plexiform layer and are generated by the neural interactions between the bipolar cells, amacrine cells, and ganglion cells; an origin within the bipolar cells has also been postulated (Heynen, Wachtmeister, & van Norren, 1985; Wachtmeister, 1998; Wachtmeister & Dowling, 1978). More specifically, OPs are thought to reflect the inhibitory feedback circuitry initiated by the amacrine cells, such as those involving the dopaminergic,

* Corresponding author. Fax: +617 3138 6030.
E-mail address: jc.chen@qut.edu.au (J.C. Chen).
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GABAergic, and glycine-mediated neuronal pathways (Dong, Agey, & Hare, 2004; Hare & Ton, 2002; Rangaswamy, Hood, & Frishman, 2003; Wachtmeister, 1980, 1981, 1998).

The use of OPs has been applied to a number of retinal diseases to study functional abnormalities of the retina (Wachtmeister, 1998). In studies of diabetic retinopathy, OPs have long been established as a sensitive indicator of retinal dysfunction associated with the disease process (Bresnick & Palta, 1987; Bresnick, Korth, Groo, & Palta, 1984; Holopigian, Seiple, Lorenzo, & Carr, 1992; Shirao, Okumura, Ohta, & Kawasaki, 1991; Tzekov & Arden, 1999; Yoshida, Kojima, Ogasawara, & Ishiko, 1991). Alterations in OP implicit time and/or amplitude have been shown to occur in absence of any clinical signs of diabetic retinopathy; once the retinopathy is present, they can even predict the progression of further retinal changes (Bresnick et al., 1984; Simonsen, 1980). More recently, the development of the multifocal electroretinogram (mfERG) (Bearse & Sutter, 1996; Sutter & Tran, 1992) has allowed OPs to be examined at multiple retinal locations in studies of diabetes mellitus (Bearse et al., 2004; Kurtenbach, Langrova, & Zrenner, 2000; Onozu & Yamamoto, 2003), where there is an added advantage of studying the regional variations of OPs and determining whether changes in OPs correspond to retinal sites of retinopathy or not. Multifocal OPs have also been applied clinically to study inner retinal function in normal ageing (Kurtenbach & Weiss, 2002), and in patients with hydroxycholoroquine retinopathy (Tzekov, Serrato, & Marmor, 2004), congenital stationary night blindness (Schuster et al., 2004) and glaucoma (Fortune et al., 2003; Rangaswamy, Zhou, Harwerth, & Frishman, 2006). In these studies, OPs have been observed to be reduced and delayed in many patients without signs of hydroxychloroquine toxicity (Tzekov et al., 2004) or diabetic retinopathy (Bearse et al., 2004; Kurtenbach et al., 2000). This suggests OPs are a sensitive index that reflects an alteration of inner retinal sensitivity that may be explained by impaired rod–cone interactions (Bearse, Shimada, & Sutter, 2000; Wu & Sutter, 1995).

Given the evidence that OPs are a sensitive index of inner retinal function, investigations of OPs in individuals with myopia should reveal useful information on the retinal-mediated mechanisms of myopia development. So far studies of OPs derived from flash ERGs in myopia have been limited to animal models, where Fujikado, Hosohata, and Omoto (1996) found that OP amplitudes were attenuated in chick eyes with longer axial length, suggesting altered inner retinal function of these form deprived, myopic eyes. OPs have also been found to differ between chick eyes with form-deprivation myopia and lens-induced myopia (Fujikado, Kawasaki, Suzuki, Ohmi, & Tano, 1997). Fujikado et al. (1997) found that flash ERG OPs were significantly reduced in form-deprivation myopia compared to lens-induced myopia, while a- and b-waves for the two types of myopia were similar. Other evidence of inner retinal involvement in the development of myopia has come from animal studies which have identified several transmitters and alterations to gene expression that are thought to be involved in the regulation of eye growth (i.e., dopamine, ZENK-glucagon, Pax-6 expression, and serotonin). Many of these signals originate from the inner retina and these substances are known to be involved in amacrine cell and ganglion cell processing (Bhat, Rayner, Chau, & Ariyasu, 2004; Bitzer & Schaeffel, 2004; Morgan, 2003; Rymer & Wildsoet, 2005).

As information on inner retinal function in human myopic eyes using electrophysiological techniques is limited, the aim of this study was to investigate the characteristics of inner retinal function in myopia and compare multifocal OPs measured with the slow flash mfERG paradigm in adult myopes and emmetropes. We have previously used the same paradigm to study the late response components of the first-order slow flash responses in myopia (Chen, Brown, & Schmid, 2006b). This current paper focussed on the OPs. We speculated that characteristics of the OPs may be a parameter of retinal function that differentiated myopic and emmetropic eyes and also stable and progressing myopic eyes.

2. Methods

2.1. Subjects

Twenty-nine subjects (11 emmetropes and 18 myopes) aged 18–30 years participated in the study. First-order slow flash response data of the twenty-six subjects was published in Chen et al. (2006b) and their original data included and reanalysed here. Readers are directed to the study of Chen et al. (2006b) for the analysis of the first-order components of the slow flash response. Inclusion and exclusion criteria, classification of subjects into refractive errors groups, determination of myopia progression rate and axial length measurement technique were as described in Chen et al. (2006b). Mean spherical refractive errors of the subjects ranged from plano to −9.50 D. The mean age of emmetropes and myopes was 21.1 ± 1.9 and 20.8 ± 2.9 years, respectively. The axial length of subjects ranged from 21.78 to 27.00 mm. The study was conducted in accordance with the tenets of the Declaration of Helsinki and the requirements of the Queensland University of Technology Human Research Ethics Committee. Informed consent was obtained from the subjects after explanation of the nature of the study and possible consequences of participation.

2.2. MfERG measurements

MfERG stimulation was performed with the Visual Evoked Response Imaging System (VERIS 5.1.5× refractor/camera system, Electro-Diagnostic Imaging Inc., Redwood City, CA, USA) using the slow flash mfERG paradigm as previously described (Chen et al., 2006b). The refractor/camera unit was used for refractive correction and to monitor eye movements and fixation stability during recordings. Responses were recorded on right eyes following pupil dilatation, using the Dawson–Trick–Litzkow (DTL) thread electrode. The slow flash mfERG stimulus array consisted of 103 hexagons scaled with eccentricity (stretch factor, 10.46). Each hexagon was temporally modulated between black (<2 cd/m^2) and white (200 cd/m^2) according to a pseudorandom binary *m*-sequence (2^{13}–1 steps in length). As a relatively long flash interval is required for reliable recordings of OPs, the stimulation sequence was slowed by inserting three dark frames such that each step in the *m*-sequence was four frames in length (53.3 ms). Each session of recording took approximately seven minutes to complete and was divided into 16 equal segments for subject comfort (each of 27 s duration). Two complete mfERG recordings were