British Journal of Ophthalmology, 1987, **71**, 762–765

Rod-cone interaction in patients with fundus flavimaculatus

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SUMMARY Dark adaptation and the rise of cone flicker threshold (25 Hz) during dark adaptation were measured psychophysically in three patients with fundus flavimaculatus. The dark adaptation curve showed a delayed rod-cone break but a normal final rod threshold in all these patients. However, the rise of cone flicker threshold during dark adaptation was not delayed and also reached a normal final value. This indicates that the delay in rod dark adaptation does not influence the rise of cone flicker threshold during dark adaptation. This finding contrasts with current concepts that the rise of the cone flicker threshold reflects an increasing inhibitory influence of dark adapting rods.

It has been suggested that the rise in cone flicker threshold (CFT) during dark adaptation reflects an inhibitory rod-cone interaction.[1–3] Usually, the luminance threshold for the detection of flicker has been measured at a constant high temporal frequency (20 Hz or more) in these experiments. At such temporal frequencies the threshold for flicker detection is cone mediated. The CFT was found to be highest under scotopic conditions and lowest when either measured against a large background saturating the rod system[3] or immediately after the offset of an intensive bleaching light.[4] A recent study has shown that the loss of cone flicker sensitivity provided by an inhibitory influence of unstimulated rods goes in parallel with changes in rod absolute threshold across the visual field.[5]

In patients with fundus flavimaculatus, a hereditary retinal disease, dark adaptation is frequently found to be slower than normal when sufficient preadaptation is applied, but final rod thresholds are normal or only slightly elevated.[6] On the assumption that the rise of CFT during dark adaptation is due to the increasing inhibitory influence of dark adapting rods the rise of CFT should be delayed in patients with fundus flavimaculatus showing a delayed rod-cone break. This was studied in three patients.

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Material and methods

Three patients (two females, 18 and 75 years old, and a male, 30 years old) with retinal lesions typical of fundus flavimaculatus were studied. A detailed description of the clinical findings in these patients is given elsewhere.[7] During the experiments the subjects' pupils were dilated with tropicamide (Mydriaticum) and phenylephrine (Neo-Synephrine 5%) eye drops. With a Tübinger perimeter dark adaptation and CFT were measured in a similar manner to that outlined by Alexander and Fishman.[3] After 10 minutes of intensive light adaptation with a Ganzfeld illumination of 890 cd m^{-2} the change in perception threshold was determined for a white circular stimulus with a diameter of 104′, presented for 500 ms at a temporal retinal eccentricity of 20°. Foveal fixation was maintained by presenting a deep red central mark. The luminance was increased in steps of 0·1 log units from subthreshold values until the subject responded by means of a buzzer. After renewed identical light adaptation the change in CFT was measured during a second run of dark adaptation. In this case the stimulus flickered with a constant frequency of 25 Hz and the subject was asked to activate the buzzer as soon as flicker became detectable. For each trial the luminance was set below the flicker threshold initially, in order to avoid

flicker adaptation, and then the luminance was increased in 0·1 log unit steps. Threshold was defined as the mean of two repetitions of this procedure.

Results

The rod-cone break in the dark adaptation curve was delayed in all three patients studied. It occurred after 12, 14, and 19 min respectively, whereas the normal range for the rod-cone transition, as determined in more than 20 healthy persons, was from 6 to 10 min after the beginning of dark adaptation under our experimental conditions. There was an apparent positive correlation between the delay in rod-cone transition and the age of the patients, but the number of patients is much too small to tell whether this is of any significance.

The delay of the rod-cone break was most pronounced in patient M (75 yr), known to have fundus flavimaculatus for more than 40 years. In her better, left eye the rod-cone transition occurred during the 19th minute of dark adaptation. The fundus of this eye showed the typical deep yellowish white retinal deposits of various sizes and shapes in the posterior polar region. Simultaneously she had a macular lesion, most probably senile macular degeneration. Since she had seen much better in her earlier years, a concomitant macular degeneration of Stargardt's type can be regarded as unlikely. She had a small absolute central scotoma in this eye and a visual acuity of 0·2. The ERG and EOG were normal. Her colour vision showed a slight blue-yellow defect, but this might also be due to an early senile cataract.

As shown in Fig. 1 (filled squares), her dark

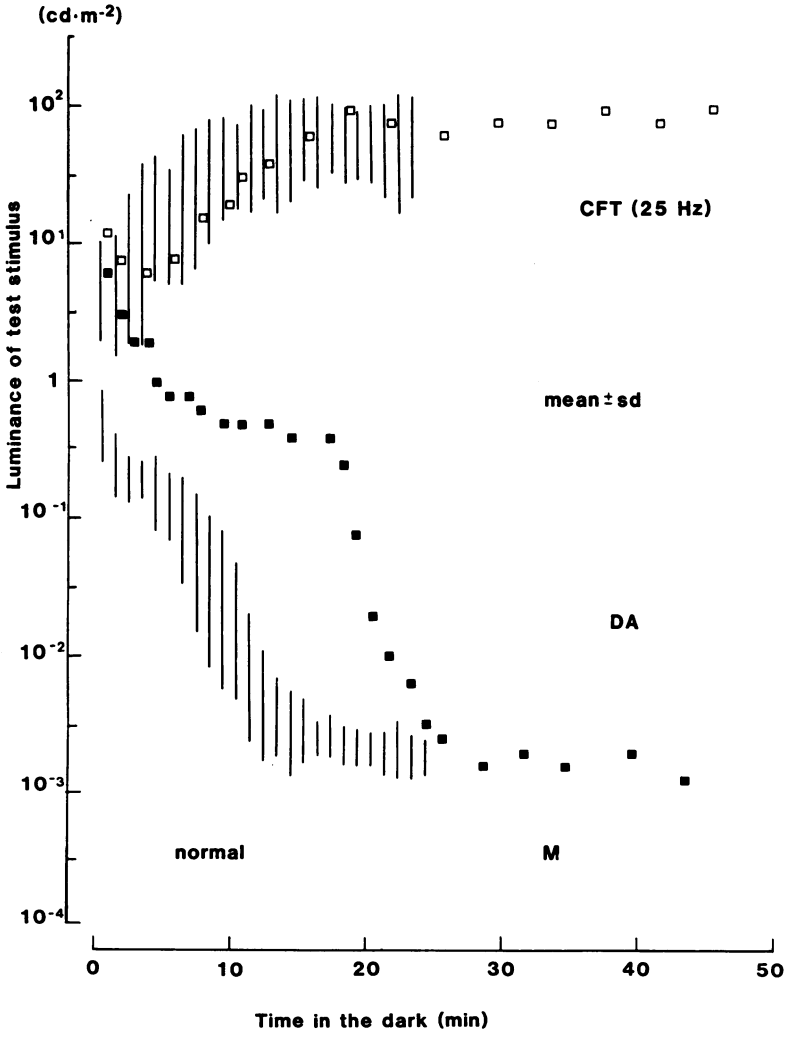

Fig. 1 *Dark adaptation curve (DA, filled squares) and cone flicker threshold during dark adaptation (CFT, open squares) of patient M. The vertical lines represent the normal values ± standard deviation. The dark adaptation curve of the fundus flavimaculatus patient shows a delayed rod-cone break but a normal final rod threshold. The rise in cone flicker threshold is normal. Further details are given in the text.*

adaptation curve reached a normal final rod threshold despite the massive delay of her rod-cone transition. The same was true for the other two patients, who also reached normal thresholds after less than 35 minutes of dark adaptation.

Fig. 1 also shows the values for the CFT (open squares) of patient M. After a small initial drop, which is often but not always seen in normal persons too, her CFT showed a completely normal rise. It is especially noteworthy than the CFT had already reached its final threshold, approximately 1·0 log units above the initial value, when the dark adaptation curve showed a rod-cone break.

Similar results were obtained in the two other patients with fundus flavimaculatus. They had a normal time course in the rise of CFT during dark adaptation, although their rod-cone transition during dark adaptation was delayed. Both the final CFT values and the final rod thresholds of these patients were in the normal range.

Discussion

After exposure to an adapting light that bleaches a high percentage of the visual pigments in the retina, peripheral cone thresholds fall to a plateau within 3 to 5 minutes. Only after approximately 8 to 10 minutes does the rapidly increasing sensitivity of the rods lead to the rod-cone break in the dark adaptation curve.[8,9] In patients with fundus flavimaculatus this rod-cone transition is delayed,[6] most probably due to a disturbance of rhodopsin regeneration.[10]

Bearing in mind the current concept that the rise of cone flicker threshold during dark adaptation is induced by an increasing inhibitory influence of dark adapting rods on cones,[1-3] one might expect this rise to be delayed also in fundus flavimaculatus. This is not the case. The three patients with a delayed rod-cone break in fundus flavimaculatus had a normal rise of CFT during dark adaptation. Arden and Hogg[11] made a similar observation on a patient with retinitis pigmentosa. This patient had a slowed dark adaptation, and a normal sized increase in the cone flicker threshold occurred at a time when the patient's rods were very insensitive.

Examination of CFT during dark adaptation has been shown to be valuable in the differential diagnosis of retinal disease,[11-13] and it is therefore of great interest to know which mechanism is responsible for the CFT rise under normal conditions. As outlined by Alexander and Fishman[5] recently, it is unlikely that the threshold rise depends directly on the recovery of rod system sensitivity, as both can be fitted with rather different mathematical equations. Moreover, caffeine and theophylline, two phosphodiesterase inhibiting drugs, affect the human CFT while leaving dark adaptation unchanged.[14]

It has been suggested[13,15] that the interaction between rods and cones in flicker detection is mediated by a lateral pathway within the outer retina involving horizontal cells. Horizontal cells have been shown to exert a continuous negative feedback on to cones in the dark,[16,17] and it is known that after a bleach the membrane potential of horizontal cells returns to the resting level well before responses to test flashes re-establish their prebleach amplitudes.[18] Consequently, the electrical signals that mediate this interaction are at least partially independent of the photochemical process of adaptation. If the rod-cone interaction underlying the rise in CFT during dark adaptation occurs via horizontal cells, as is likely,[13,15] a normal rise in CFT should depend on normal horizontal cell electrical activity. The rod inhibition on CFT is maximal when the rods are completely dark adapted and unstimulated[2]—that is, when rods with a dark current at its maximum[19] modulate horizontal cell activity. Thus our observation that in patients with fundus flavimaculatus the time course of the CFT rise is normal despite a marked delay in the rod-cone transition suggests that in these patients horizontal cell function is normal and that after a bleach the rod dark current returns with normal kinetics. The delay in regaining normal rod sensitivity is therefore probably due to a disturbance in a preceding stage of the rhodopsin-transducin cascade sequence of phototransduction.

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Accepted for publication 16 October 1986.