Cone Photopigment Bleaching Abnormalities in Diabetes

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We have used a color-matching technique to obtain estimates of the optical density of cone photopigments as a function of retinal illuminance in patients with insulin-dependent diabetes mellitus (IDDM). We found that the half-bleach illuminance of some patients is abnormally high. That is, it takes more light to bleach an equivalent amount of photopigment in these patients. Since low illuminance color matches for these patients are normal, this implies that these patients have normal amounts of photopigment, but the photopigment is not bleaching normally. This result clearly points to abnormalities in the outer retina of these diabetic patients. The most likely causes of this abnormality are either decreases in the ability of the cones to absorb light, or an increased rate of regeneration of the cone photopigments.
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A noninvasive technique for measuring the bleaching of the cone photopigments has been developed.[1,2] This article describes results obtained when this technique is applied to patients with insulin-dependent diabetes mellitus. Previous reports have measured abnormalities in both light and dark adaptation in diabetic patients.[3–7] However, it is difficult to determine whether the previously-measured abnormalities are due to dysfunction in the photoreceptors, or to abnormalities of neural adaptation mechanisms.[8,9] Since there is ample evidence for diabetes-related abnormalities at multiple loci, a technique capable of measuring adaptational abnormalities at a single locus in the visual system is desirable.

A technique based on color-matching, has been developed that is sensitive to the bleaching of the cone photopigments (see previous article[1]). This technique is based on the fact that the absorption spectrum of a pigment depends on the concentration of the pigment.[10] Thus when the concentration of photopigment in the retina is decreased by bleaching, the photoreceptors undergo a change in their spectral sensitivity. This change in spectral sensitivity causes a predictable change in the color-match. We have shown that color-matching is a reliable technique for measuring photopigment bleaching in normal observers.[2]

This article presents data showing that more light is required to bleach the photopigment of some diabetic patients, yet these patients have normal cone photopigment optical densities. These results limit the possible explanations of the source of the abnormality measured in these patients.

Materials and Methods

Twenty-two volunteers with insulin-dependent diabetes mellitus (IDDM) were recruited from the patients at the Department of Ophthalmology, University of Pittsburgh. All patients had visual acuity 20/40 or better, and no visually significant media opacifications in the eye tested. We did not perform fluorescein angiography on all patients, so this study does not address the possible functional changes associated with parafoveal capillary infarction. Patients with perifoveal epiretinal membranes were excluded from this study. Patients were 14–52 years of age. On the basis of retinal exams, the patients were placed into three categories: 1) no retinopathy, 2) retinopathy (including both preproliferative and proliferative), and 3) patients having undergone pan-retinal photocoagulation for proliferative retinopathy according to the DRS criteria.[11] Since there were wide-spread differences in our test results among patients with similar retinopathy classifications, additional grades were deemed unnecessary. Tables 1 and 2 show the distribution of patients by sex, age, and duration, as well as results that are discussed below. The mean age of both the diabetic patients and the 27 normal observers (previous paper) was 30. Testing of the normal and diabetic population occurred during

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Table 1. Clinical data and half-bleach illuminance

Subject/sex	Group	Age (yr)	Duration (yr)	VA	Macular edema	I_0 (log td)	Test date	Eye tested
1/F	1	14	4	20/15		4.36	3/03/84	OD
1/F	1	15	4	20/15		4.44	1/12/85	OD
2/M	1	15	10	20/20		4.36	6/09/84	OD
3/M	1	16	0	20/15		4.33	6/17/86	OD
4/F	1	25	8	20/15		4.62*	8/01/83	OD
5/M	1	27	7	20/15		4.44	3/15/83	OD
6/F	1	28	9	20/20		6.09**	11/04/82	OD
6/F	1	28	9	20/20		4.65**	12/03/82	OD
7/F	2	20	14	20/20		4.55	5/16/83	OS
8/F	2	20	17	20/20	Y	5.00**	9/24/83	OS
8/F	2	21	18	20/25	Y	4.40	11/17/84	OD
8/F	2	21	18	20/20	Y	4.64**	11/17/84	OS
9/F	2	23	13	20/20		4.43	6/19/85	OD
10/F	2	25	10	20/15	Y	4.57*	3/16/83	OD
11/M	2	26	23	20/25	Y	4.47	8/04/84	OS
12/M	2	28	15	20/25		4.98**	9/19/83	OD
12/M	2	28	15	20/25		4.47	9/19/83	OS
12/M	2	28	15	20/15		4.73**	12/07/83	OS
13/F	2	34	24	20/25		4.58*	9/17/83	OS
14/F	2	35	14	20/15		4.55	3/06/86	OS
14/F	2	35	14	20/25	Y	4.35	3/06/86	OD
14/F	2	35	15	20/15		4.47	6/04/86	OS
14/F	2	35	15	20/25	Y	4.42	6/04/86	OD
15/F	2	36	17	20/20		4.38	4/02/85	OD
16/M	2	46	28	20/25		4.42	6/13/83	OD
17/F	2	50	37	20/40		4.69**	9/17/84	OS
18/M	2	52	24	20/20	Y	5.24**	4/02/84	OS
7/F	3	21	14	20/20	Y	4.48	9/13/83	OS
10/F	3	25	10	20/30	Y	4.21	7/08/83	OD
11/M	3	27	24	20/25		4.26	8/24/85	OS
12/M	3	28	15	20/25		4.74**	12/07/83	OD
19/M	3	29	21	20/30		5.27**	3/04/83	OS
14/F	3	34	24	20/30		4.54	9/01/83	OD
20/F	3	35	23	20/20		4.40	3/21/84	OD
14/F	3	35	24	20/30		4.41	12/09/83	OD
14/F	3	35	24	20/25		4.47	11/14/83	OS
21/F	3	36	18	20/40		4.86**	11/14/83	OD
21/F	3	36	18	20/40		5.34**	11/14/83	OS
20/F	3	38	25	20/15		4.33	7/10/86	OD
22/M	3	40	29	20/20	Y	5.23**	2/26/83	OD

* Significantly greater than the normal population at $P < 0.05$, one-tail t-test.

** Significantly greater than the normal population at $P < 0.01$, one-tail t-test.

the same time period. Informed consent was obtained from each subject after the nature of the test and the study were explained fully.

The color matches were performed as previously described.[1,2] The visual stimulus was a 4 deg bipartite field. The left side of the field was a 589.6 nm standard,

Table 2. Clinical data and half-bleach for patients with more than two sessions for a given eye

Subject/sex	Group	Age (yr)	Duration (yr)	VA	Macular edema	I_0 (log td)	Test date	Eye tested
1/F	1	16	6	20/15		4.25	7/10/86	OD
6/F	1	28	9	20/20		4.38	1/09/83	OD
6/F	1	30	10	20/20		4.64**	6/29/84	OD
12/M	2	29	15	20/25		4.62*	7/12/84	OS
14/F	2	35	15	20/25	Y	4.78**	7/09/86	OD
14/F	2	35	15	20/15		4.38	7/09/86	OS
7/F	3	22	15	20/20	Y	4.54	10/09/84	OS
10/F	3	26	10	20/30		4.58*	11/14/83	OD
11/M	3	28	25	20/40		4.40	3/07/86	OS
12/M	3	29	15	20/25		4.65**	7/12/84	OD

* Significantly greater than the normal population at $P < 0.05$, one-tail t-test.

** Significantly greater than the normal population at $P < 0.01$, one-tail t-test.

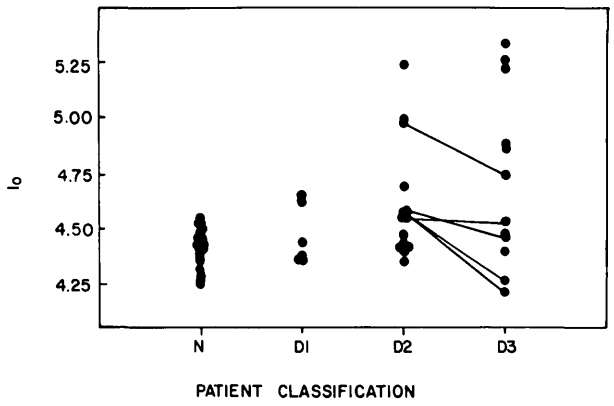

Fig. 1. The retinal illuminance required to bleach half the photopigment (I_0) in log td, by patient and observer classification as follows: N—normal control observers, D1—diabetic patients with no retinopathy, D2—diabetic patients with retinopathy, D3—diabetic patients post panretinal laser photocoagulation. The results of patients who have been retested are shown only if there was a change in category.

while the right half of the field was a mixture of a 546 and a 650 nm light. By turning one knob the observer could alter the color of the mixture field, without altering its luminance, while by turning a second knob the observer could alter the luminance without changing the color. Each patient made ten matches at each of eight retinal illuminances 260–130,000 td. During this time, the position of the patient's pupil relative to the entry position of the test light was monitored. Following the session, the settings were calibrated,[2] and the log of the average ratio of red to green primaries, the (R-G) ratio, was calculated. From these values the optical density, the illuminance that causes half of the photopigment to be bleached (the half-bleach illuminance or I_0), and the low illuminance (baseline) color match were calculated by computer as described previously.[1,2]

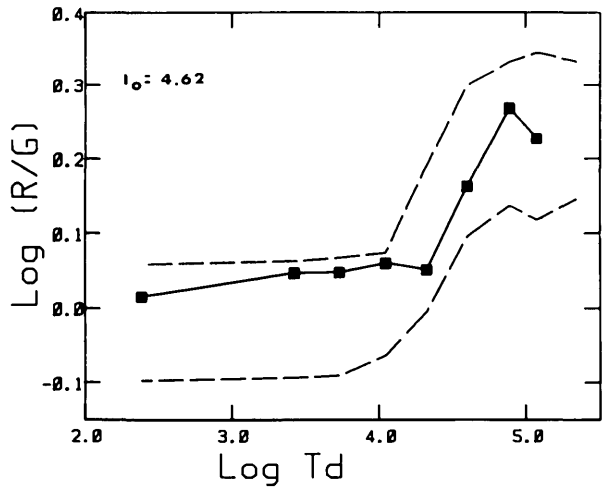

Fig. 2. Color matching data for Patient 6. The squares and solid line show the patient's data, the dashes represent plus or minus two standard deviations of the mean of our normal observers. The estimate of the half-bleach illuminance is shown in the upper left corner.

Results

Most diabetic patients showed a dependence of their color-match on retinal illuminance (the color-match illuminance effect); that is, as retinal illuminance increased, the color-matches required more of the red primary than matches made at lower illuminances. However, many of the patients required higher retinal illuminances for the color match change than did normal observers (Fig. 1). The half-bleach illuminance value (I_0) is a quantitative measure of the amount of light required to bleach one-half of the photopigments. Many of the I_0 estimates for the diabetic differed significantly from the normal population (Table 1). Higher half-bleach illuminance values were found even if the patient was young, had no retinopathy (Patient 6 of Table 1, Figs. 2, 3) or visual complaints, and had normal Farnsworth Munsell 100-Hue Test results. In five extreme cases (Patients 10, 12, 18, 19, 22) no color-match illuminance effect was obtained (Figs. 4–6). That is, even the highest illuminance did not cause appreciable bleaching. Two of these patients were tested just prior to pan-retinal photocoagulation treatment for proliferative diabetic retinopathy (Patients 10, 12). The low-illuminance color matches of our diabetic population (Fig. 7, bottom), were not significantly different from those of the normal population (Fig. 7, top).

Effect of Laser Photocoagulation

Of the five patients tested both prior to and post-photocoagulation with an argon laser, all had an initial decrease in the half-bleach illuminance following panretinal argon laser photocoagulation (Patients 7, 10–13; see Fig. 1). One of the patients with no color-match illuminance effect prior to photocoagulation had more normal data post-photocoagulation (Patient 12, Fig. 6). For this patient there was no overlap in the high illuminance settings pre- and post-photocoagulation. Two patients (Patients 11, 12) have maintained the lower values on follow up testing. It should be noted that two patients with normal half-bleach-illuminances prior to photocoagulation, were still within normal limits after photocoagulation (Patients 7, 19). Although these results may indicate that photocoagulation improves photoreceptor function, this benefit may not be long term. Three of the five patients who had no color-match-illuminance effect on at least one test session had undergone argon laser panretinal photocoagulation 4 months to 4 yr prior to testing (Patients 10, 19, 22).

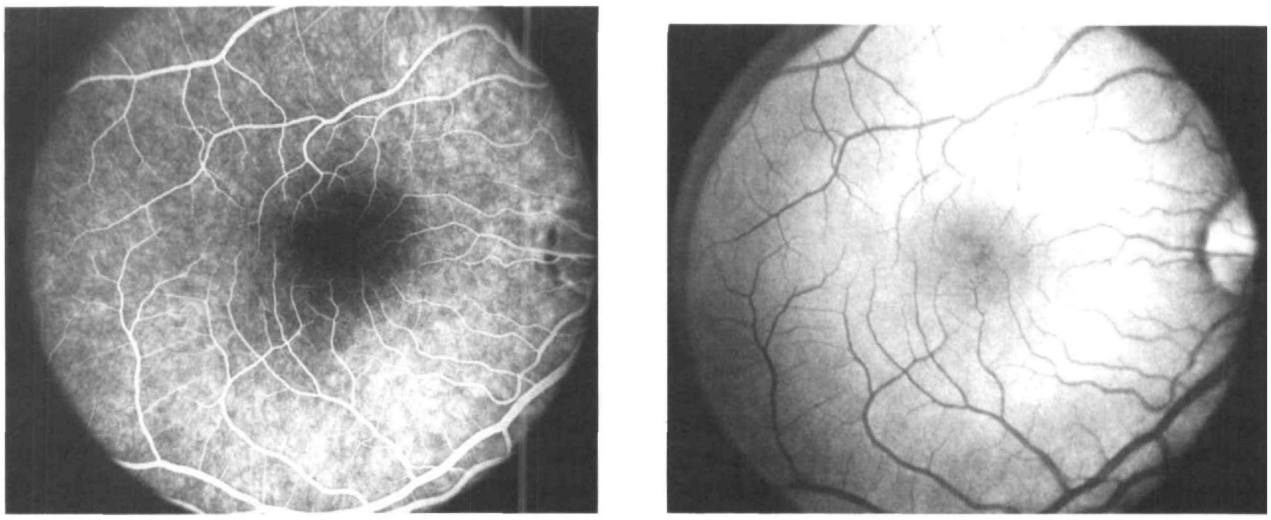

Fig. 3. Fundus photograph (left) and fluorescein angiogram (right) for Patient 6.

(The other two patients were tested immediately prior to photocoagulation, Patients 12, 18.)

Retinopathy Classification and I_0

The relation between the half-bleach illuminance, I_0, and retinopathy is not simple (Fig. 1). Thus far, all patients showing no evidence of bleaching at high illuminances have retinopathy severe enough to warrant panretinal laser photocoagulation by the DRS criteria[11] and were tested immediately prior to scheduled treatment or afterwards. However, abnormally high values for the half-bleach illuminance have been obtained from patients with no retinopathy in either eye, while normal values have been obtained from patients just prior to panretinal photocoagulation.

Clinical Follow-up of Selected Patients

Change is to be expected in a population with IDDM. That is, patients with background retinopathy go on to develop more severe retinopathy and possibly proliferative retinopathy. However of the five patients with no color-match-illuminance effect on at least one session, two went on to develop severe vision loss (Patients 10, 22), one underwent 9 months of sporadic hemorrhage (Patient 19), and the other remaining two patients required laser photocoagulation for proliferative diabetic retinopathy (Patients 12, 18). Patients who have had more normal I_0 have not had severe vision loss during the testing period. However, 2 yr after the last test, Patient 13 did have severe hemorrhage and required vitrectomy. This patient is now doing well, and has 20/30 visual acuity.

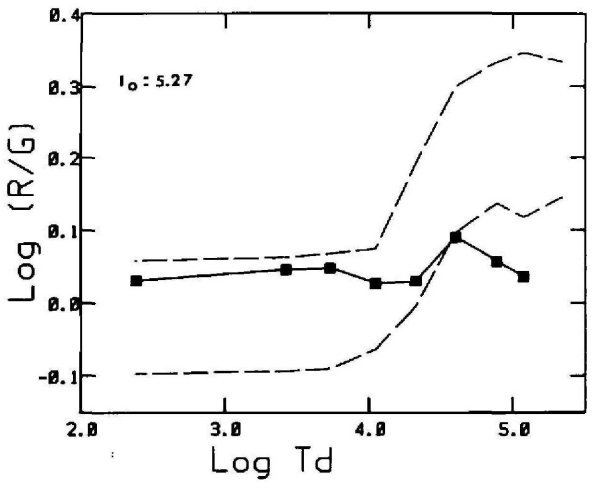

Fig. 4. Color matching data for a 29-year-old diabetic patient (Patient 19) more than 1 yr following panretinal photocoagulation. Symbols as in Figure 2.

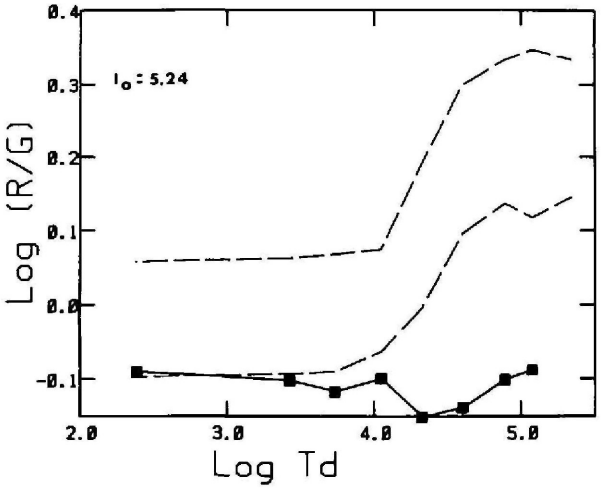

Fig. 5. Color matching data for a 52-year-old diabetic patient (Patient 18) just prior to panretinal photocoagulation. Symbols as in Figure 2.

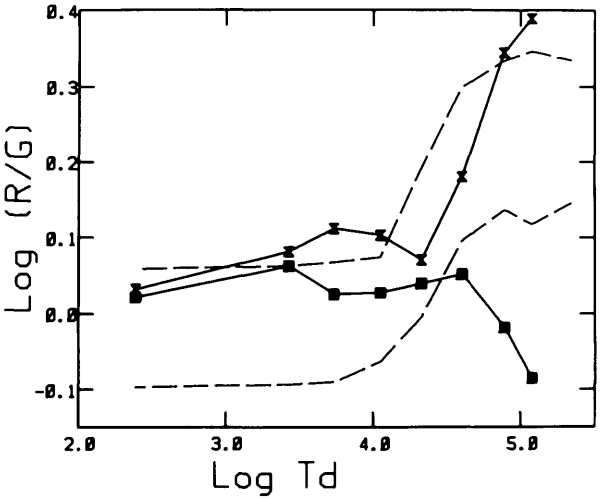

Fig. 6. Color matching data for a 28-year-old diabetic patient (Patient 12) just prior to (squares), and 73 days post-panretinal laser photocoagulation (double triangles). Follow-up testing 9 months post-panretinal photocoagulation indicated no further change. Dashes as in Figure 2. The half-bleach illuminance value for the second test was 4.74.

Variability of the Data

Some, but not all, diabetic observers had more variable data than normal control observers, particularly at the highest illuminance. The variability of the highest illuminance settings decreased for one observer following photocoagulation. We have not yet tested enough patients in follow up to estimate the test-retest repeatability of our technique over time. Patient 6, who had no retinopathy (Fig. 2), was tested four times over a period of 20 months. The baseline color matches for this patient varied from 0.025 to 0.045. This patient's I_0 varied from 4.38 to 6.09 log td, with three of the measurements significantly different from normal (with a one-tailed test, $P < 0.01$). A younger patient, Patient 1, with no retinopathy was tested three times in 3 yr, with I_0 values ranging from 4.25 to 4.44. Four patients who had undergone panretinal photocoagulation were tested twice and had highly repeatable results. Three of these (Patients 7, 11, 20), maintained good vision during the testing period; the other (Patient 13) had small, sporadic hemorrhages. In contrast, an observer (Patient 10) whose vision was reduced to counting fingers in the eye tested (and hand motion in the other eye) showed results that changed significantly over time prior to the hemorrhaging that reduced vision in the eye tested. Both the baseline color match and the half-bleach illuminance changed, with almost no color-match-illuminance effect measured in the test session prior to the hemorrhage.

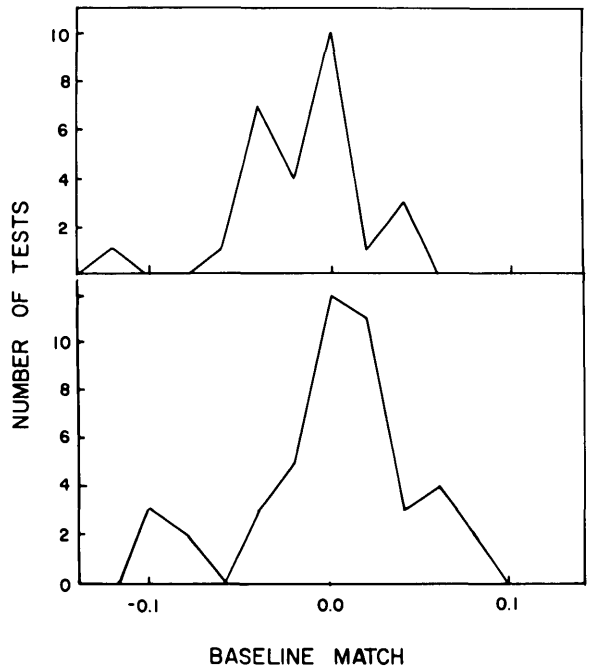

Fig. 7. The distribution of the baseline (or moderate illuminance) color matches for normal control observers (top) and patients (bottom); log (R/G) as in Figure 2.

Discussion

Optical Density of the Cone Photopigments

The optical density of the long and middle wavelength-sensitive cone photopigments in patients with IDDM appears to be normal. This is supported by the normal estimates of the difference between the low and high illuminance color matches for those patients with a measurable color-match-illuminance effect. However, since the color matches of many diabetics did not reach a high illuminance asymptote, no optical density estimate could be obtained for many diabetic observers. However, if the optical densities of diabetic observers were abnormal, the low illuminance color matches should have been abnormal. Although there was scatter of the color matches, the color matches were scattered symmetrically around the midpoint of the range of settings by normal observers (Fig. 7). This normality of color matches at moderate retinal illuminances is in agreement with previous results.[12] The normal baseline color matches, along with the normal high-illuminance assymptote measured for most patients implies that the cones have a normal concentration of photopigment at moderate illuminances. However, it should be noted that Bresnick et al[13] have measured normal color matches in a patient with an abnormal Stiles-Crawford effect due to macular drag. This would not seem to affect our study group, since none had evidence of macular drag, or preretinal membranes. In addition, the measurement of only low-illuminance color-matches in the Bresnick et al study cannot be used to

positively identify patients with normal vs abnormal optical densities due to the intraobserver variability of color-matches.

Bleaching of the Cone Photopigments

Some diabetic patients require a higher than normal retinal illuminance to bleach their cone photopigments. We have considered several hypotheses to explain this result. The first, and simplest, is that a filter could be reducing the amount of light reaching the cones. A spectrally neutral filter should cause a shape invariant translation of the entire color match vs illuminance curve to the right (see Fig. 1, previous paper). This is similar to what we measure in the diabetic patients, since we find no shift in the color-matches at moderate retinal illuminances. Thus, we tested the implications of this hypothesis. If the high I_0 was due to an increased density of preretinal filters, then the view of the retina should be affected by the filter. If we measure a 0.5 log unit increase in I_0, then the view should be equivalent to viewing through a 0.5 log unit filter, and the amount of light exiting the eye would be decreased by 1 log unit. One of us (a retina specialist) viewed the retina of test subjects through a series of filters and found that filters of 0.6–1.0 log units would be easily detected. Similarly, such dense preretinal filters would effect fundus photography. Since the dynamic range of the film used in color photography is about 1 log unit, the presence of such preretinal filters would necessitate large changes in the flash intensities of the fundus cameras (Fig. 3). No such changes were required. Spectrally-selective filters would cause differential filtering of the red and green primaries and, therefore, are not consistent with the normal baseline color matches. We conclude that a preretinal filter is an unlikely explanation for the high I_0.

A second possibility is that eye pathology could result in a receptoral abnormality that mimics the filter hypothesis. For instance, if there are changes in the cones resulting in less efficient capture of light, then higher illuminance could be required to cause a change in the color match. Similarly, there could be a screening pigment in the inner segments of the cones. Or, the light capturing ability of the cones could be diminished by local environmental changes, such as changes in the refractive index of the retina. Our test of the funduscopic view of the retina cannot address this particular hypothesis, since the changes are assumed to be local. However, any such changes must be reversible, as our pre- and post-photocoagulation data show, and be able to decrease the light capture ability of the photoreceptors by at least 1 log unit. Although this is a large effect for local phenomena, we cannot reject this hypothesis with our data.

A third possibility is that an abnormality of photopigment kinetics could cause the photopigments in diabetic patients to be regenerated faster than in normal observers. A small increase in the rate of regeneration could cause an increased half-bleach illuminance, while a large increase in rate could cause the lack of color-match illuminance effect we see in some patients. This hypothesis has the advantage that it could be controlled by metabolic factors, which are likely to be abnormal in diabetic observers. A possibly related finding is that young, diabetic patients can have abnormally high renal clearances.[14] Finally, the hypothesis of abnormal kinetics has the advantage that an imbalance is reversible, and would be consistent with the observed changes pre- and post-photocoagulation. We plan to test these hypotheses by measuring the rate of change of the color match with time following changes in retinal illuminance.

Caveats

At this time we can make no strong statement about our test results and patient prognosis. The relation between half-bleach illuminance and retinopathy may be stronger than our data indicate because we cannot test some patients with severe retinopathy, eg patients with severe hemorrhage. By recruiting additional diabetic patients who do not have retinopathy, and by following the natural history of those who do, we may better understand the relation of photopigment abnormalities and long-term prognosis of diabetic patients.

Implications

Our results also affect interpretation of clinical testing of light and dark adaptation. For instance, diabetic observers have been found to have dark adaptation abnormalities, such as elevated final thresholds or a longer time required to reach threshold.[3–5] Many tests of dark adaptation are performed following exposure to a bleaching or adaptation light. Since we found that diabetic observers can require more light than normal observers to bleach a comparable proportion of photopigment, then these dark adaptation tests may not be appropriate for comparing recovery times in the two populations. More important, the mechanisms responsible for causing changes in dark adaptation in diabetics remain uncertain. Our data imply a receptoral abnormality in at least some diabetic observers. This abnormality could be due to either an increased rate of photopigment regeneration, or a decreased ability of the cones to absorb light. The decreased light capture hypothesis is consistent with the increased absolute thresholds of diabetic observers.[3,4] However, a loss of sensitivity alone cannot explain the delayed recovery of visual acuity following exposure to bright lights,[6,7,15]

nor the increased time required to reach absolute threshold. These previous findings are consistent with abnormalities of neural processing in individuals with IDDM. That is, typical tests of visual function are sensitive to abnormalities of visual function at a number of loci, but cannot provide information concerning the function of specific portions of the visual system. The presence of a photoreceptoral abnormality makes results from such tests difficult to interpret, since the photoreceptor signal sent for later neural processing can be abnormal.

In conclusion, we have measured abnormalities in the bleaching of cone photopigments of some patients with insulin dependent diabetes mellitus. These abnormalities are most likely to arise from either abnormalities in the collection of light by the photoreceptors, or due to abnormalities of photopigment kinetics. Although it is clear that many more patients need to be studied to understand the relation of these abnormalities to diabetic retinopathy and vision loss, the presence of the outer retinal abnormality is clear.

Key words: photoreceptor, diabetic retinopathy, cone, color vision, diabetes

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