Selective reduction of the S cone electroretinogram in diabetes

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Abstract

Aims—To determine whether the short wavelength sensitive (S) cone electroretinogram (ERG) is selectively altered in diabetic patients with and without retinopathy.

Methods—Ganzfeld spectral flashes in the presence of bright white background illumination were used to elicit S cone ERGs in 15 non-retinopathic diabetics, 16 background retinopathic diabetics, and 16 age matched normal controls.

Results—The amplitude of the S cone ERG b-wave was significantly reduced in both non-retinopathic and retinopathic diabetics. An action spectrum based on equal response criteria revealed a selective loss of S cone sensitivity in diabetics. However, no significant difference was observed in the long and middle wavelength sensitive cone ERG.

Conclusions—Diabetic patients showed selective reduction of the S cone ERG, which is thought to reflect changes in the outer retina.

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It is known that patients with diabetic retinopathy show tritan defects on colour vision tests.^{1,2} Psychophysical studies using an increment threshold technique have revealed a selective loss of the short wavelength sensitive (S) cone pathway in patients with diabetes who have varied degrees of retinopathy.³⁻⁵ Furthermore, a histochemical study showed loss of disproportionate numbers of S cones in human eyes with diabetic retinopathy supporting these psychophysiological studies.⁶ We report the S cone electroretinograms (ERGs) to spectral flashes with a Ganzfeld stimulus in diabetic patients. A brief abstract describing our results has been published.⁷

Materials and methods

Fifteen patients with diabetes who had no ophthalmoscopic evidence of retinopathy and who ranged in age from 23 to 60 (mean 49.8) years and 16 patients with background diabetic retinopathy who ranged in age from 39 to 60 (mean 50.8) years participated in this study. Fluorescein angiograms were performed on all diabetic patients to determine whether background retinopathy was present. Among the diabetic patients without retinopathy, five were taking insulin and 10 used oral hypoglycaemic agents. Among the retinopathic diabetics, 11 were taking insulin and five used oral hypoglycaemic agents. All patients had visual acuity of 20/25 or better and clear crystalline lenses.

None of the patients had received retinal photocoagulation treatment before this study. Sixteen subjects, ranging in age from 30 to 60 (mean 47.8) years without ophthalmic abnormalities, comprised the control group. Colour vision was tested by means of the Farnsworth panel D-15; all subjects showed normal functions, and no tritan defect was observed. Informed consent was obtained from all subjects after the nature and possible consequences of the study were explained.

The method used to record the ERG was basically identical to that of Gouras and associates.^{8,9} A Ganzfeld stimulator provided a full field white background illumination (50 cd/m²) and flash stimuli. The subject's pupils were fully dilated with 0.5% tropicamide drops. The ERGs were recorded from both eyes simultaneously, in general, using Burian-Allen bipolar contact lens electrodes. The chromatic stimuli were obtained with Wratten colour filters (Eastman Kodak, Rochester, NY, USA) 98 (450 nm), 48 (471 nm), 61 (534 nm), 21 (593 nm), and 29 (633 nm). (The numbers in parentheses indicate the nominal wavelength of maximum transmission of each filter.) The intensities of the flashes were changed by neutral density filters. The flash duration was 10 microseconds and the stimulus frequency was 5 Hz. Responses were averaged with use of the Neuropack 2 averager (Nihon Kohden, Tokyo, Japan). To determine the difference in relative light intensity required to match the long wavelength sensitive (L) and middle wavelength sensitive (M) cone b-wave produced by the blue (450 nm) flash and that produced by the red (633 nm) flash, we determined the relation between L, M cone b-wave amplitude and light intensity that produced an equal amplitude L, M cone b-wave for the blue (450 nm) flash. To compare the lens yellowing, we obtained the L, M cone balance—namely, the log density units of the neutral density filter required to produce the L, M cone b-wave elicited with red stimuli, which is identical to that with blue stimuli. The lens yellowing reduces short wavelength transmissivity and reduces the L, M cone b-wave amplitude as well as the S cone amplitude. Thus, the L, M cone balance increases with the lens yellowing because long wavelength transmissivity is not greatly affected.⁹ We obtained permanent recordings using the maximum flash intensity available at 450 nm and dimming the other stimuli with neutral density filters to produce approximately equal long wavelength sensitive (L) and middle wavelength sensitive (M) cone ERGs, because all longer wavelength stimuli had more effective energy for the L and M cones. To obtain action spectra based on equal

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Figure 1 Cone electroretinograms (ERGs) showing responses to different chromatic stimuli from a 49-year-old normal subject (A) and a 48-year-old non-retinopathic diabetic patient (B). The number on the left signifies the nominal wavelength of maximum transmission of each filter in nanometres. Numbers in parentheses indicate the neutral density filter used to adjust the energies of the flashes to produce approximately equal early (L, M cone) b-waves. The broken lines indicate the S cone b-waves that were measured. S signifies S cone b-wave, and L, M signifies L, M cone b-wave.

amplitude criteria, intensity amplitude function was determined for all spectral stimuli in each subject.

Comparisons among diabetics without retinopathy, those with background retinopathy, and normal subjects were performed by means of ANOVA and post hoc tests.

Results

In normal subjects, the S cone ERG elicited by short wavelength (450 and 471 nm) stimuli appeared as a separate b-wave riding on an early mixed L and M cone b-wave. Middle and long wavelength stimuli produced only the mixed L and M cone b-waves (Fig 1A). We measured the S cone b-wave response from its initial appearance, after the peak of the L, M cone b-wave, to its own peak for the 450 nm stimulus (Fig 1A). In a diabetic patient who had background retinopathy, the S cone b-wave was reduced in amplitude and increased in implicit time (Fig 1B).

Table 1 summarises amplitudes and implicit times of the S cone b-wave to 450 nm stimuli and those of the L, M cone b-wave to 633 nm stimuli in diabetic patients without retinopathy (non-retinopathic diabetics), those with background retinopathy, and normal controls. The range for the S cone ERG amplitude was 0.54–2.46 μ V in normal controls. The S cone b-wave amplitudes were significantly lower in non-retinopathic diabetics and in retinopathic diabetics compared with controls ($p < 0.001$).

Table 1 S cone and L, M cone electroretinogram (ERG) b-wave. Values represent mean (SD)

	S cone ERG b-wave (450 nm)		L, M cone ERG b-wave (633 nm)		L, M cone balance (LDU)
	Amplitude (μ V)	IT (ms)	Amplitude (μ V)	IT (ms)	
Non-retinopathic diabetics (27 eyes)	0.79 (0.29)*	47.0 (4.22)	2.12 (0.91)	27.9 (1.69)	0.51 (0.13)
Retinopathic diabetics (30 eyes)	0.72 (0.41)*	47.8 (2.94)	2.45 (0.62)	27.8 (1.38)	0.59 (0.08)
Controls (18 eyes)	1.25 (0.32)	45.5 (2.41)	2.66 (1.23)	27.1 (1.78)	0.50 (0.11)

IT=implicit time; LDU=log density unit.

All analyses were done using ANOVA and post hoc tests.

* $p < 0.001$ compared with controls.

Figure 2 Action spectrum of the S cone and L, M cone b-wave based on constant amplitude criteria. The standard error of the mean is shown by vertical lines. The ordinate is in log relative sensitivity (reciprocal number of quantal flash); the abscissa is wavelength in nanometres. All analyses were done using ANOVA and post hoc tests. * $p < 0.05$ compared with controls.

There was no significant difference in the S cone b-wave amplitude between diabetics with and without retinopathy. For the L, M cone b-wave, there were no significant differences in amplitudes and in implicit times between the three groups.

We determined the action spectrum of the S cone and L, M cone b-wave based on equal amplitude criteria (Fig 2). The S cone b-wave has its peak sensitivity at 450 nm and the L, M cone b-wave at 534 nm. The S cone sensitivity was significantly decreased at 450 and 471 nm in retinopathic and non-retinopathic diabetics, compared with controls, respectively ($p < 0.05$). The action spectrum of the L, M cone b-wave was almost identical in three groups and no statistical differences were observed at any wavelength.

There was no significant difference in the L, M cone balance—namely, the ratio of long (633 nm) to short (450 nm) wavelength filtering required to produce identical L, M cone b-waves. This finding implied that the lens yellowings were almost identical in the three groups and that differences in the opacity of dioptric media could be negligible in this study (Table 1).

Discussion

Several psychophysical studies have demonstrated the vulnerability of the S cone system in diabetes¹⁻⁵; however, no electrophysiological report has been published and the affected locus has not as yet been determined. Diabetes reportedly decreases the sensitivity of the S cone pathway more selectively than retinitis pigmentosa or open angle glaucoma, suggesting that multiple sites could contribute to the selective loss in diabetes.⁵ Electrophysiological studies showed that mild changes in the inner retina alter the oscillatory potentials¹⁰ and the scotopic threshold responses¹¹ in diabetes.

Our results indicate that diabetes affects the S cone ERG selectively. Both retinopathic and non-retinopathic diabetes reduce the amplitude of the b-waves of the S cone ERG and decrease its sensitivity significantly; on the other hand, the L and M cone responses are not affected in either stage of diabetes. It has been reported that hypoxia caused tritan-like defects in normal subjects.¹² The S cone pathway is thought to be more vulnerable to hypoxia than the L and M cone systems.⁵ Since we measure only the S cone b-wave the defect in diabetes must occur at either the S cone bipolar or photoreceptor level. If we could detect the S cone a-wave we might be able to distinguish a receptor from a second order neuron defect. The method we employed in this study was first reported by Gouras and MacKay.⁸ Although the amplitude of the S cone b-wave is relatively small, both S and L, M cone mechanisms can be examined simultaneously at the same state of retinal adaptation with equipment that can be available in any ERG laboratory.

It is well known that cataracts occur 20 to 30 years earlier in diabetic patients than in normoglycaemic patients.¹³ Changes in dioptric media reduce the amplitude of the S cone b-wave.⁹ A psychophysical study, in which the lens yellowing was taken into account, revealed a selective loss of short wavelength sensitivity in the older diabetic eyes.⁴ In our results, obtained from both older and younger subjects, the L, M cone balance is almost identical in non-retinopathic, retinopathic diabetics, and controls. The L, M cone balance is the amount of neutral density filtering required to be placed before the red (633 nm) flash to produce an L, M cone b-wave equal to that of

the blue (450 nm) flash. With lens yellowing this value increases.⁹ From these results, we can conclude that the transmission characteristics of the crystalline lenses are similar in the three groups and that the selective reduction of the S cone ERG in diabetes is probably due to diabetic changes in the retina and not in the lens.

Reports have suggested that the sensitivity loss of the S cone pathway may precede ophthalmoscopic changes in the fundus.^{2,3} Also, oscillatory potentials in single flash ERG reportedly could be a predictor of retinopathy progression.¹⁴ It will be interesting to follow diabetic retinopathy prospectively in patients whose S cone ERGs are reduced below the normal range. Such studies would be needed to determine whether the S cone ERG can be a predictor of diabetic retinopathy.

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- 1 François J, Verriest G. On acquired deficiency of colour vision, with spectral reference to its detection and classification by means of the tests of Farnsworth. *Vision Res* 1961;1:201-19.
- 2 Lakowski R, Aspinall PA, Kinner PR. Association between colour vision losses and diabetes mellitus. *Ophthalmic Res* 1972;73;4:145-59.
- 3 Zwas F, Weiss H, McKinnon P. Spectral sensitivity measurements in early diabetic retinopathy. *Ophthalmic Res* 1980;12:87-96.
- 4 Adams AJ. Chromatic and luminosity processing in retinal disease. *Am J Optom Physiol Opt* 1982;59:954-60.
- 5 Greenstein VC, Hood DC, Ritch R, Steinberger D, Carr RE. S (blue) cone pathway vulnerability in retinitis pigmentosa, diabetes and glaucoma. *Invest Ophthalmol Vis Sci* 1989;30:1732-7.
- 6 Nork TM, Wang LP, Poulsen GL. Selective loss of photoreceptors in human diabetic retinopathy. *Invest Ophthalmol Vis Sci* 1994;35:1588.
- 7 Kamiyama M, Yamamoto S, Hirata H. S-cone ERG in diabetes with and without retinopathy. *Invest Ophthalmol Vis Sci* 1995;36:S480 (abstract).
- 8 Gouras P, MacKay CJ. Electroretinographic responses of the short-wavelength sensitive cones. *Invest Ophthalmol Vis Sci* 1990;31:1203-9.
- 9 Gouras P, MacKay CJ, Yamamoto S. The human S-cone electroretinogram and its variation among subjects with and without L and M-cone function. *Invest Ophthalmol Vis Sci* 1993;34:2437-42.
- 10 Yonemura D, Kawasaki K. New approaches to ophthalmic electrodiagnosis by retinal oscillatory potentials, drug-induced responses from retinal pigment epithelium and cone potential. *Doc Ophthalmol* 1979;48:163-222.
- 11 Alward GW. The scotopic threshold response in diabetic retinopathy. *Eye* 1989;3:326-30.
- 12 Smith VC, Ernest JT, Pokorny J. Effect of hypoxia on FM 100-hue test performance. *Mod Probl Ophthalmol* 1976;17:248-56.
- 13 Streeten BW. Pathology of the lens. In: Albert DM, Jakobiec FA, eds. *Principles and practice of ophthalmology*. Philadelphia: Saunders, 1994:2180-239.
- 14 Bresnick GH, Palta M. Predicting progression to severe proliferative diabetic retinopathy. *Arch Ophthalmol* 1987;105:810-4.