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Investigation of changes in the myopic retina using multifocal electroretinograms, optical coherence tomography and peripheral resolution acuity

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ABSTRACT

We investigated relationships between retinal structure using optical coherence tomography (OCT) and retinal function using peripheral resolution acuity and multifocal electroretinograms (mfERG) in 56 subjects with a range of refractive errors (+0.50 to −15.00 D). Retinal thinning occurred in moderate and high myopia which appeared to be primarily due to reduced thickness of the middle to inner retina (MIR) (outer plexiform layer to the nerve fiber layer). MIR thickness was correlated with reduced spatial resolution and delayed mfERG timing in the peripheral retina. The findings suggest the structure and function of the post-receptor retina is susceptible to disruption in moderately and highly myopic eyes.

1. Introduction

It is known that the functional performance of myopic eyes is reduced compared to emmetropic eyes. Visual acuity (Strang, Winn, & Bradley, 1998), grating resolution acuity (Atchison, Schmid, & Pritchard, 2006; Chui, Yap, Chan, & Thibos, 2005; Coletta & Watson, 2006), contrast sensitivity (Fiorentini & Maffei, 1976; Liou & Chiu, 2001), spatial summation (Atchison et al., 2006; Jaworski, Gentle, Zele, Vingrys, & McBrien, 2006) and the electroretinogram (Chan & Mohidin, 2003; Chen, Brown, & Schmid, 2006a, 2006d; Flitcroft, Adams, Robson, & Holder, 2005; Kawabata & Adachi-Usami, 1997; Luu, Lau, Koh, & Tan, 2005; Luu, Lau, & Lee, 2006; Perlman, Meyer, Haim, & Zonis, 1984; Westall et al., 2001; Yamamoto, Nitta, & Kamiyama, 1997) can all be adversely affected in myopia. In many cases, functional deficits in myopia can be primarily associated with an inner retinal involvement through changes to retinal neurons and altered retinal biochemistry (Chen, Brown, & Schmid, 2006b; Chen, Brown, & Schmid, 2006c; Fujikado, Hosohata, & Omoto, 1996; Iuvone, Tigges, Stone, Lambert, & Laties, 1991; Li, Schaeffel, Kohler, & Zrenner, 1992; Stone, Lin, Laties, & Iuvone, 1989). Studies have shown that altered neural processing could result, in part, from retinal stretching in the enlarged myopic eye, which may produce both increased retinal cell spacing and post-receptoral retinal dysfunction and lead to a decrease in retinal sampling (Atchison et al., 2006; Chui et al., 2005; Coletta & Watson, 2006).

Indeed, in addition to the functional changes reported, various ocular structures can be altered in myopic eyes when compared to emmetropic eyes. Clinical studies show the increased risk of chorioretinal abnormalities in highly myopic eyes (>6D) (Saw, Gazzard, Shih-Yen, & Chua, 2005) and structural changes to the sclera, choroid and retina are all reported in myopia (Crewther, 2000; McBrien & Gentle, 2003; Rada, Shelton, & Norton, 2006; Rymer & Wildsoet, 2005). Furthermore studies of lens-induced and form-deprived myopic animal retinae, have found direct relationships between retinal thickness (including thinning of the choroid and sclera, and elongation of photoreceptor outer segments) and myopia (Beresford, Crewther, Kiely, & Crewther, 2001; Hung, Wallman, & Smith, 2000; Liang, Crewther, Crewther, & Barila, 1995). In human eyes, in vivo imaging studies of retinal thickness using third generation OCT demonstrate significant correlation between axial length and macular thickness (Lam et al., 2007; Wu et al., 2007). Thinning of the peripheral retina and thickening of the fovea occurs in myopia and is attributed to mechanical stretching of the retina/sclera due to the eye elongation.

Although myopic changes to the inner retina and post-receptor pathways are implicated in many studies, there has been little information linking retinal structure to function or the impact of myopic retinal stretching on the microstructure of the different retinal layers in human eyes. The present study aims to investigate in vivo the retinal laminar structure in myopia and compare this to measured changes in retinal function. A strategic element of the present study is to generate comparative retinal structure–function data at specific retinal locations within the same eyes.

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2. Methods

2.1. Participants

Fifty-six subjects (40 female (f), 16 male (m)) aged between 19 and 45 years old (median 23 years) and with right eye spherical equivalent (SE) refractive errors of +0.50 to −15.00 Diopters (D) (median −3.00 D) participated. Subjects were classified as having, emmetropia between +0.50 D and −0.50 D, mild myopia between −0.75 D and −2.75 D, moderate myopia between −3.00 D and −5.75 D and high myopia over −6.00 D. None of the subjects had more than 1.50 D of astigmatism (median 0.50 D). Each refractive group contained 14 subjects and the groups were matched for age and sex (Table 1). Subjects showing signs of myopic retinal degeneration were excluded from the study as were subjects with any history of eye disease or visual complaint other than refractive error. The study adhered to the requirements of the Office for Research Ethics Committees Northern Ireland (ORE-CNI) and to the tenets of the Declaration of Helsinki. Subjects gave informed consent prior to participation.

The right eye of each subject was used in this study and the pupil was maximally dilated using 1% tropicamide. The spherical, cylindrical and mean SE refractive errors were measured using an open-view autorefractor (WR-5100K, Grand Seiko, Hiroshima, Japan). Three readings were taken to obtain an average. The axial length and corneal curvature were measured using the IOLMaster (Carl Zeiss Meditec, Dublin, CA, USA), for which accuracy and repeatability have been established (Lam, Chan, & Pang, 2001; Sheng, Bottjer, & Bullimore, 2004). Three measurements were taken and the average derived.

Refractive correction was applied using large diameter (50 mm) corrective lenses placed at the estimated anterior focal plane (AFP) of the eye (vertex distance of 16 mm). The purpose of this was to implement Knapp's Law and maintain equal relative spectacle magnification (RSM) between subjects with different refractive errors (Bennett & Rabbetts, 1989; Chui et al., 2005). The correcting lens power included the determined refractive correction combined with an appropriate near addition for the stimulus distance to remove any accommodative requirement.

2.2. Peripheral resolution acuity

Resolution acuity thresholds were measured using an orientation-identification task at locations of 14° eccentricity in the superior temporal and inferior nasal visual field along the 45° meridian (chosen to avoid the region of the optic disc). Sinusoidal grating stimuli (VSG2/3, Cambridge Research Systems, Rochester, UK) consisting of 2° radius circular Gabor patches with gratings orientated at either 0° or 90° rotation were presented against a mean luminance background. The subject's left eye was occluded and right eye corrected for the test distance. Subjects fixated a central target and used their peripheral vision to perceive the stimulus. Fixation was monitored by an observer. Peripheral refractive errors were not corrected since it is known that they are little different from the fovea at this eccentricity and that peripheral grating acuity is robust to significant levels of blur (Anderson, 1996b; Wang, Thibos, & Bradley, 1997). Resolution threshold was measured using a two-alternative forced choice paradigm (2AFC). Stimuli were presented for one second (s) (which included 0.3 s attack and decay times) and three seconds were given to respond. A linear staircase method with 1.6 dB step size was used. The spatial frequency of the grating was increased by one step if three consecutive responses were correct and decreased by one step after one incorrect response. The subject used a response box to indicate whether they perceived the grating stimulus to be orientated in a horizontal or vertical direction. The cut-off spatial frequency was determined from the average of six reversals for each stimulus location.

2.3. Multifocal electroretinogram (mfERG)

mfERG stimulation (VERIS 4.1, Electro-Diagnostic Imaging, Inc., San Mateo, CA, USA) was performed using a standard protocol (Marmor et al., 2003) with Dawson–Trick–Litzkow (DTL) corneal contact thread electrodes. The right eye was corrected for the test distance and the subject instructed to fixate a central target. The left eye was occluded. The mfERG stimulus consisted of a high luminance, high contrast, 61 hexagonal element pattern array, scaled with eccentricity and was placed 33 cm from the subject covering 50° of the central visual field. Each hexagon was modulated between black (<10 cd/m^2) and white (450 cd/m^2) and the test performed in normal room lighting conditions (surface luminance ~150 cd/m^2) with a recording time of four minutes. The mfERG signals were sampled at 1 kHz, filtered between 10 and 300 Hz and amplified by 100 K. The first 80 ms of each signal from each stimulus element was analyzed. The response density amplitude (nV/deg^2) and implicit timing of the major peak P1, and trough N2, of the waveforms were measured (Fig. 1). Individual responses from the superior temporal to inferior nasal retina were measured along with responses grouped into concentric rings as a function of retinal eccentricity.

2.4. Retinal thickness

Overlapping OCT (Stratus OCT 3.0, Carl Zeiss Meditec, Dublin, CA, USA) images of the retina were acquired from the right eye of each subject along the 45° meridian and covered the central 32° of the retina. Five millimeter OCT line scan protocols consisting of 512 A-scans/image were used. Accurate central fixation was confirmed in each patient by observing the location of the foveal depression in each scan. Three measurements of retinal thickness were determined; total retinal (TR) thickness was defined as the distance between the inner boundary of the highly reflective border (HRB) representing the retinal pigment epithelium (RPE) (which included distinguishing the hyper-reflective junction of photoreceptor inner/outer segments from the RPE (Huang et al., 1998; Pons & Garcia-Valenzuela, 2005)) and the outer boundary of the HRB representing retinal nerve fiber layer (RNFL). The retina was then divided into photoreceptor retinal (PR) thickness, defined as the distance from the inner boundary of the RPE to the outer boundary of the low reflective band representing the outer plexiform layer (OPL) and mid-inner retinal (MIR) thickness defined as the distance between the outer boundary of the OPL and the boundary of the RNFL (Shahidi, Wang, & Zelkha, 2005) (Fig. 1). Concerns expressed regarding the accuracy of some automated analysis techniques (Costa et al., 2004; Sadda et al., 2006), prompted the use of manually placed electronic calipers for retinal thickness measurements. For each scan, retinal thicknesses (at 0.5° intervals) were measured on two occasions and an average value calculated. All the measurements were performed by a single operator who was blinded to the subject type. Repeatability of the manual thickness measurements was determined. Average retinal thickness values were calculated for retinal regions which corresponded with the size and location of the mfERG stimulus elements.

2.5. Statistical analysis

Analyses concentrated on the two peripheral retinal regions; between 12° and 16° in the inferior nasal retina and superior temporal retina where results from all tests could be combined, as well as the foveal region where mfERG and OCT results could be combined (Fig. 1).

For each retinal location, the continuous data from all subjects was analyzed using correlation analysis and multiple linear regression analysis. This included exploring the relationships between refractive error as a continuous dependent variable with spatially corresponding independent variables (average retinal thickness values, resolution acuities and mfERG response amplitudes and timings). Hierarchical regression analyses were also performed to control for eye length to investigate the contribution of axial length to the statistical significance.

Differences in test results between the refractive error groups were evaluated, depending on retinal location, using multivariate analysis of variance (MANOVA) and Tukey post hoc multiple comparisons. Between groups MANOVA's were performed using TR thickness, resolution acuity, mfERG amplitude and mfERG timing as dependent variables with refractive error type as the independent variable for each peripheral retinal location. The MANOVA's were repeated after replacing TR thickness with MIR and PR thickness. The level of significance was 0.05 (Bonferroni adjusted for multiple comparisons).

Table 1
Characteristics of emmetropic and myopic subject groups

	N (female, male)	Age (years) median (range)	SE refractive error (D) median (range)	Cylindrical refractive error (D) median (range)	Axial length (mm) mean (95% confidence limits)
Emmetropes	14 (10f, 4m)	24 (20–41)	0.00 (+0.25 to −0.50)	−0.25 (0.50 to −1.00)	23.60 (23.17–24.04)
Myopes					
Mild	14 (10f, 4m)	22 (19–35)	−1.50 (−0.75 to −2.75)	−0.50 (0.00 to −1.25)	24.17 (23.72–24.62)
Moderate	14 (10f, 4m)	22 (19–41)	−3.50 (−3.00 to −5.75)	−0.50 (0.50 to −1.25)	24.96 (24.41–25.51)
High	14 (10f, 4m)	27 (19–43)	−9.75 (−6.00 to −15.00)	−0.75 (0.00 to −1.50)	27.63 (26.72–28.55)