ELSEVIER

Kinetics of Foveal Cone Photopigment in Myopia Without Chorioretinal Degeneration

Naoichi Horio, Yozo Miyake and Masayuki Horiguchi

Department of Ophthalmology, Nagoya University School of Medicine, Nagoya, Japan

Purpose: To study the early changes in the outer retina of myopic eyes, we performed fundus reflection foveal cone densitometry in 45 subjects with normal visual acuity and no chorioretinal degeneration (ages: 18–47 years, refraction; +2.00–−14.50 diopters).

Methods: After full bleaching, the density of the photopigment was measured for 7 minutes by using a test spot, 562 nm in wavelength and 1° in diameter, focused on the fovea. We calculated the density difference (DD) and the time constant (TC) of photopigment regeneration.

Results: Although we found no correlation between the DD and the refractive error, there was a significant increase in TC as the refractive error increased ($r = 0.50$, $P < 0.01$).

Conclusions: These findings indicated that the kinetics of cone pigments become abnormal preceding the loss of cone cells or chorioretinal degeneration in high myopia. **Jpn J Ophthalmol 1999;43:44–47**

Key Words: Chorioretinal degeneration, density difference, foveal cone densitometry, myopia, photopigment kinetics, time constant of photopigment regeneration.

Introduction

Pathologic myopia is the type of myopia that is accompanied by degenerative changes in the posterior segment of the globe and is associated with elongation of the axis of the eye. One of the early histological changes in pathologic myopia consists of the thinning of the retinal pigment epithelium (RPE),[1,2] which may cause a loss of visual acuity in the late stage. Recently, pathologic myopia without chorioretinal degeneration has been studied by electrophysiological[3–7] and psychophysiological[8,9] methods. Koike and Tokoro[8] found an abnormal blue cone function by use of a spectral sensitivity test. Mäntyjärvi and Tuppurainen[9] reported that the error scores of the myopic subjects in (blue) box III of the Farnsworth-Munsell 100 hue test were significantly higher than in the controls, and the rod thresholds of the myopic subjects also were significantly higher than in the controls following dark adaptation. However, the mechanism for these psychophysiological findings is unknown. Blach et al[10] reported that the electroretinograms (ERGs) were abnormal in a variety of ways, and the electro-oculographic (EOG) values were definitely reduced in degenerative myopia, which suggested dysfunction of the RPE. The drug-induced responses of the EOG, which reflect the function of the RPE more precisely,[11,12] were decreased in high myopia.[6,7] These electrophysiological data suggested an early functional impairment of the outer retina, including the photoreceptor cells and the RPE in myopia. We investigated the photopigment kinetics by foveal cone densitometry (FCD) in subjects with myopia without chorioretinal degeneration, in an effort to explain the early changes in pathologic myopia.

Material and Methods

We examined 45 healthy Japanese, 22 men and 23 women, with refraction of +2.00–−14.50 D. Because the changes due to aging occur earlier in high myopia,[13] we selected subjects in the age range of 18–47 years. Informed consent was obtained from all participants. All subjects underwent a routine ophthal-

Received: January 30, 1998

Correspondence and reprint requests to: Naoichi HORIO, MD, Department of Ophthalmology, Nagoya University School of Medicine, 65 Tsuruma-cho, Showa-ku, Nagoya 466-0065, Japan

Published by Elsevier Science Inc.

0021-5155/99/$–see front matter
PII S0021-5155(98)00062-8

mological examination. Criteria for patient selection were good physical and mental health, no eye disease, visual acuity >1.0, clear media, and no fundus abnormalities except the tigroid appearance of high myopia.

Foveal cone densitometry is a noninvasive technique for examining visual photopigment kinetics in the photoreceptors. The principle of FCD is that the difference in fundal reflection of the fully bleached and the fully dark-adapted retina is directly related to the amount of visual photopigment in the photoreceptors. This difference between the fully bleached and the fully dark-adapted conditions is called the density difference (DD). When reflected light is measured continuously, the time constant (TC) of photopigment regeneration can also be obtained.

The apparatus and technique for FCD used in this study were previously described in detail.[14,15] In brief, a 500 W xenon lamp is the light source for the bleaching, reference, and measuring beams, which are brought to a modified fundus camera via an optic fiber. The wavelength of the measuring beam is 562 nm, and that of the reference beam is 803 nm. The retinal areas of both the measuring and reference beams are 1° in diameter and centered on the fovea. The bleaching area is the central 3°. Retinal illumination of the bleaching beam is 6.0 log photopic trolands, and that of the measuring beam, 950 trolands. After 5 minutes of bleaching, the FCD is recorded continuously for 7 minutes. The density of the measuring beam detected by the photomultiplier after being reflected from the fundus was calculated by computer. We used the reference beam to remove noise caused by blinking and head or eye movements during the measurement.[15] A change in the density of the reference beam indicates a change in the property of the subject, because the reference beam is not absorbed by photopigments. The density of the photopigment was calculated by subtracting the density of the reference beam from the density of the measuring beam, as follows:

$$R(t) = -Ae^{-t/To} + B,$$

where A was the DD between the fully dark-adapted and the fully bleached condition, To was the TC (1/e value), R(t) was the density difference at the time "t," and B was the constant.

We used an autorefractometer (Model AR3300 Nidek, Gamagori), and determined the minimal diopter that gave the best visual acuity as the refractive error.

Pupils were dilated with tropicamide 0.5% and phenylephrine 0.5%. The subject's head was immobilized with a head pad and chin rest during the measurements. The subject was asked to fixate on the center of the bleaching beam or the measuring beam. Fixation was monitored through the fundus camera during measurement. We used a contact lens ("Seequence"® Bausch & Lomb Japan, Tokyo) to correct myopic refractive errors over −4.0 D. Because this lens may cause noise in FCD, data with a large drift in the density of the reference beam were excluded from the analysis.

Results

The mean (± standard deviation) of the DD was 0.37 ± 0.10 (log). We found no correlation between the DD and the refractive error (Figure 1). However, we found a significant increase in the TC as the refractive error increased ($r = 0.50$, $P < 0.01$) (Figure 2).

An example of the FCD from a 27-year-old woman with high myopia (−9.00 D) is shown in Figure 3. The DD was 0.46 and the TC was 163.0 seconds. The pluses (+) represent the density of the reference beam at 803 nm. Because this beam is little absorbed in the outer retina, the tracing of the reference should be a horizontal line in an ideal measurement without noise. In actual recordings from human eyes, however, small drifts are always observed in the tracing of the reference beam (+). Similar drifts are also observed in the tracing of the measuring beam at 562 nm (★). The drifts are canceled by subtracting the density of the reference beam from

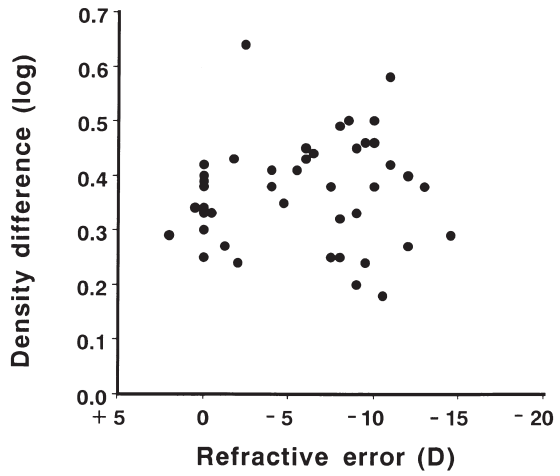

Figure 1. Density difference versus refractive error. Mean and standard deviation of density difference was 0.37 ± 0.10 (log). We found no correlation between density difference and refractive error.

Jpn J Ophthalmol
Vol 43: 44–47, 1999

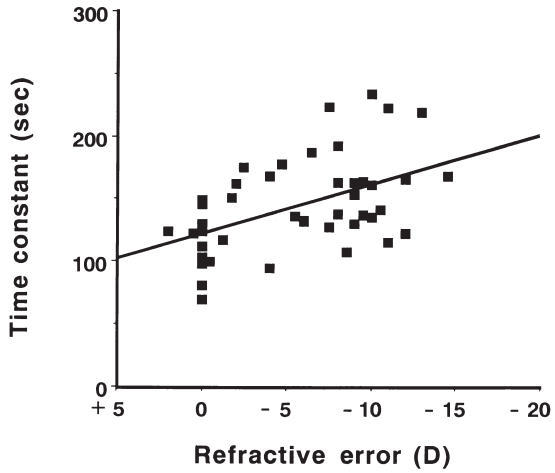

Figure 2. Time constant of photopigment regeneration versus refractive error. We found an increase in time constant of photopigment regeneration with increases in refractive error ($r = 0.50$, $P < 0.01$).

that of the measuring beam, resulting in a tracing of the density with a lower signal-to-noise ratio (□).

Measurements with a large deviation in the reference tracing, indicating blinking, eye movement, or contact lens dislocation, were not included in this study.

Discussion

We found no correlation between the DD and the refractive error (Figure 1), but did find a statistically significant increase in the TC as the refractive error increased (Figure 2). These findings indicate a delay in photopigment regeneration without a reduction in the amount of photopigment or decreased light absorption in myopic subjects without chorioretinal degeneration.

A reduction in the DD can be caused by the following factors: (1) reduction of foveal cone photopigment, including loss of the photoreceptor cells and a decrease of cone outer segments, (2) photoreceptor disorientation,[16] which may reduce the Stiles-Crawford effect, (3) disorder of the interaction between photoreceptor cells and RPE, which may be accompanied by retinal detachment, and (4) an opacity in the medium, which causes stray light before and after the beam is reflected at the outer layer of the retina. Our results for the DD suggest that myopia does not cause these changes unless chorioretinal degeneration occurs. In spite of the increase in axial length of the eye, the arrangement and the normal number of cone cells are maintained until chorioretinal degeneration affects the receptors.

On the other hand, we found that the TC increased as the refractive error increased. In highly myopic eyes (over −9.00 D), the TC showed a significant increase when compared with normal eyes under −3.00 D ($P < 0.01$). We reported recently that the recovery time in the photostress recovery test (PSRT) was also increased in high myopia without chorioretinal degeneration.[17] Photostress recovery test had been introduced as a way of evaluating the function of the outer layer in central serous choroidopathy.[18] Following exposure to a flash of light for bleaching the photopigment, the recovery time was increased in 13 of 15 high myopic eyes.

An increase in the TC may be caused by four factors: (1) functional disorder of the outer segment, (2) functional disorder of the RPE, (3) impairment of the interaction between the photoreceptor cells and RPE, and (4) a decrease of choroidal blood supply. Although data are not available on the choroid and RPE of myopic eyes without chorioretinal degeneration, numerous reports demonstrated their abnormality in advanced myopia. Histological studies disclosed a general thinning of the choroid and RPE[1,2] and occlusion of the choriocapillaries.[19] Angiography using fluorescein and indocyanine green confirmed these circulatory abnormalities in the choroid.[20,21] In myopia, such morphological changes may cause a functional disorder in the outer retina.

In electrophysiological studies, a normal ERG and a decrease in the EOG ratio supposedly reveal a functional disorder of the RPE in high myopia.[10]

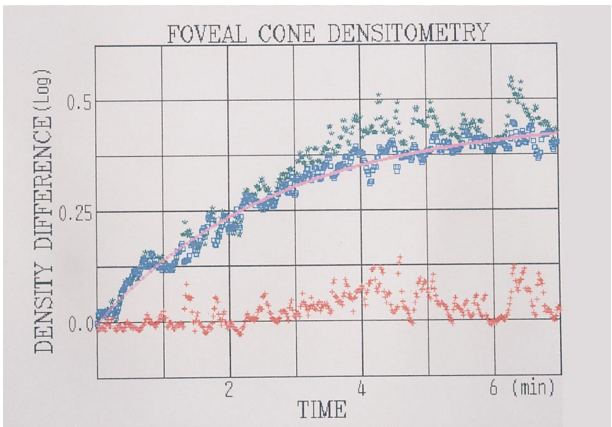

Figure 3. Example of foveal cone densitometry in 27-year-old woman with high myopia (−9.00 D). Density difference was 0.46. Time constant of photopigment regeneration was 163.0 seconds. + represents density of reference beam at 803 nm. ★ represents density of measuring beam at 562 nm. □ represents density of photopigment. Red line is best fit curve.

Uchida et al[6] and Ushimura et al[7] reported decreases of drug-induced responses, brought about by hyperosmolarity, acetazolamide, or bicarbonate in myopia, and inferred a dysfunction of the RPE. Silverstone et al[22,23] reported that metabolic impairment of the RPE in high myopia affected plasma levels of zinc and copper. It is likely that these changes exist subclinically in early myopia, causing dysfunction of the pigment epithelium-outer segment complex.

Our conclusion is that a delay in the photopigment regeneration precedes the loss of cone cells in myopia, which can be a causative factor in psychophysical abnormalities in myopic subjects.

This study was supported by grants for Retinochoroidal Atrophy Research (Nos. 62480362, 02670784) from the Ministry of Education, Science, Sports and Culture, Japan, and by a special grant for Retinochoroidal Atrophy Research from the Ministry of Health and Welfare, Japan.

References

1. Curtin BJ. The myopias, Basic science and management. Philadelphia: Harper & Row, 1985:257–61.
2. Duke-Elder S. System of ophthalmology. Vol. V. London: Henry Kimpton, 1970:300–21.
3. Ishikawa M, Miyake Y, Shiroyama N. Focal macular electroretinogram in high myopia. Nippon Ganka Gakkai Zasshi (Acta Soc Ophthalmol Jpn) 1990;94:1040–7.
4. Kawabata H, Murayama K, Adachi-Usami E. Sensitivity loss in short wavelength sensitive cones in myopic eyes. Nippon Ganka Gakkai Zasshi (J Jpn Ophthalmol Soc) 1996;100: 868–76.
5. Mikawa T. EOG ratio in myopia. Nihon Ganka Kiyo (Folia Ophthalmol Jpn) 1973;24:583–5.
6. Uchida A, Tokoro T, Hayashi K, et al. EOG in high myopia under osmotic stress. Nihon Ganka Kiyo (Folio Ophthalmol Jpn) 1979;30:1794–8.
7. Ushimura S, Wakabayashi K, Kawasaki K. Electro-oculographical features of high myopia. Rinsho Ganka (Jpn J Clin Ophthalmol) 1992;46:449–53.
8. Koike A, Tokoro T. Spectral sensitivity in high myopic eyes. Nippon Ganka Gakkai Zasshi (Acta Soc Ophthalmol Jpn) 1986;90:556–60.
9. Mäntyjärvi M, Tuppurainen K. Color vision and dark adaptation in high myopia without central retinal degeneration. Br J Ophthalmol 1995;79:105–8.
10. Blach RK, Jay B, Kolb H. Electrical activity of the eye in high myopia. Br J Ophthalmol 1966;50:629–41.
11. Kawasaki K, Yamamoto S, Yonemura D. Electrophysiological approach to clinical test for the retinal pigment epithelium. Nippon Ganka Gakkai Zasshi (Acta Soc Ophthalmol Jpn) 1977;81:1303–12.
12. Yonemura D, Kawasaki K. New approaches to ophthalmic electrodiagnosis by retinal oscillatory potential, drug-induced responses from retinal pigment epithelium and cone potential. Doc Ophthalmol 1979;48:163–222.
13. Curtin BJ, Karlin DB. Axial length measurement and fundus changes of the myopic eye. Am J Ophthalmol 1971;71:42–53.
14. Miyake Y. Layer-by-layer analysis of macular diseases with objectively measured visual functions. Jpn J Ophthalmol 1990; 34:225–38.
15. Saito A, Miyake Y, Wang J, et al. Foveal cone densitometer and changes in foveal cone pigments with aging. Nippon Ganka Gakkai Zasshi (J Jpn Ophthalmol Soc) 1995;99:212–9.
16. van Meel GJ, Smith VC, Pokorny J, van Norren D. Foveal densitometry in central serous choroidopathy. Am J Ophthalmol 1984;95:359–68.
17. Horio N, Miyake Y, Horiguchi M. Foveal cone densitometry in high myopia. Nippon Ganka Gakkai Zasshi (J Jpn Ophthalmol Soc) 1996;100:235–9.
18. Magder H. Test for central serous retinopathy based on clinical observations and trial. Am J Ophthalmol 1960;49:147–50.
19. Ohno H. Electron microscopic studies of myopic retinochoroidal atrophies I. Choroidal changes. Nihon Ganka Kiyo (Folia Ophthalmol Jpn) 1983;34:1244–53.
20. Tokoro T. Mechanism of axial elongation and chorioretinal atrophy in high myopia. Nippon Ganka Gakkai Zasshi (J Jpn Ophthalmol Soc) 1994;98:1213–37.
21. Yoshihara M. Clinical studies on fundus changes and hemodynamics in degenerative myopes. Nippon Ganka Gakkai Zasshi (Acta Soc Ophthalmol Jpn) 1978;82:610–25.
22. Silverstone BZ, Berson D, Seelenfreund MH. Plasma zinc levels in high myopia and retinitis pigmentosa. Metabol Pediatr Ophthalmol 1981;5:187–90.
23. Silverstone BZ, Berson D, Seelenfreund MH, et al. Copper metabolism study in high myopia in the African. Metabol Pediatr Ophthalmol 1983;7:173–6.