

Visual Function and Rhodopsin Levels in Humans with Vitamin A Deficiency

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(Received 12 June 1987 and accepted 7 August 1987)

Details of rod and cone dysfunction in vitamin A deficiency have been studied in two subjects with primary biliary cirrhosis and one with Crohn's disease, all of whom presented with symptoms of night blindness. Visual function in the mid-peripheral retina was monitored with two-color adaptometry and rhodopsin levels were measured by fundus reflectometry.

Initially all three subjects had no measurable rod function and delayed cone adaptation. In one case the dark-adapted cone threshold was also elevated. Oral supplementation with vitamin A restored visual function to normal within 8 days in all subjects. During supplementation, cone function was restored more rapidly than that of rods, though the pattern of recovery was similar for each receptor type. Final thresholds improved first, though the rates at which they were reached were abnormally slow. As recovery continued, adaptation kinetics returned to normal. When rod adaptation was delayed, the regeneration of rhodopsin was also abnormally slow. When rod final threshold was 2 log units higher than normal, rhodopsin regeneration was incomplete, reaching about 70% of the normal level.

The initial stages of visual dysfunction during onset of vitamin A deficiency were studied in one subject, and were found to mirror the pattern seen during recovery: rod adaptation was initially slower than normal, but reached completion. Cone adaptation remained normal until rod function was almost absent.

Key words: cone, dark adaptation, fundus reflectometry, perimetry, regeneration, rhodopsin, rod, visual pigment, vitamin A.

1. Introduction

Although there have been many reports of the effects of systemic vitamin A deficiency on visual function, both in man (Ripps, Brin and Weale, 1978; Kemp and Faulkner, 1981; Fulton, Hanson, Underwood, Schwachman and Barg, 1982) and in animals (Dowling and Wald, 1958; Dowling and Gibbons, 1961; Hayes, 1974), several aspects are not fully documented. While it is clear that once the deficiency has caused significant depletion of ocular stores of the vitamin, symptoms of night blindness develop (Wald, Jeghers and Arminio, 1938; Duke-Elder and Dobree, 1967), details of the progress of early dysfunction are lacking. Similarly, it is known that in long-term deficiency cone as well as rod function is lost (Wald, Jeghers and Arminio, 1938) but again the intermediate stages of photopic dysfunction have been less fully described. In the rat, the time course of the recovery of function (Dowling and Wald, 1958; Dowling and Gibbons, 1961) following supplementation of systemic vitamin A levels has been documented. In man, however, less information is available concerning the time course and pattern of recovery of visual function in these circumstances.

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(Sandberg, Rosen and Berson, 1977; Perlman, Barzilai, Haim and Schramek, 1983; Walt, Kemp, Lyness, Bird and Sherlock, 1984).

Knowledge of the functional abnormalities of vision in systemic vitamin A deficiency is of some clinical importance in that it has often been questioned whether retinal degenerations, such as retinitis pigmentosa (RP), may arise from systemic or ocular deficits of the vitamin (see Bridges, 1982). Critical comparisons may be improved if the characteristics of the dysfunction in vitamin A deficiency have been established in detail. The relationship between the perturbations of the visual threshold and of the visual cycle is also of interest to the biochemist and physiologist, since it may provide information about the mechanisms of visual adaptation (Dowling, 1960; Rushton, 1961; Pugh, 1975).

In the present study, we monitored patients with vitamin A deficiency before and after vitamin A supplementation. We used psychophysical testing to determine visual thresholds during dark adaptation and measured rod visual pigment levels with the non-invasive technique of fundus reflectometry. Two of the subjects had primary biliary cirrhosis (PBC) leading to systemic vitamin A deficiency as a result of malabsorption of fat. Measurements were also carried out on a subject whose vitamin A deficiency was caused by malabsorption secondary to complications of Crohn's disease, an inflammatory bowel disease.

Methods

Subjects

Subject P1 was a 38-yr-old man with Crohn's disease for 20 yr. He had undergone multiple abdominal surgeries and at his last operation, further intestinal and colonic resections were performed, leaving only 4 ft of small intestine. There was no history of visual complaints or eye disease until 16 months following this last surgery when he noted difficulty seeing at night. On an eye examination about 3 weeks after onset of his visual symptoms, there were no obvious ocular abnormalities but testing revealed visual sensitivity loss from vitamin A deficiency. Vitamin A supplementation was started 3 days later.

Subjects P2 and P3 were women (aged 58 and 55 yrs respectively) with PBC and cholestasis. They had been given monthly i.m. supplementation with Vitamin A (100 000 units of Ro-A-Vit, Roche). Both reported symptoms of night blindness as their liver disease became more advanced. Apart from the loss of visual sensitivity arising from vitamin A deficiency, they had no significant ocular abnormalities.

During and after the study, oral supplementation of vitamin A (25 000 unit capsules; Macarthy's) was used for all subjects (Walt, Kemp, Lyness, Bird and Sherlock, 1984). The patients gave informed consent to the studies reported here after the nature of the procedures had been fully explained.

Dark adaptometry

Two-color dark adaptometry was performed with an instrument previously described (Ernst, Faulkner, Hogg, Powell, Arden and Vaegen, 1983). The pupil of the eye selected for testing was fully dilated with phenylephrine (10%) and cyclopentolate (1%). The eye was then exposed to a 30 msec white xenon light flash sufficient to bleach essentially all the pigment in an area of retina of angular subtense of about 30°, the region within which subsequent fundus reflectometric testing would be carried out (i.e. the mid-periphery of the nasal field). The subject was then allowed to dark adapt and the changes in visual threshold were monitored at a point 25° from the fovea along the horizontal meridian in the nasal field. The test stimulus used was a circular flashing (1 Hz) light which subtended an angle of diameter 0.9° at the retina. Thresholds were determined for both red (660 nm) and green (530 nm) stimuli, in order to establish whether visual function was subserved by rods or by cones (Ernst

et al., 1983). Testing was continued either until the threshold had reached normal dark-adapted levels or, if it remained elevated, until no further increase in sensitivity could be detected.

Fundus reflectometry

The TV-based broad-field imaging fundus reflectometer (IFR) used to determine the levels of rhodopsin present during dark adaptation has been described elsewhere (Faulkner and Kemp, 1984; Kemp, Faulkner and Jacobson, 1983, 1987b). The instrument yields pigment data within a circular retinal area of angular subtense 25° with a spatial resolution of approx. 0.5° . For the present study, where regional variations in pigment levels were expected (and found) to be small, the signal/noise ratio of each measurement was improved by spatially averaging the data obtained from a rectangular area of retina of angular subtense $5 \times 5^\circ$ centered on the site where dark adaptometric measurements had been carried out.

Fundus reflectometric testing was always started within 2 hr after completion of the dark adaptometry test. The procedure used has been previously described (Faulkner and Kemp, 1984; Kemp, Faulkner and Jacobson, 1983). In brief, after alignment with the instrument, the subject was light adapted with a white light of sufficient intensity ($7.8 \log$ scotopic troland sec, delivered over 45 sec) to bleach essentially all the rhodopsin within the area of retina under examination. Fundus reflectometric measurements were then made at intervals during a period similar to that over which measurable dark adaptational changes had been observed in the preceding psychophysical test. At the end of this time the patient was given another light-adapting exposure in order to obtain a second set of fundus reflectometric data from the bleached retina.

Measurement of serum vitamin A

The levels of serum vitamin A were determined by HPLC (Varian, Model 5000) using the procedure of Bieri, Tolliver and Catignani (1979). All blood samples were obtained from the subjects when they had been fasting for at least 12 hr. The range determined by the same method for control subjects was $20\text{--}90 \mu\text{g d}^{-1}$.

Results

Visual fields and dark adaptation

When P1, the subject with Crohn's disease, was initially tested, Goldmann kinetic perimetry with IV/4e and I/4e test targets was normal. Serum vitamin A level was $7 \mu\text{g d}^{-1}$.

Figure 1 illustrates the results obtained from two-color dark adaptometry of P1. When first tested, dark adaptation in P1 occurred solely during the first 10 min: there was no further increase in sensitivity to either the green (○) or red (+) stimulus over the following 70 min (Fig. 1A). After supplementation with vitamin A, when the serum level had risen to $13 \mu\text{g d}^{-1}$, dark adaptometry showed (Fig. 1B) that P1 had recovered a substantial amount of scotopic function. After the initial rapid decline in threshold following light adaptation, which was complete within about 5 min, the subsequent recovery of sensitivity to the green stimulus followed the normal pattern, with a 'cone plateau' lasting until about 17 min, followed by a second phase of recovery (the 'rod branch') that continued until 70 min. Thus, at this stage, the kinetics of cone adaptation were close to normal (Ernst et al., 1983). While rod

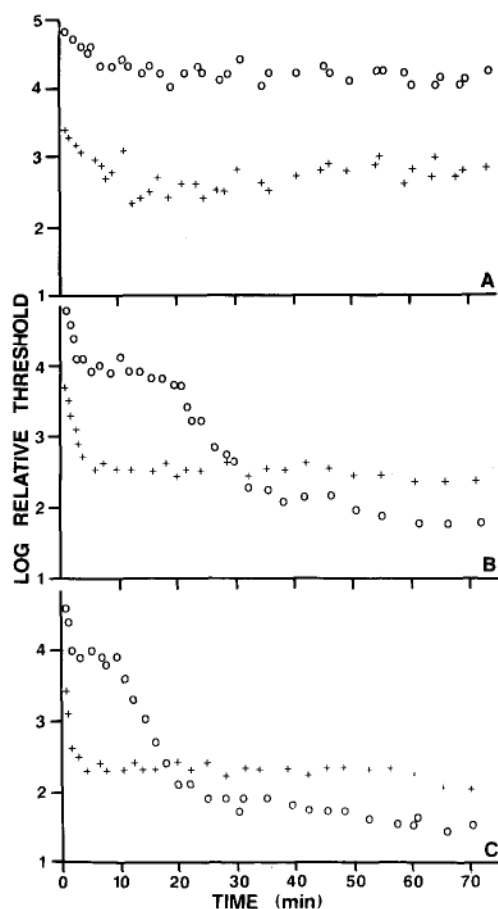


FIG. 1. Two-color dark adaptometry of subject P1: relative thresholds to the green (O) and red (+) stimuli. Measurements were made at a retinal eccentricity of 25° along the horizontal meridian in the nasal field, and followed a white bleaching exposure which removed virtually all visual pigment. A, Results obtained on first test. B, Data obtained when vitamin A supplementation had led to partial recovery of visual function. C, Data obtained when systemic vitamin A levels were normal. See text for further details.

adaptation also proceeded to completion (final threshold was normal), the rate at which it did so was slower than normal, as is evident when compared to the data of Fig. 1C, which were obtained from subject P1 when his vitamin A levels were normal ($41 \mu\text{g d}^{-1}$). On this occasion, the recovery of rod function began after about 11 min of dark adaptation and was essentially complete by 45 min.

Figure 2, trace A, shows the Goldmann visual fields for the right eye of subject P2 when she first presented with night blindness. Dark adaptometry confirmed that there was complete absence of observable rod function (see below, and Fig. 3). The serum level of vitamin A determined at that time was less than $5 \mu\text{g d}^{-1}$. For comparison, the Goldmann field performed after oral supplementation with vitamin A is shown in Fig. 2, trace B. At this time she was no longer deficient in vitamin A (serum level $27 \mu\text{g d}^{-1}$) and had no visual symptoms. The difference in extent of the visual fields before and after supplementation indicates that visual sensitivity of the

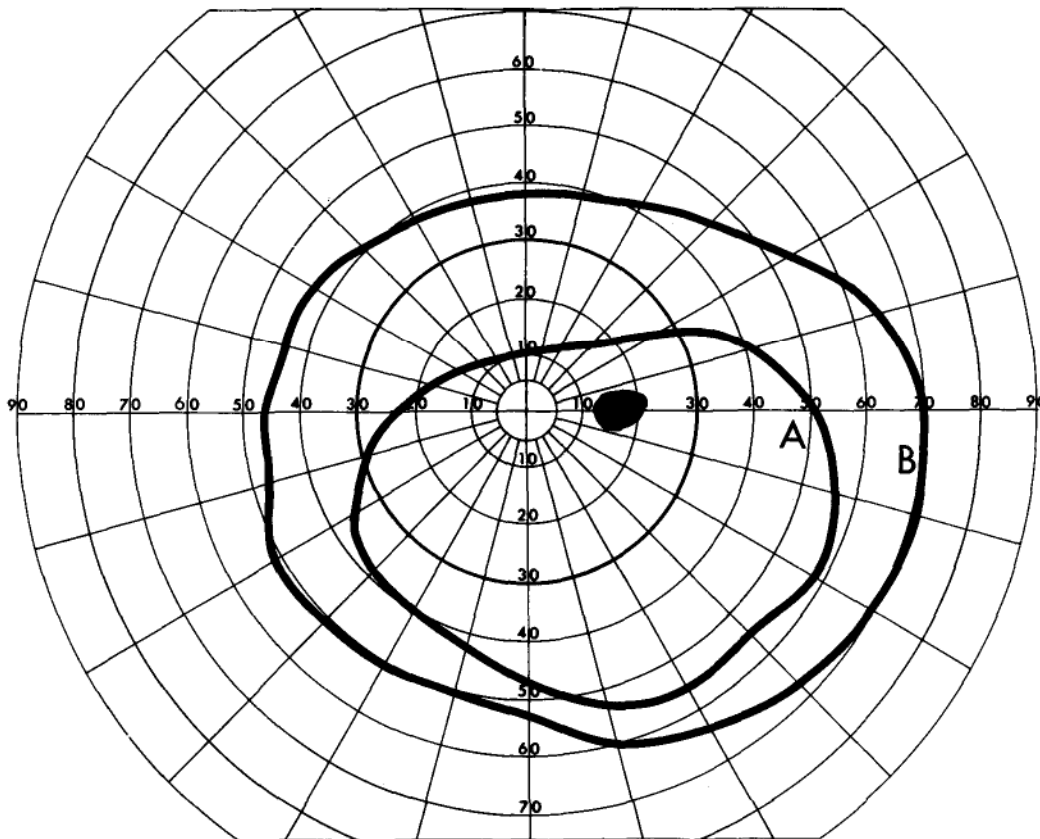


FIG. 2. Goldmann fields of P2, for target I/4e. A, Field obtained on first visit, when scotopic function was absent in the mid-peripheral retina. B, Field obtained after supplementation when systemic vitamin A levels and dark adaptation were normal.

cone as well as the rod system was affected when night blindness was most severe. The field was generally depressed, but the effect was more pronounced in the superior hemifield. (Care was taken to ensure that the upper eyelid did not occlude vision during testing.)

Two-color dark adaptometry (Fig. 3A) was carried out on subject P2 immediately after the Goldmann field (Fig. 2, trace A) had been determined. Testing was continued for 60 min, during which time the visual threshold remained so high that the responses to the green stimulus (○) indicate that it was only rarely detected even at its maximum intensity. Thresholds for the red stimulus (+) were also abnormal. Although reliable measurements were not obtained during the first few minutes of dark adaptation, thresholds remained elevated by about a log unit from normal for the cone system throughout the period of testing.

Oral vitamin A supplementation ($50\,000\text{ U day}^{-1}$) was begun ('day 0'), and dark adaptometry and Goldmann perimetry were carried out on days 3 and 7. On both these occasions, Goldmann fields had recovered and were indistinguishable from that shown in Fig. 2, trace B. On day 3, thresholds for the red stimulus (i.e. those determined by cone sensitivity) recovered to normal levels (Fig. 3B, + symbols), though the rate of cone adaptation remained slow. In contrast to the extensive

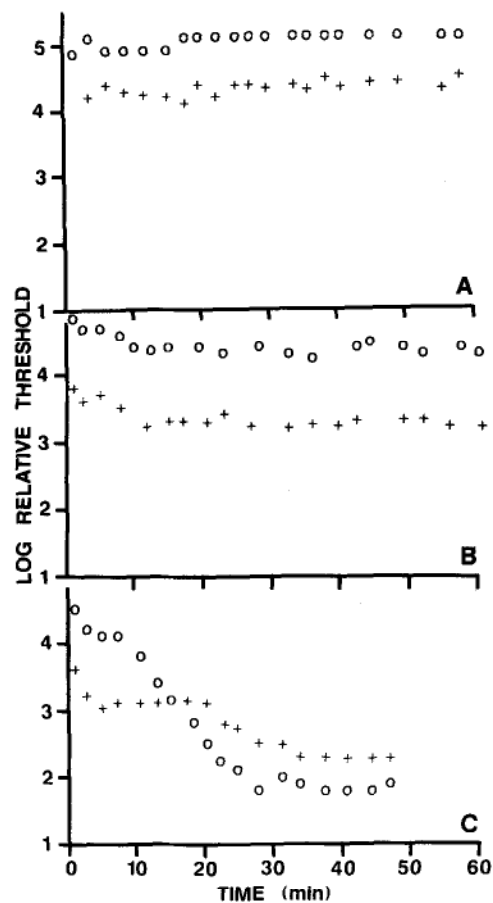


FIG. 3. Two-color dark adaptometry of subject P2 to green (O) and red (+) stimuli; other conditions as for Fig. 1. A, Thresholds when tested on first visit. B, Thresholds obtained 3 days after oral vitamin A supplementation was started. C, Thresholds obtained 7 days after supplementation was started.

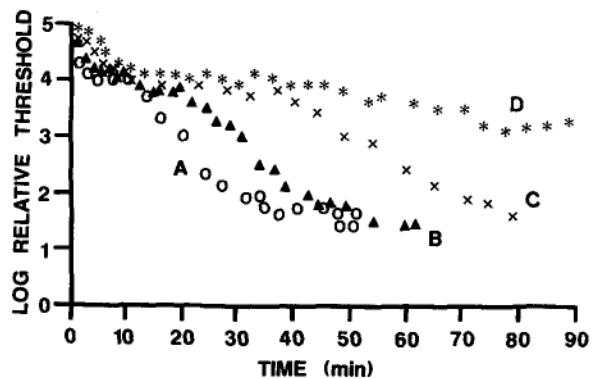


FIG. 4. Dark adaptometry of subject P2. Data are shown only for the green stimulus; other conditions as for Fig. 1. Data set A was obtained when serum vitamin A level was normal and supplementation was temporarily suspended. Sets B, C and D were obtained 6, 15 and 20 days later, respectively.

recovery shown by the cones there was still no observable rod function on day 3, with marked elevation of the thresholds persisting after 70 min in darkness (Fig. 3B, ○ symbols). Serum vitamin A level on that day was $23 \mu\text{d}^{-1}$.

On day 7, both cone and rod adaptation were normal (Fig. 3C) and serum vitamin A concentration ($31 \mu\text{d}^{-1}$) was within the normal range. The dose of vitamin A was halved (in order to avoid the possibility of systemic overdose) and continued for 1 month. On day 32, results of both kinetic perimetry and dark adaptometry were normal. Serum vitamin A concentration was $28 \mu\text{g d}^{-1}$. With the informed consent of subject P2, who was under constant medical supervision as a hospital in-patient, vitamin A supplementation was withdrawn temporarily on day 36, when serum vitamin A concentration was $35 \mu\text{g d}^{-1}$.

The time course over which the scotopic vision of subject P2 declined is illustrated by the dark adaptometry data in Fig. 4 (for clarity, only the responses to the green stimuli are shown). Curve A was obtained when P2 was normal (day 36). Six days later (day 42), serum vitamin A concentration was $14 \mu\text{g d}^{-1}$ and dark adaptometry showed mild disturbance of scotopic function, with the rod-cone break occurring at about 20 min, and full recovery requiring almost 60 min (Fig. 4, curve B).

Although subject P2 remained asymptomatic, testing carried out on day 51 (Fig. 4, curve C) revealed that despite cone adaptation being little changed (final threshold was normal and was reached within 7 min), recovery of rod function was further delayed, with the rod-cone break occurring at around 40 min. Final threshold was normal, but was not attained until after more than 75 min. Serum vitamin A concentration was $10 \mu\text{g d}^{-1}$. After a further 6 days, throughout which she reported no symptoms, light-adapted kinetic visual fields were retested (day 57) and found to be normal. However, while dark adaptometry confirmed that cone final threshold remained normal, 12 min were needed for it to be attained. Rod dark adaptation was also further impaired (Fig. 4, curve D), with thresholds falling barely into the scotopic range and no clear evidence of a rod-cone break. Threshold was still more than 2 log units higher than normal after 90 min in darkness. Serum vitamin A concentration on day 56 was $8 \mu\text{g d}^{-1}$. Although subject P2 still reported no symptoms (probably because of the ambient lighting conditions in the hospital in which she was staying), oral supplementation with vitamin A was resumed after this test and visual function was normal when testing was next repeated 13 days later. A further test performed after an interval of 4 months confirmed that her adaptation and final thresholds remained normal.

Subject P3, the other PBC patient who presented with symptoms of night blindness despite receiving monthly i.m. vitamin A supplementation, showed a pattern of visual improvement similar to that of subject P2 when oral supplementation restored her serum vitamin A levels to within the normal range (see below and Fig. 6B).

Fundus reflectometry

Fundus reflectometry was only performed when new information was likely to be obtained. Thus, levels of rhodopsin and details of the time course of its regeneration were determined when rod function was normal, when adaptation was delayed, and also, in subject P3, when it was virtually absent.

Figure 5A illustrates the measured recovery of rhodopsin in subject P2, normalized to the maximum value obtained (0.113 density units). When she was mildly vitamin A deficient (and her serum vitamin A concentration was $16 \mu\text{g d}^{-1}$) rhodopsin recovery in this subject (◆), was found to be substantially slower than normal, with

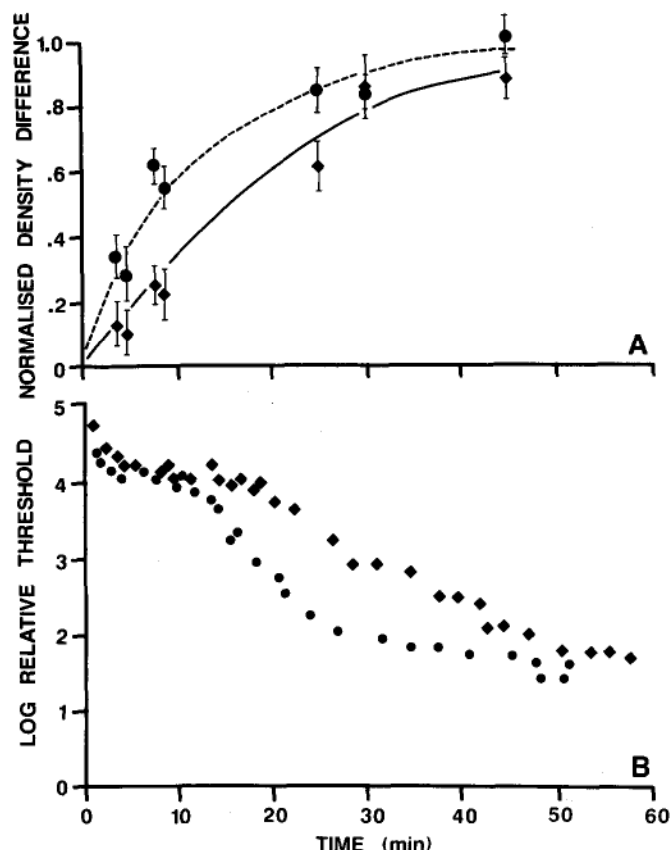


FIG. 5. A, Recovery of rhodopsin in subject P2 following a full bleaching exposure on days when serum vitamin A levels were normal (●), and mildly abnormal (◆). All double density changes have been normalized to the value obtained at 45 min on the day when vitamin A level was normal. Error bars denote 1 s.d. B, Corresponding dark adaptometry data (for the green stimulus) for subject P2. See text for further details.

a $t_{\frac{1}{2}}$ of about 15 min. The final double density difference value reached was within the normal range. The data obtained when vitamin A supplementation had led to full restoration of rod function (●), yielded a half time of regeneration ($t_{\frac{1}{2}}$) of about 6 min, which is in the normal range (Ripps and Weale, 1969; Ripps, Brin and Weale, 1978). The final level of rhodopsin reached was not significantly different from that obtained on the previous occasion.

The dark adaptometric data (for the green stimulus only) obtained from subject P2 on the days when IFR was carried out are shown in Fig. 5B. On the first occasion (◆), the rod-cone break was delayed until about 20 min, while on the second (●), it occurred at about 11 min.

Normalized fundus reflectometric data from subject P3 are shown in Fig. 6A. When P3 was first tested, reliable IFR data (○) could only be obtained at 2, 16 and 60 min following bleaching. These suggested, however, that rhodopsin recovery was much slower than normal, and the level reached at 60 min was also only about 70% of the normal final value. The corresponding dark adaptometric measurements (Fig. 6B, ○

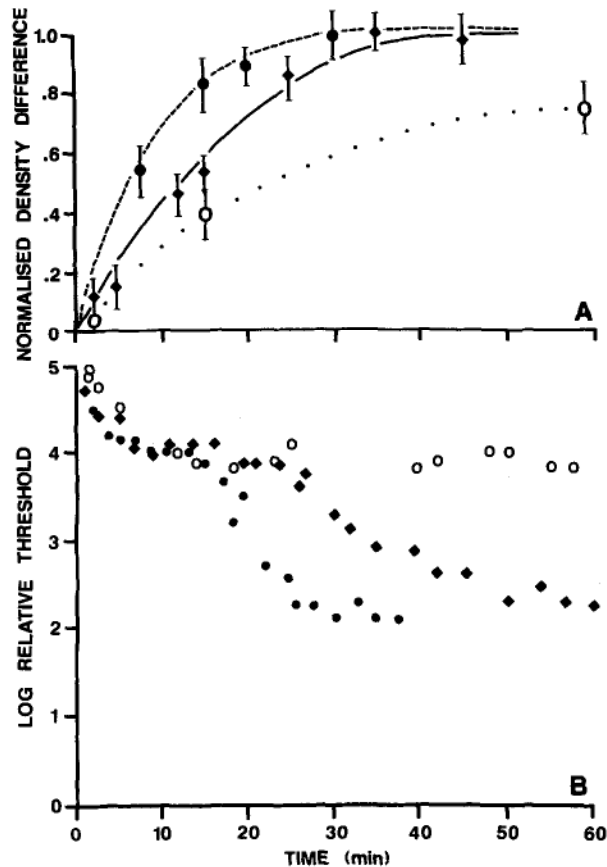


FIG. 6. A, Recovery of rhodopsin in subject P3 following a full bleaching exposure on days when serum levels were normal (●), mildly abnormal (◆), and more severely abnormal (○). All double density changes have been normalized to the value obtained at 30 min (0.12 density units) on the day when serum vitamin A level was normal. Error bars denote 1 s.d. B, Corresponding dark adaptometry data (for the green stimulus) for subject P3. See text for further details.

symbols) showed that cone adaptation was slow, and rod function was absent. Serum vitamin A concentration was $8 \mu\text{g d}^{-1}$. Oral supplementation was initiated and P3 was retested 3 days later. The rate of recovery of rhodopsin (Fig. 6A, ◆ symbols) was considerably increased ($t_{1/2}$ about 15 min), and the final level of pigment attained was normal. Dark adaptometry carried out on that day (Fig. 6B, ◆ symbols) showed partial recovery of scotopic function, with a rod-cone break at about 20 min and final threshold reached at about 60 min. Serum vitamin A concentration was $11 \mu\text{g d}^{-1}$. When tested after a further 6 days the IFR measurements (Fig. 6A, ● symbols) showed that both the rate of regeneration of rhodopsin ($t_{1/2}$ about 6 min) and the final level reached were within normal limits. Corresponding adaptometric data (Fig. 6B, ● symbols) were normal, with the rod-cone break occurring at about 14 min. Serum vitamin A level was not determined.

Subject P1 was not available for IFR measurements, so it was not possible to investigate the relationship between abnormalities in rod adaptation and rhodopsin regeneration in his case.

Discussion

Although several previous studies have shown that rod function is lost in prolonged vitamin A deficiency, the present results provide details of the manner in which this stage is reached. Thus, the initial effect of deficiency is a reduction in the rate at which the rods dark adapt, but final thresholds eventually fall to normal levels. It therefore appears that depletion of the ocular supplies of the vitamin leads to a reduction in the rate at which one or more of the regeneration processes of the visual cycle occurs. That this is the case is confirmed by the IFR data, which show that the recovery of rhodopsin in these circumstances is abnormally slow, but reaches normal final levels, within experimental error.

As the deficiency continues, rod function is more seriously affected. Rod adaptation becomes progressively slower, and even after very long periods in darkness the visual threshold remains elevated. Finally, all signs of rod function are lost, and dark adaptation is confined to recovery of cones. At this stage rhodopsin levels are still substantial, as shown by the present and previously reported fundus reflectometry data (Ripps, Brin and Weale, 1978; Kemp and Faulkner, 1981; Fulton, Hanson, Underwood, Schwachman and Barg, 1982), and reach more than two-thirds of the normal level.

At this level of deficiency cone function appears to be less severely affected, with no elevation of final threshold, but some slowing of the rates of dark adaptation. Only when the deficiency continues further does it also become seriously abnormal. The pattern of cone abnormalities parallels that seen previously in rods: initially an increased slowing of the rate of dark adaptation followed by elevation of the final threshold reached in darkness. The sequence of visual loss, with cone function retained whilst that of rods is disturbed, is perhaps not surprising, in view of the greater dependence of the rods' visual cycle on the transport of vitamin A between them and the retinal pigment epithelium (Bridges, 1984). It is of interest, however, that the extent of cone degeneration has been shown to be more severe than that of the rods in some (Dowling and Gibbons, 1961; Hayes, 1974) though not all (Carter-Dawson, Kuwabara, O'Brien and Bieri, 1979) studies of the anatomical effects of vitamin A deficiency.

Regional variations in the degree of dysfunction could not be tested in the present study because of patient considerations. However, the asymmetric nature of the depression of the Goldmann field, with by far the greater loss occurring in the upper hemifield (Fig. 2), suggests the possibility that the extent of dysfunction may be related to the light history of the receptors. Since the lower retina (upper field) may be exposed to more light than the upper retina (lower field), so that the turnover of the visual pigment in the cells in this region is greater, it seems plausible that loss of chromophore from these receptors via some 'leakage' pathway in the visual cycle causes them to become dysfunctional more rapidly than those in the upper retina. There is evidence that photoreceptor cell degeneration is dependent on visual pigment bleaching; in vitamin A deficient rats reared in darkness, the photoreceptors remain normal (Noell, DelMelle and Albrecht, 1971). It is also of interest that altitudinal differences in sensitivity and visual pigment levels have been observed in certain types of RP (Kemp, Faulkner and Jacobson, 1983; Faulkner and Kemp, 1984) and that the degree of degeneration observed in vitamin A deficient rats also follows a similar regional pattern (Carter-Dawson, Kuwabara, O'Brien and Bieri, 1979). Further studies are warranted to determine whether this variation is indeed due to light or to some other factor, such as regional metabolic variables.

The question arises as to whether the time course of recovery of function observed in P2 was limited by the availability of retinol to the photoreceptors, or to the renewal of the outer segments themselves. In contrast to the rapid recovery of cone function at first testing after 3 days of supplementation, rod function was still absent at that time, though it had fully recovered on the seventh day (Fig. 3C). It could be argued that this was due to the slow rate at which the vitamin reached the eye. However, the levels of the vitamin in the blood rose to close to normal within 1 day of the first oral dose, implying that the delay was due to incomplete recovery of one or more of the intraocular mechanisms by which the vitamin is known to enter the retina and thence the visual cycle (Bridges, 1984).

An alternative possibility—that the rods may have partially degenerated, and that the delay in returning to normal was due to the need for renewal—gains some support from animal studies which have demonstrated that outer segments undergo degeneration and shortening in severe vitamin A deficiency (Dowling and Gibbons, 1961; Hayes, 1974; Carter-Dawson, Kuwabara, O'Brien and Bier, 1979) and the observation that in monkeys the time required for full renewal of rod outer segments is about 10 days (Young, 1971), a period similar to that required for full restoration of function in the present case.

Other evidence suggests that outer segment renewal does not limit the rate of recovery: it has been shown that when cats which have been vitamin A deficient for several months receive supplementation, their recovery of sensitivity occurs over more than 10 days. However, the sensitivity levels during that period are limited by the probability of quantal absorption, which is determined by the level of rhodopsin present (Kemp, Jacobson, Borruat, Chaitin and Knighton, 1987e). Moreover, the time course for rhodopsin regeneration following bleaching was normal. In the present study, a different pattern was observed, with delayed rod adaptation and normal final thresholds in the later stages of recovery. Together, these characteristics suggest that the recovery was limited by supply of chromophore, rather than an intrinsic abnormality of the receptor. This hypothesis has also been proposed to explain regional variations observed in vitamin A deficient chronic alcoholic subjects (Sandberg, Rosen and Berson, 1977), where it was found that recovery of dark-adapted thresholds after vitamin A supplementation occurred sooner in the peripheral retina than at the fovea.

The time needed to deplete the ocular stores of vitamin A during deficiency gives some indication of the rate at which they are used in the normal eye. Following extensive oral doses of vitamin A to subject P2, which presumably substantially restored the ocular levels, only initial signs of night blindness were induced by withdrawal of supplementation 7 days later, when rod adaptation was found to be slightly delayed (Fig. 4). In contrast, her serum vitamin A level at that time was well below the normal range. Given that residual systemic vitamin A might be expected to be preferentially delivered to the eye (Bridges, 1984), it is not possible to estimate accurately the rate of loss of the store. Nevertheless, it is clear that this was not fully depleted within less than 7 days, and a further 14 days elapsed before there was a substantial loss of scotopic function.

The present fundus reflectometric measurements confirm previous reports that even when the deficiency is sufficiently severe that observable rod function is lost, the rods are still able to regenerate a substantial fraction of the normal amount of rhodopsin (Ripps, Brin and Weale, 1978; Kemp and Faulkner 1981; Fulton, Hanson, Underwood, Schwachman and Barg, 1982). They also show that when adaptation is slower than normal, the rate of regeneration of the visual pigment is reduced.

Although it is not possible to obtain precise estimates of the time constants for regeneration, the correlation between the extended regeneration times and the delayed occurrence of the rod-cone break is fairly good, suggesting that the rates of both processes are affected in a similar manner. Thus the data provide qualitative support for the Dowling-Rushton relationship (Dowling, 1960; Rushton, 1961) in that the control of rod receptor sensitivity appears to be linked to rhodopsin regeneration, at least in conditions where extensive light adaptation has occurred.

The pattern of behaviour observed in the current study indicates that the visual effects of vitamin A deficiency are very different from what is usually seen in RP. In most reported cases of RP, rod adaptation follows normal rates, as does rhodopsin regeneration (Highman and Weale, 1973; Ripps, Brin and Weale, 1978; Kemp, Faulkner and Jacobson, 1983). Visual loss is caused by a reduction in the extent to which adaptation occurs. Exceptions are the reports of Alexander and Fishman (1984) and Ernst, Kemp and Moore (1987), who reported that rod adaptation is slowed in some RP patients. However, the form which scotopic adaptation took in those subjects was very different from that reported here: the rod-cone break occurred at the normal time, and after an initially rapid partial recovery, the threshold of the rods drifted down over extended periods.

In most of the reported cases of RP, visual loss is directly accountable for by loss of visual pigment (Highman and Weale, 1973; Ripps, Brin and Weale, 1978; Perlman and Auerbach, 1981), so that if the latter has fallen by up to 50%, little loss of sensitivity would be detectable. In the present study, in contrast, all rod function was lost at this stage of rhodopsin depletion. While this pattern has been reported for some cases of RP (Perlman and Auerbach, 1981; Kemp, Faulkner and Jacobson, 1984a; Ernst, Kemp, Arden, Moore and Bryan, 1986), no abnormalities in the rate of adaptation or rhodopsin regeneration were found.

ACKNOWLEDGMENTS

We are grateful to the late Dr W. Ernst for help with psychophysical testing; and to Prof. A. Bird, Dame S. Sherlock, Dr B. Creamer, Dr R. P. H. Thompson and Miss L. Lyness for their co-operation in this study. This work was supported by the British Retinitis Pigmentosa Society, the M.R.C., the National Retinitis Pigmentosa Foundation (U.S.A.) and the R.N.I.B.

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