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Parallel Increase of Heterochromatic Increment Threshold and Postadaptation Thresholds in Parkinson's Disease and in Neuroleptic Treatment

BERNHARD A. HAUG,*‡ EVA-MARIA HERMSTEINER,* BORWIN BANDELOW,† WALTER PAULUS*

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Following reports on a predominant loss of blue/yellow contrast sensitivity in Parkinson's disease, we revisited the physiological phenomenon of transient tritanopia. Normative data were collected from 33 healthy individuals using different colour and time combinations. Stimuli of 440 nm wavelength (blue) proved optimal, if flashed for 50 msec within the early phase of a 2 sec pause in the 600 nm adaptation light. These conditions were then applied to 15 patients with Parkinson's disease. We found a parallel increase of increment threshold ($P < 0.001$) and postadaptation thresholds ($P < 0.01$), with little change in the extent of transient tritanopia. The same tendency at a lower significance level was found in 15 psychiatric patients under chronic treatment with depot neuroleptics. © 1997 Elsevier Science Ltd

Transient tritanopia Heterochromatic increment threshold Parkinson's disease Neuroleptic treatment Dopaminergic retinal transmission

INTRODUCTION

In 1949, Stiles (1949a,b) developed the theory of π mechanisms in human colour vision. He applied a two-colour threshold technique, using monochromatic adaptation lights and measuring the sensitivity to superimposed test stimuli of different wavelengths (increment threshold). At that time he first described the physiological phenomenon, later called transient tritanopia (Mollon & Polden, 1977), which we applied in this clinical study. It consists of a paradoxical transient loss of sensitivity to blue test lights, after a long wavelength adaptation light is switched off (postadaptation threshold). Only after some seconds the sensitivity increases gradually, as would be expected, approaching the dark adaptation value asymptotically. For other colour combinations the sensitivity starts to recover immediately.

Mollon *et al.* showed by psychophysical experiments, that transient tritanopia is mediated by retinal interactions between medium/long wavelength cones and blue cones (Mollon & Polden, 1975, 1976, 1979). It is also detected in protanope and deuteranope subjects, but it cannot be elicited, when the adaptation light is presented to one, and the test light to the other eye (Mollon & Polden, 1977). Later, based on extracellular recordings of blue-sensitive ganglion cells in primates, Zrenner (1983) developed an electrophysiological hypothesis for this phenomenon, in which he assumes horizontal cells as the connecting links: long wavelength cones act via glutamate (Brandon & Lam, 1983; Bolz *et al.*, 1984) on horizontal cells, which in turn release GABA (Yazulla & Kleinschmidt, 1982; Moran & Pasantes-Morales, 1986; Wässle *et al.*, 1989; Wässle & Chun, 1989) as an inhibitor (Tachibana & Kaneko, 1984; Kaneko & Tachibana, 1986) of blue cones. In his doctoral thesis, Schuurmans (Schuurmans, 1981; Schuurmans & Zrenner, 1981) proved that GABA antagonists make the transient tritanopia disappear in feline optic nerve recordings. Dopamine also reduces GABA release from horizontal cells by two different means of action: via D1 receptors on horizontal cells (Denis *et al.*, 1990) it inhibits GABA release through cAMP mechanisms (Yazulla & Kleinschmidt, 1982; Piccolino *et al.*, 1984; Lasater & Dowling, 1985; Knapp & Dowling, 1987; McMahon *et al.*, 1989) and, indirectly via D2 receptors on photoreceptor cells (Witkovsky *et al.*, 1988), it reduces the release of glutamate (Schorderet & Nowak, 1990; Kamisaki *et al.*, 1991).

Ichikawa *et al.* were the first who introduced the phenomenon of transient tritanopia to clinical applications, for the diagnosis of retinal diseases (Ichikawa *et al.*, 1982; Ichikawa & Ichikawa 1982a,b). Zrenner

*Department of Neurology and Clinical Neurophysiology, Georg-August University, Robert Koch Str. 40, 37075 Göttingen, Germany.

†Department of Psychiatry, Georg-August University, von Siebold Str. 6, Göttingen, Germany.

‡To whom all correspondence should be addressed [*Tel/Fax*: (49) (551) 39-8457/-8126; *Email*: bhaug@gwdg.de, b.haug@med.uni-goettingen.de].

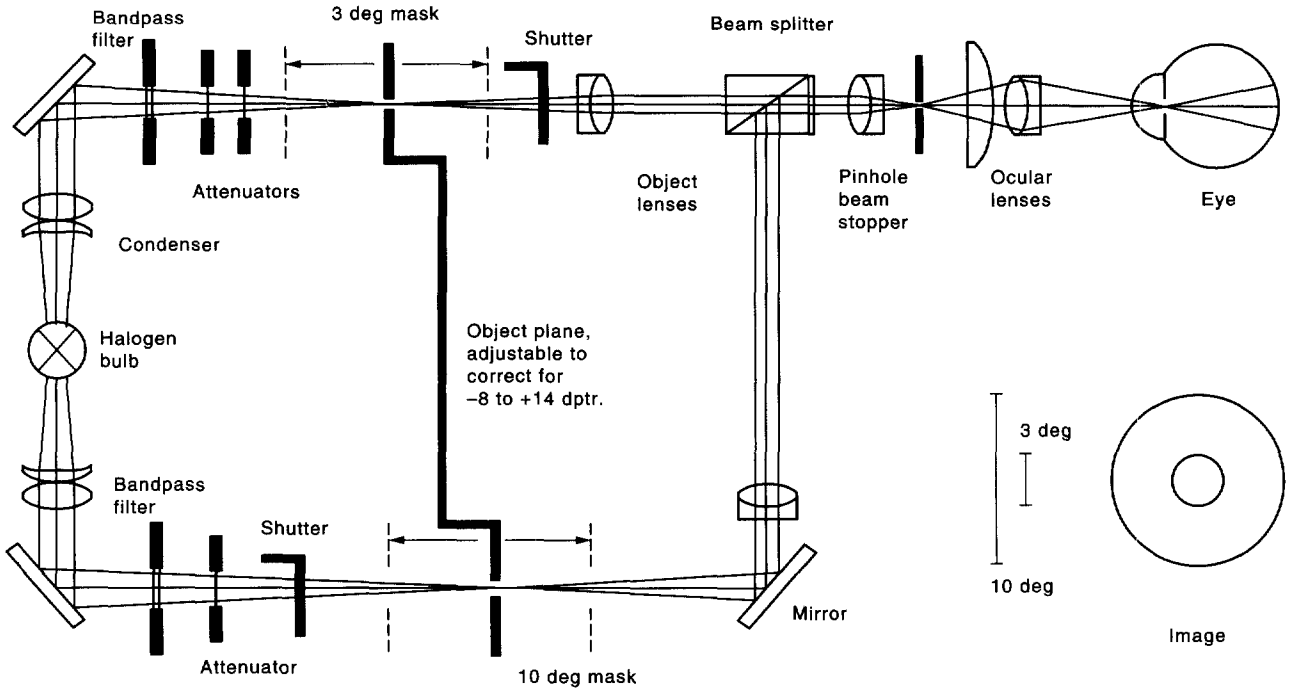

FIGURE 1. The modified retinal function test instrument has two independent light channels fed from one halogen bulb. The images are superimposed by an inversed beam-splitter and projected by a Maxwellian view system through the observer's pupil onto the retina.

continued examinations in particular on hereditary degenerations of the retina (Zrenner *et al.*, 1986) and extended his studies to the effect of medication (Zrenner & Nowicki, 1985). Phenytoin and carbamazepine have been found to reduce the degree of transient tritanopia, probably by the inhibition of transmembrane ion currents. Additional administration of vigabatrin antagonized this reduction, which could be explained by its effect of increasing the postsynaptic GABA concentration as an inhibitor of GABA breakdown (Bayer, 1991). Paulus *et al.* (1993) gathered indirect evidence for a retinal dysfunction in Huntington's disease. They could show that these patients had an impaired increment threshold and a concurrently diminished transient tritanopia effect, while the postadaptation thresholds were unaltered.

There have been several reports on a disturbance of colour perception in Parkinson's disease (Price *et al.*, 1992; Büttner *et al.*, 1993; Barbato *et al.*, 1994; Büttner *et al.*, 1995). The idea for this study on transient tritanopia arose from our previous findings of a predominant loss of tritan colour contrast sensitivity in Parkinson's disease (Haug *et al.*, 1994a,b, 1995). Would the examination of this effect involving the sensitivity to blue test lights help to localize the deficit within the complex retinal circuitry? Our first task was to re-examine the physiological phenomenon of transient tritanopia in a larger group of normal subjects, especially to analyse its nature in respect to possible other colour combinations and to determine an optimal presentation sequence of the stimuli. In the second part, we had to apply the optimized paradigm to Parkinson's disease patients. As a counterpart to this dopaminergic deficiency, we extended the study to long-term neuroleptic treatment in patients with schizophrenia as an example of a iatrogenic dopaminergic deficiency.

MATERIALS AND METHODS

Equipment

Core of the experiments was a modified "retinal function test instrument" manufactured by Nidek Corp., Japan (Fig. 1). A single 20 W 12 V halogen bulb feeds two independent light channels, each of which has its own condensers, colour filter housings, fast electromagnetic shutters and grey scale attenuators adjustable in 0.1 log and 1 log units driven by step motors. The beams are reunited by an inverse beam splitter and projected by a Maxwellian View system (Westheimer, 1966) to the subject's retina. Its principle is to display the stimulus through an ocular lens system comparable with that of microscopes, but with the focus of the beam in the plane of the pupil. With this method, the pupil's size does not affect the quantity of light passing through. To ease the exact placement of the head with the beam centred on the pupil, we used adjustable forehead and chin rests and, following a suggestion of G. Arden, a ring, into which the subject actively positioned his nose tip during the examination.

The two channels were used to display a 10 deg diameter background field and a concentric 3 deg test field, which could be superimposed independently. Individual refractive errors were compensated for by shifting the beam stops to and fro. Sixteen interference colour filters with band pass wavelengths between 400

and 700 nm in steps of 20 nm and narrow cutoff (10–15 nm) were fitted with additional grey scale filters to provide equal light intensity at each wavelength, if used with the built-in light source. For calibration, a Research Radiometer IL 1700 (International Light Inc., Newburyport, MA, U.S.A.) was fitted to the ocular. The background intensity was 70 ± 9 nW in all experiments and the maximum test light intensity was 220 ± 13 nW with the possibility for attenuation at 0.1 log steps down to 4.9 log. An external computer was used to drive the shutters with a precision of ±5 msec.

Paradigms

We used two successive paradigms in all subjects. The first was the *increment threshold*. The subject was allowed to adapt to the darkened room for 10 min. Then, sitting in front of the ocular of the retinal function test instrument, he/she was instructed to fixate with one eye (the one with the better corrected visus was chosen) on the centre of the bright, 10 deg diameter background field. After 2 min of adaptation, the concentric 3 deg test field of another colour was superimposed with exposure times of 50 or 500 msec in time intervals of 6 sec. The subject indicated by hand movement, whether he/she perceived the test stimulus or not. Using a modified binary search method to vary the intensity of the test field, the individual increment threshold for the respective colour combination and presentation time was determined. In order to make the influence of possibly reduced alertness and slowed reaction time in different subgroups as small as possible, the stimulus was repeated with equal intensity every 6 sec, until the subject could reliably determine and signal whether he/she has perceived the stimulus or not.

For assessment of the *postadaptation threshold*, the same test stimuli were applied within a short pause of background illumination (50–2050 msec) following continuous adaptation for 2 min. Testing at different time intervals after the offset of the background illumination allowed us to record the time course of the sensitivity to the test light during the postadaptation phase. In the classical setting described by Stiles (1949a,b) there is a marked decrease of sensitivity to blue test lights following adaptation to yellow background lights, which has been named "transient tritanopia". An index for transient tritanopia (TTI) can thus be obtained by dividing postadaptation threshold through increment threshold or by calculating the difference of their log values.

Experiments

Optimizing the colours. All possible combinations of test light wavelengths between 400 and 700 nm with background filters of 440 (blue), 520 (blue–green), 540 (light green), 600 (yellow) and 640 nm (red) were examined in order to check for the limitation of the transient tritanopia effect to yellow background and blue stimulus. For this experiment a standard timing was chosen: 50 msec test stimuli, 6 sec repetition time and, in case of postadaptation threshold, stimulus onset 100 msec after beginning of the 2 sec background pause.

Optimizing the timing. For postadaptation thresholds various timings have been applied:

- the duration of test stimuli was either 50 or 500 msec;
- pauses in background illumination were chosen from the mere time of the stimulus display to additional intervals of 100, 500, 1000, 1500 and 2000 msec;
- the timing of test stimuli was either at the beginning or immediately preceding the end of the various background pauses;
- for 2000 msec pauses the test stimuli were also placed at various time intervals within this, starting at 0, 100, 500, 1000, 1500 and 1950 msec from the beginning of the background pause.

In these experiments standard colours were chosen: yellow 600 nm for the adaptation field, blue 440 nm for the test field.

Study on patients. The most promising combination of colours (440 nm test field on 600 nm background) and timing were chosen for the larger study including patients: for the increment threshold a test stimulus of 50 msec was superimposed on the background; for the postadaptation thresholds the test stimulus was delivered at 0, 100, 500, 1000, 1500 or 1950 msec from the beginning of the 2 sec background illumination pause.

Additional examinations

All subjects underwent a Snellen test to assess and confirm a visual acuity of at least 0.6 cum correctione.

The Ishihara plate test was used to exclude inherited colour vision anomalies on the red–green axis.

The Lanthony-D-15-désaturé test was applied to assess finer colour vision anomalies, including acquired ones and those on the tritan axis. The subjects had to sort the coloured caps according to the manufacturer's instructions under the light of a OSRAM Dulux S No. 12 fluorescent tube, which provided daylight quality illumination of 250 lux at table level. In addition to visually judging the plotted results, a total error score was calculated for further mathematical analysis. Each piece was assigned a score according to the added differences between its number and the numbers of its two neighbour pieces. Finally, all scores were added up and 60 was subtracted from the sum so that the correct alignment corresponds to a total error score of 0.

Subjects

Experiments 1 and 2 were completed on four healthy and normal-sighted subjects aged 23–36 yr. Experiment 3 was performed in larger groups of patients and separate sets of sex- and age-matched normal volunteers, on the total 63 subjects. All gave their informed consent prior to

the examination. The following exclusion criteria were imposed:

- Physical or mental handicap interfering with correct examination (such as inability to maintain the necessary constant fixation of the adaptation field and to give reliable answers)
- Diabetes mellitus
- History of retinal detachment or other retinal diseases
- Cataract
- Glaucoma
- Snellen visual acuity less than 0.6
- Significant colour vision anomaly in the Ishihara plate test.

Four subjects had to be excluded owing to insufficient visual acuity, and one each due to red–green anomaly, glaucoma and diabetes mellitus.

Fifteen Parkinson patients (eight female, seven male) along with their matched controls could be included based on these selection criteria. The mean age within each group was 65.8 ± 10.1 yr. According to the Webster scale the Parkinson patients scored 10.2 ± 5.9 points. Antiparkinson medication was maintained during the study and consisted of various combinations of L-DOPA/benserazide, L-DOPA/carbidopa, amantadine, metixen, biperiden, selegiline and bromocriptine. The average disease duration was 5.87 ± 5.59 yr.

Fifteen psychiatric outpatients (eight female, seven male) on long-term treatment (6 months and longer) with depot neuroleptics formed another group. They were examined on the day of their regular visits just prior to the regular depot injection with haloperidol, flupentixol, fluphenazine, perphenazine or cis-clopenthixol. Their mean was age 47.1 ± 13.7 yr, and hence required another age-matched group of normal volunteers.

Statistics

Two way ANOVA analyses have been performed with groups as "between" factor (normals vs Parkinson and normals vs neuroleptics) and postadaptation delays as "within" factor with five levels (0, 100, 500, 1000 and 1500 msec). Where the ANOVA showed a significant effect of the factors, single differences were assessed by two-tailed Student's t tests. Following the recommendations of Rothman (1990), Bonferroni corrections, Greenhouse Geisser corrections (Greenhouse & Geisser, 1959) or other adjustments for multiple comparisons were not applied. The psychophysical data had been acquired in log format, which yielded results compatible with the assumptions of normality (Winer *et al.*, 1991). A statistical error probability of $2P < 0.05$ was considered as the minimum requirement for significance. The significance threshold was adjusted according to the Satterthwaite procedure to compensate for unequal variances.

Linear regression analyses were performed on the data in order to evaluate a possible correlation with age in normal controls, with disease duration in Parkinson patients and with the effective neuroleptic dosage equivalent in psychiatric patients.

RESULTS

Colours

We measured heterochromatic increment thresholds on steady background illumination and postadaptation thresholds 100 msec after the offset of background illumination for 50 msec test stimuli. For most combinations of colours the postadaptation threshold was lower than the increment threshold, indicating that sensitivity to the test light starts to increase already within this short interval after offset of the adaptation light. Only for blue test lights with short wavelengths of 460 nm and less, the paradoxical effect of a transient further decrease of sensitivity, called transient tritanopia, could be observed (Fig. 2). This effect, however, was not limited to a yellow adaptation field (600 nm), where it was maximal, it could rather be observed for all medium and long wavelength background colours from 540 nm (light green) to 640 nm (red). If the background colour came closer to the short wavelength range as with 520 nm (blue–green), there was no clear change in sensitivity to blue test lights.

Timing

For a fixed colour combination, 440 nm stimuli on 600 nm background, the increment threshold does only depend on the test stimulus presentation time, and hence there was one value for 50 and 500 msec each. The postadaptation thresholds were set in relation to these values, mathematically calculated by subtracting the increment threshold from the various postadaptation thresholds, as both had been measured on a log scale. This difference constitutes a transient tritanopia index (TTI) in log units.

Initial experiments were carried out with the test stimulus immediately being displayed at the offset of background illumination using various "off" times for the background, which varied between the mere duration of the stimuli up to an additional 2000 msec (Fig. 3). For stimuli lasting 500 msec, we found only a small transient tritanopia index (TTI), which was 0.45–0.625 log units throughout. However, for stimuli lasting 50 msec only, the TTI rose from 0.325 for 0 msec to 1.30 for 500 msec, and finally 0.925 for 2000 msec of additional pause in background illumination. The results show that immediate reinstitution of the yellow adaptation light improved the perception of the foregoing blue test light, which means it reduces the transient tritanopia.

Accordingly, experiments with the test stimulus at the end of the pause of background illumination, varying the "off" period of the adaptation field before onset of the stimulus, showed only a small TTI with log values between 0.325 and 0.60 for both 50 and 500 msec stimuli (Fig. 4).

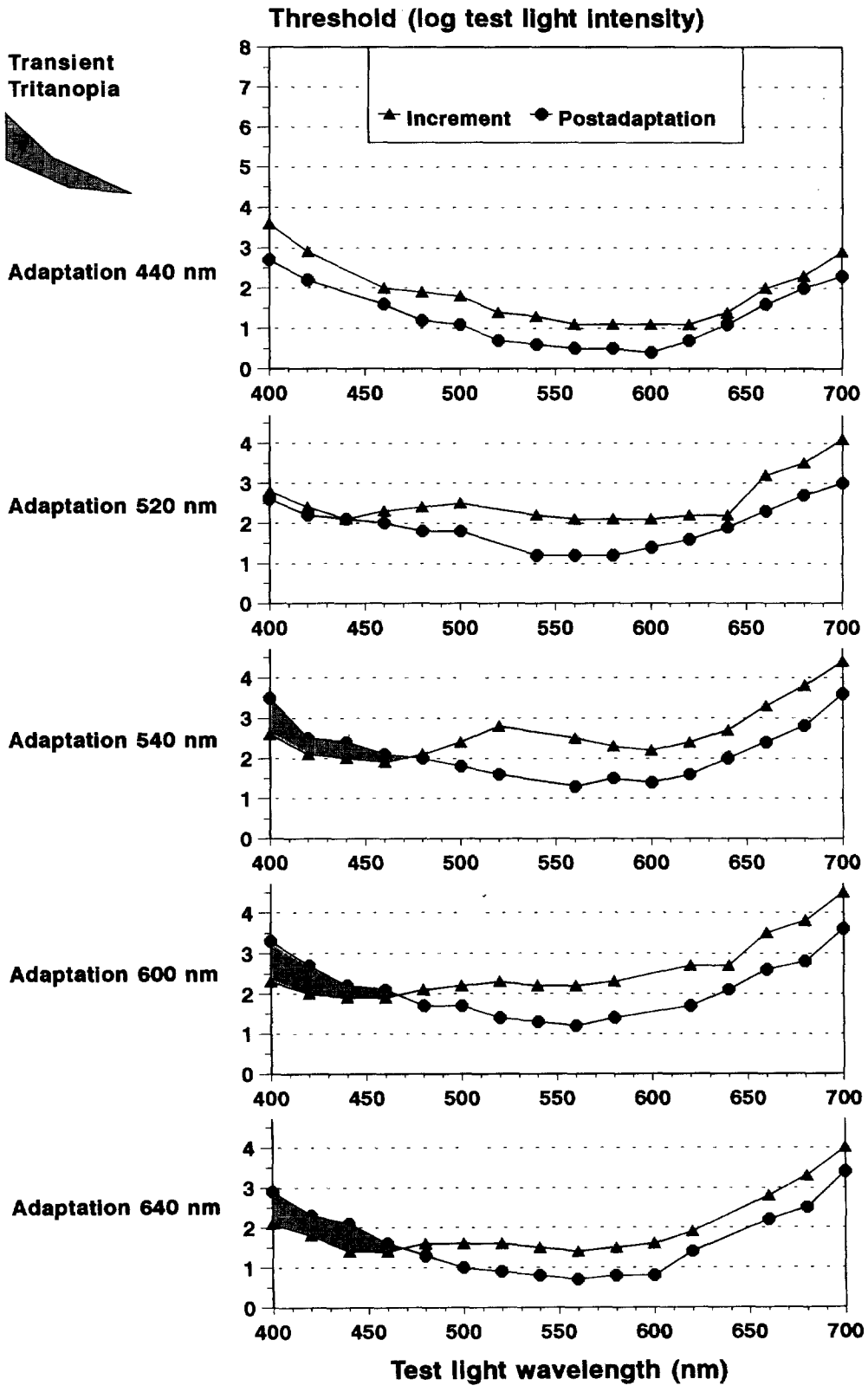

FIGURE 2. Increment thresholds and postadaptation thresholds for different wavelength combinations of test light (400–700 nm) and adaptation light (440–640 nm) in four normal observers. The area of transient tritanopia is hatched.

Finally we kept the pause of the adaptation field constant at 2000 msec and varied the interposition of the 50 msec stimulus. The data acquired from 33 normal volunteers are shown in Fig. 5. The maximum TTI of 1.46 $\pm$ 0.30 log units was observed, if the stimulus was applied at the beginning of the background illumination pause, which extended for 1950 msec after the stimulus. With later presentation of the test stimulus, the TTI gradually diminished and reached nearly 0, when the stimulus was applied 1500 msec after the offset of the

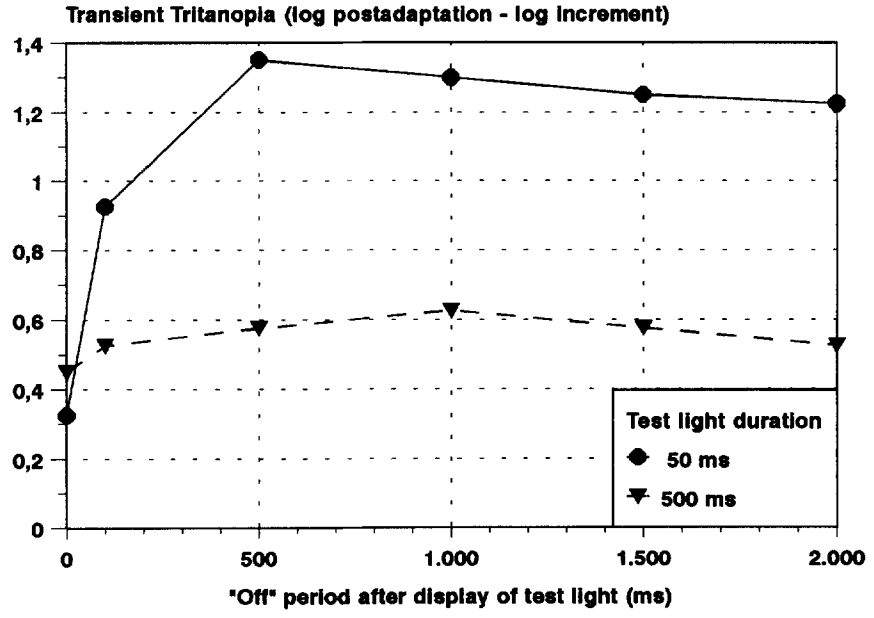

FIGURE 3. Transient tritanopia index (TTI) for 50 and 500 msec stimuli, which follow immediately to the offset of the adaptation light, as a function of the subsequent "off" period. The maximum effect is reached with a 50 msec stimulus followed by 500 msec of further adaptation pause.

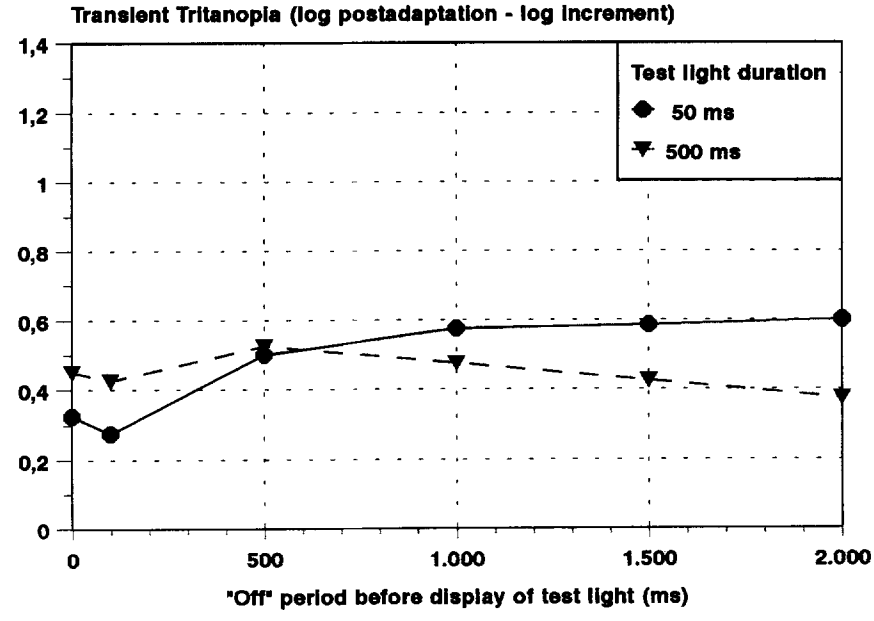

FIGURE 4. TTI for 50 and 500 msec stimuli, which are immediately followed by a re-institution of the adaptation light, as a function of the preceding "off" period. In this condition the TTI is smaller compared with the condition in Fig. 3.

adaptation light. In accordance with the foregoing experiment, however, there was again a small rise in TTI to 0.52 ± 0.27 log units, when the stimulus was immediately followed by re-illumination of the background. This effect, however, could better be referred to as backward masking or metacontrast (Breitmeyer & Kersey, 1981; Ramachandran & Cobb, 1995), and it is probably caused by a mechanism other than transient tritanopia.

Patients

Patients and the larger group of normal volunteers were finally examined with a yellow adaptation light of 600 nm and blue test stimuli of 440 nm wavelength. The increment threshold was determined, when adaptation to the background field had been achieved. The postadaptation thresholds were measured during 2000 msec pauses in background illumination, repeated every 6 sec. The 50 msec test stimuli were delivered at different time

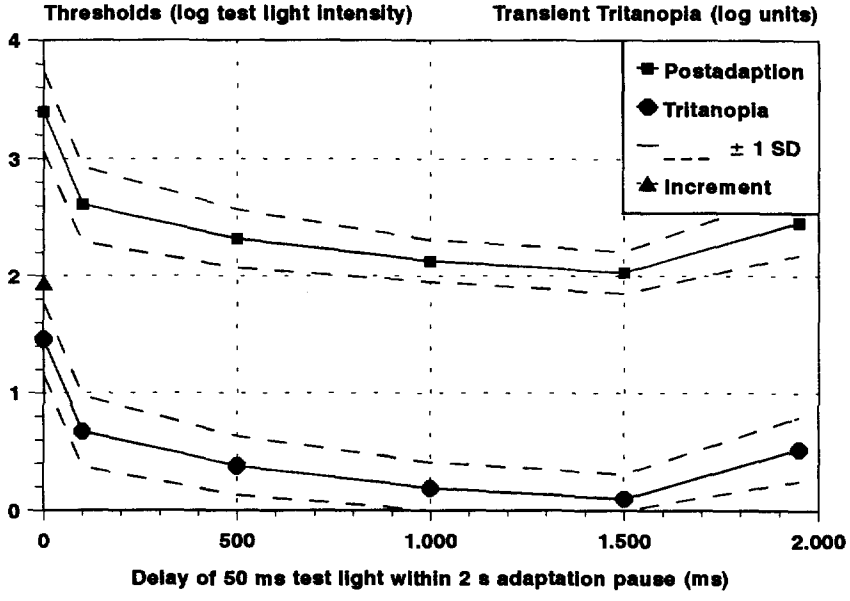

FIGURE 5. Time course of postadaptation thresholds and TTI in 33 normal observers, within a background illumination pause of 2 sec, measured with a short test stimulus of 50 msec duration. The increment threshold with steady background field is indicated as a reference value at time point 0, although it is not time-related to the adaptation pause.

intervals within these pauses to assess the time course of transient tritanopia.

Individual data of Parkinson's disease patients and of the group of normal volunteers with similar age are shown in Fig. 6, the means are indicated in Table 1, together with the statistical results (two-tailed t-tests after confirmation of a significant intergroup difference with the ANOVA procedure: for groups DF = 1, $F = 204.48$, $P > 0.0001$). Increment thresholds as well as postadaptation thresholds are significantly elevated to about the same degree. The time course of the postadaptation threshold is similar in both groups. The TTI calculated from these values shows little difference from normals, still detectable in the ANOVA, but not significant if pairs of data are compared with the t-tests.

Patients under neuroleptic medication showed analogous results with increased increment threshold and postadaptation thresholds (Fig. 7, Table 2) (ANOVA: for groups DF = 1, $F = 367.98$, $P < 0.0001$). In comparison with their matched group of normals, however, the difference was smaller and the hypothesized significance level was not reached for all time points using t-tests.

Within all normal subjects of these experiments a linear regression analysis was performed with regard to some age-dependent effects. The increment threshold was fairly independent of age ($r_i = 0.254$), but early postadaptation thresholds showed a slight positive correlation with age ($r_{0msec} = 0.543$ to $r_{1500msec} = 0.218$). TTI correlated less well ($r_{0msec} = 0.436$ to $r_{1500msec} = -0.050$). Some representative results are depicted in Fig. 8, including also the Snellen visual acuity of the examined eyes, which showed a slight decrease with age.

Within the different patient groups, there was no clear correlation of results with disease duration in Parkinson's disease or with the effective dosage equivalent in patients treated with neuroleptics.

The Lanthony test results indicated slight colour vision deficits in both the Parkinson and neuroleptic-treated patients. Visual inspection of the charts showed an unspecific pattern with no preponderance of errors along one of the colour axis. The total error scores (Tables 1 and 2) showed significant results to the level of $2P < 0.01$.

DISCUSSION

Transient tritanopia is a physiological phenomenon of the human visual system involving a transitory, paradoxical loss of sensitivity to blue test lights, when a yellow adaptation light is switched off (Stiles, 1949b).

In agreement with other authors (Mollon & Polden, 1977; Wisowaty, 1983) we found, that the decrease of sensitivity to blue light does not only follow adaptation to yellow light (580, 600 nm), but also to other wavelengths between 540 nm (light green) and 640 nm (red). Adaptation fields with a wavelength of 520 nm (blue–green) and shorter, which are predominantly detected by blue cones, do not elicit transient tritanopia. In our large number of 33 normal subjects the difference between postadaptation thresholds and increment threshold amounted to 1–2 log units.

Of course differences in comparison with other studies can arise from a variety of other factors, such as projection geometry, size of the fields, foveal or parafoveal testing, adaptation time and intensity, and the time interval in which the test stimulus is applied. To project the stimulus onto the retina, we used a Maxwellian view system (Westheimer, 1966) which controls for the effect of a varying pupil size with

TABLE 1. Lanthony test results, increment threshold and time course of the postadaptation threshold (50 msec, 440 nm test light at different time intervals following a 2 sec extinction of a 600 nm background) in Parkinson's disease patients (mean ± SD)

	Parkinson's disease $n = 15$	Age-matched controls $n = 15$	Two-tailed Student *t*-test		
			df	*t*	2*P*
Age (yr)	65.8 ± 10.1	65.8 ± 10.1			
Lanthony test score	14.0 ± 10.4	4.80 ± 6.45	21	2.84	<0.01
Increment threshold (log test light intensity)	2.42 ± 0.38	1.95 ± 0.23	22	4.10	<0.001
Postadaptation thresholds (log test light intensity)					
0 msec	3.81 ± 0.25	3.49 ± 0.38	24	2.68	<0.05
100 msec	3.07 ± 0.39	2.67 ± 0.36	27	2.92	<0.01
500 msec	2.61 ± 0.33	2.41 ± 0.27	27	1.87	–
1000 msec	2.41 ± 0.37	2.17 ± 0.19	21	2.16	<0.05
1500 msec	2.34 ± 0.28	2.05 ± 0.20	24	3.21	<0.005
1950 msec	3.03 ± 0.63	2.51 ± 0.31	20	2.87	<0.01

The differences to the control group are significant for all three parameters, but not for the transient tritanopia index (= log postadaptation threshold-log increment threshold).

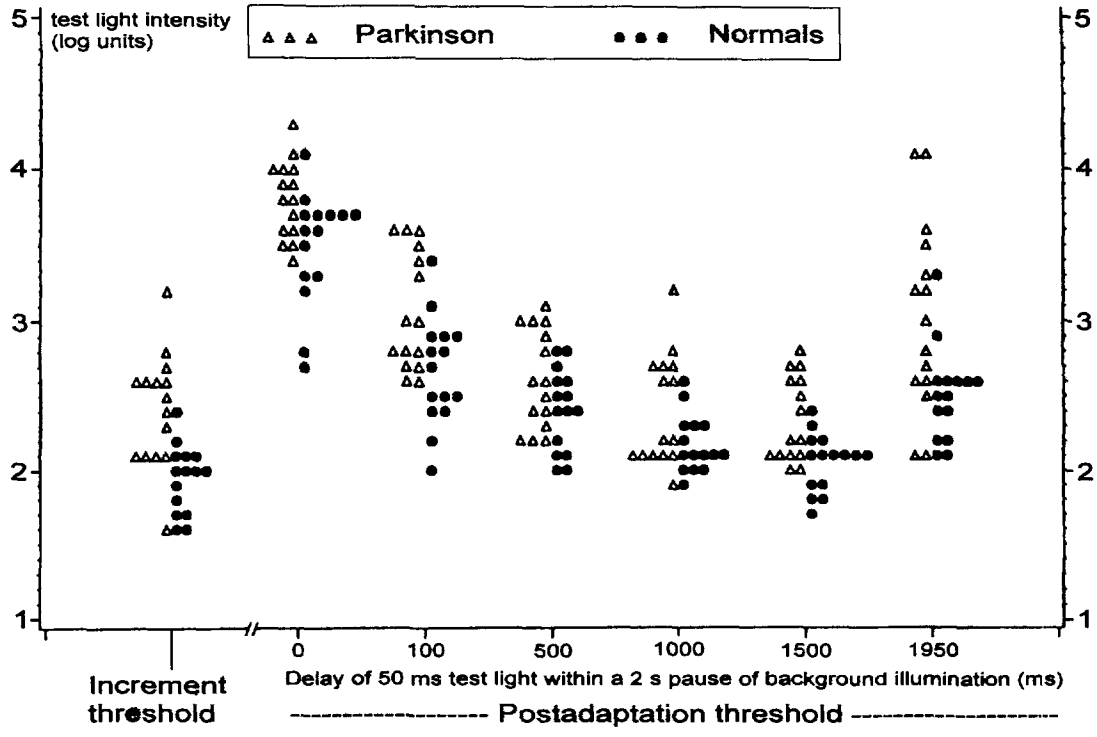

FIGURE 6. Individual results of increment threshold and time course of postadaptation threshold in 15 Parkinson patients and 15 sex- and age-matched controls.

changing background illumination. Use of mydriatica could thus be avoided, because they might influence the release, action and metabolism of retinal neurotransmitters.

The experiments varying the timing of the test stimulus showed a more marked transient tritanopia with the shorter test light of 50 msec duration. Moreover, the results indicated that the time course of TTI starts with the maximum effect immediately after switching off the adaptation light. The later the test light is displayed, the smaller is the difference between increment threshold and postadaptation thresholds. After about 1.5 sec, the value of the latter has approached the former asymptotically. However, this value corresponds only to the early minimum according to Loomis (1980), who has detected a fast and a slow phase of reaching the equilibrium threshold. In order to more or less maintain a state of adaptation to the background field, which was necessary to detect the psychophysical threshold in repeated trials, we could only choose these relatively short periods of "postadaptation" time, followed by a re-institution of the background illumination. Using this procedure, we also analysed the effect of the length and timing of the adaptation pauses. There were two interesting results: if the adaptation light was inserted immediately or 100 msec after the display of the test stimulus, the TTI

TABLE 2. Numeric and statistical results of Lanthony test, increment threshold and postadaptation thresholds in psychiatric patients treated with neuroleptics (mean ± SD)

	Neuroleptic treatment $n = 15$	Age-matched controls $n = 15$	Two-tailed Student t-test		
			df	t	$2P$
Age (yr)	47.1 ± 13.7	47.1 ± 13.7			
Lanthony test score	9.07 ± 9.50	3.73 ± 5.75	23	1.86	<0.01
Increment threshold (log test light intensity)	2.17 ± 0.28	1.91 ± 0.19	24	2.86	<0.01
Postadaptation thresholds (log test light intensity)					
0 msec	3.55 ± 0.23	3.27 ± 0.29	26	2.85	<0.01
100 msec	2.85 ± 0.36	2.49 ± 0.24	24	3.17	<0.005
500 msec	2.34 ± 0.26	2.21 ± 0.19	25	1.53	–
1000 msec	2.23 ± 0.27	2.07 ± 0.16	22	2.02	–
1500 msec	2.16 ± 0.19	2.00 ± 0.19	27	2.32	<0.05
1950 msec	2.65 ± 0.69	2.36 ± 0.23	16	1.56	–

Comparison with the control group was less significant than in Parkinson's disease.

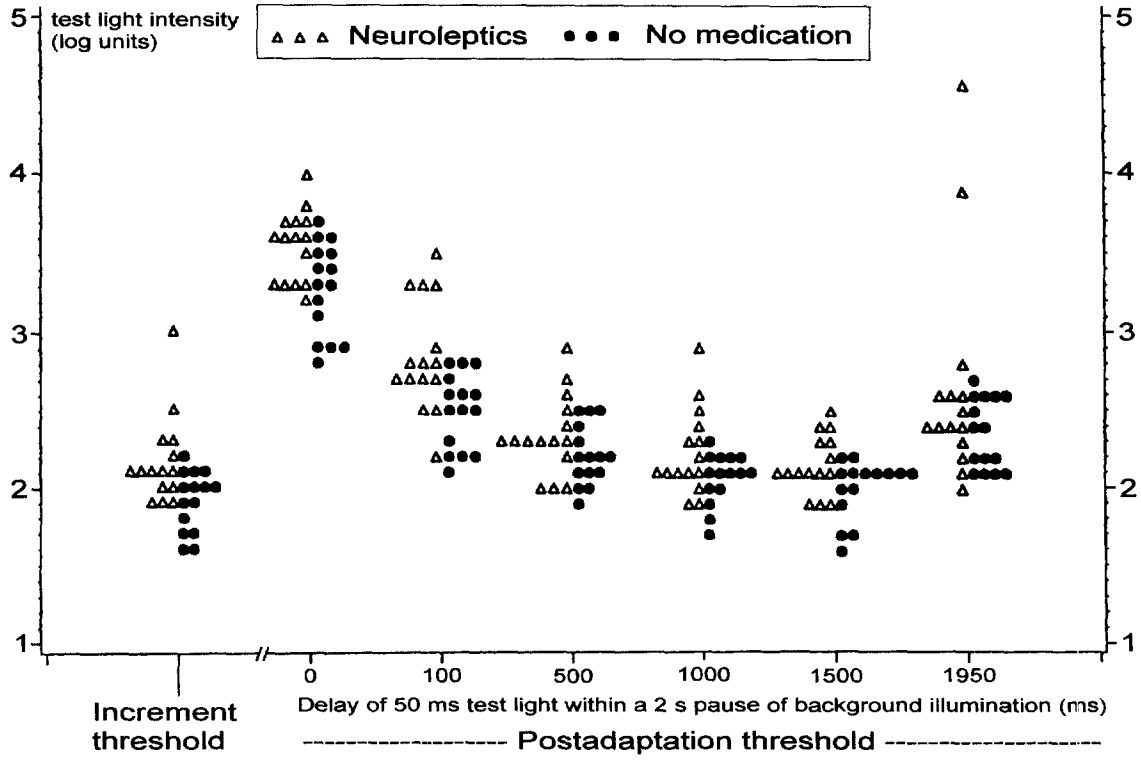

FIGURE 7. Individual results of increment threshold and time course of postadaptation threshold in 15 psychiatric patients treated with depot injections of neuroleptics in comparison with 15 sex- and age-matched controls.

index was markedly diminished. Maximum tritanopia was only reached if the stimulus was followed by at least 500 msec of further adaptation pause. This indicates that the perception of the test light can be influenced by a change of illumination within 100 msec after its presentation. On the other hand, when the test light is applied as long as 2 sec after shutting off the adaptation field, e.g. when the TTI has fallen off to undetectable levels, reinstitution of the adaptation light at this time point elicited a change in the postadaptation threshold comparable to a tritanopia effect of 0.5 log units. This, however, must be another effect different from transient tritanopia and not explicable by the electrophysiological model of Zrenner (1983) mentioned above. We did not find an explanation for this phenomenon, which might be related to backward masking (Breitmeyer & Kersey, 1981) or metacontrast (Ramachandran & Cobb, 1995), but a second look at the data of Bayer (1991) confirmed, that it is detectable in his study, too, although he does not describe it explicitly.

To illustrate the test results of Parkinson's disease patients, we first have to recall the hypothesis of Zrenner

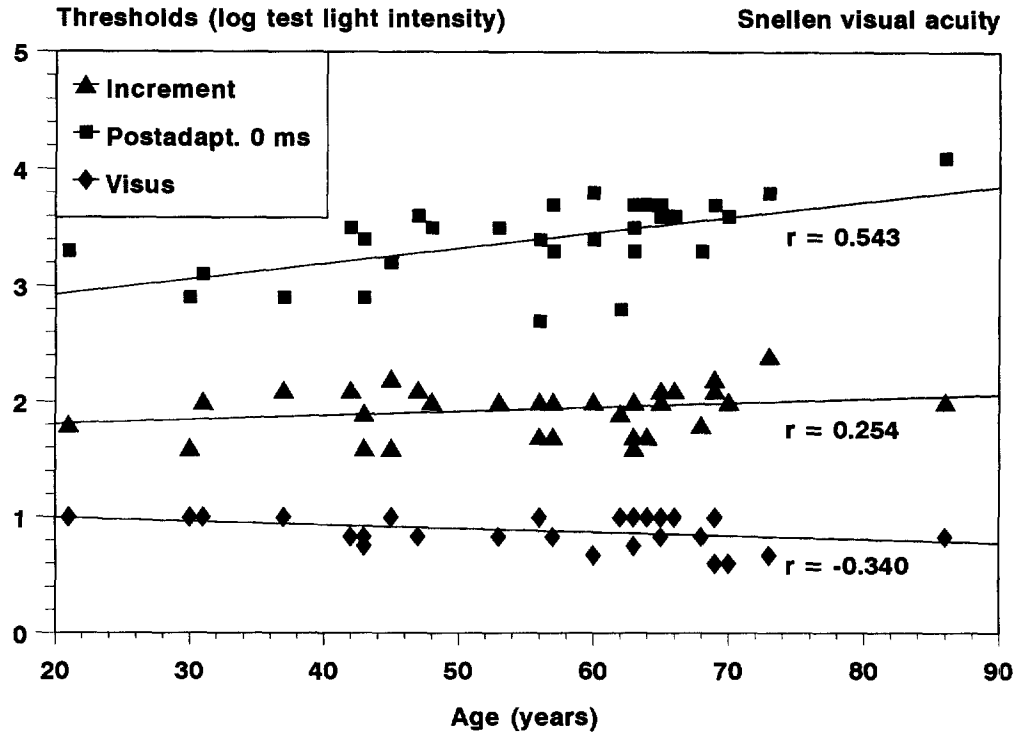

FIGURE 8. Age dependency of increment threshold, postadaptation threshold for 50 msec stimuli displayed at the beginning of a 2 sec adaptation pause, and Snellen visual acuity in 33 normal subjects.

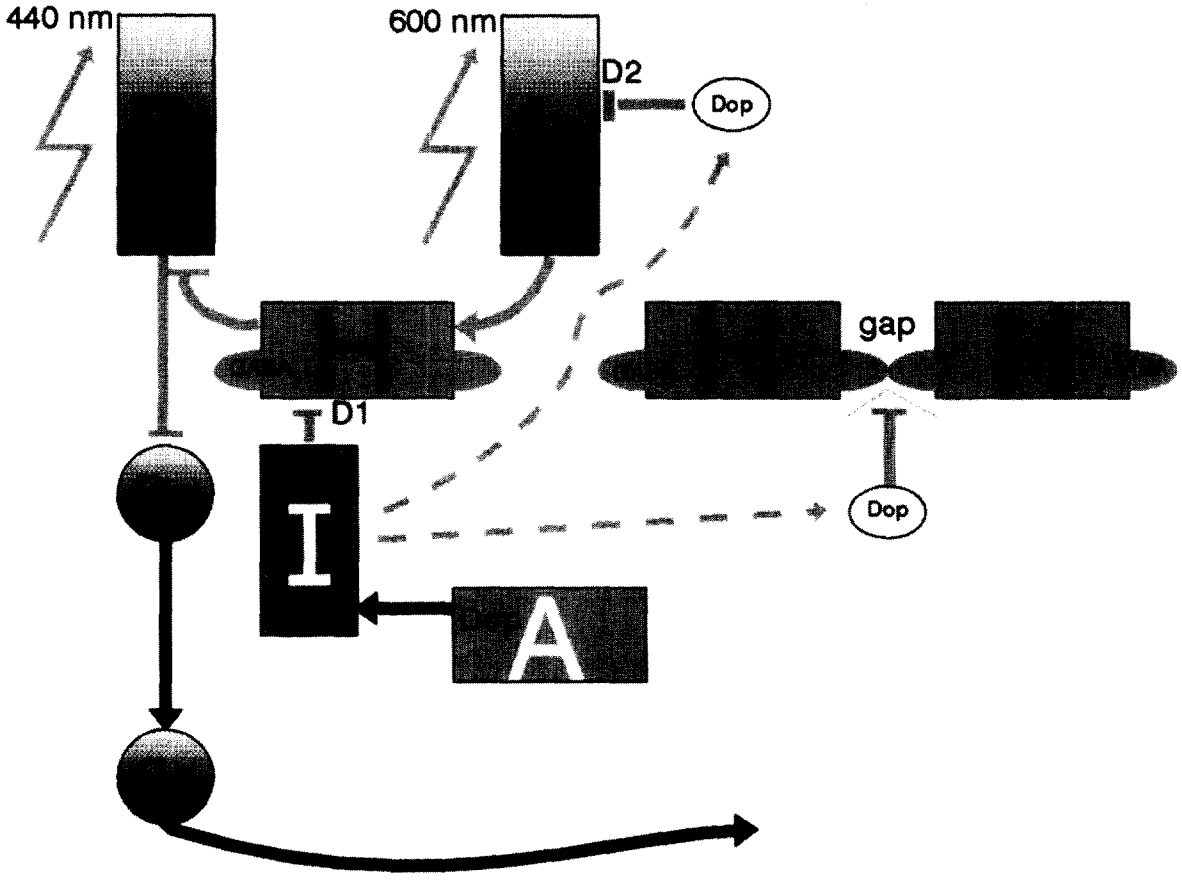

FIGURE 9. Schematized interactions of retinal cells in relation to transient tritanopia and the effect of the neurotransmitters glutamate, GABA and dopamine (*B*, blue cone; *L*, long wavelength cone; *H*, horizontal cell; *I*, dopaminergic interplexiform cell; *A*, dopaminergic amacrine cell; *Bp*, on-centre cone bipolar cell; *Gc*, ganglion cell; *Glu*, glutamate; *GABA*, gamma-aminobutyric acid; *Dop*, dopamine; *gap*, gap junction).

(1983) for the explanation of the transient tritanopia. Long wavelength cones depolarize as a response to the offset of the yellow background illumination. Via glutamate as a depolarizing transmitter they stimulate horizontal cells to release GABA (Pycock, 1985) to the postsynaptic membrane of blue cones. As a consequence, the sensitivity to the blue test stimulus is momentarily attenuated, until a new equilibrium is reached. For the understanding of these interactions it is important to bear in mind that light inhibits (hyperpolarizes) and darkness excites (depolarizes) photoreceptor cells (Tomita, 1976). For the blue channel, which features only on-centers, the signal is again inverted, as it is conveyed to invaginating cone bipolar cells. The illustration in Fig. 9 shows in simplified form the model from Zrenner (1983) without details of ionic currents, but supplemented by the possible interactions from dopaminergic neurons:

- Dowling & Ehinger (1978) described dopaminergic interplexiform cells, which receive inputs from amacrine cells in the inner plexiform layer and contact horizontal cells in the outer plexiform layer. Yazulla (1985) showed in goldfish preparations, that the carrier-mediated release of GABA from horizontal cells is enhanced by glutamate from cones and inhibited by dopamine from retinal interplexiform cells.
- Whereas D1-receptors have been found on horizontal cells, D2-receptors were detected on photoreceptor cells (Denis *et al.*, 1990; Schorderet & Nowak, 1990). By stimulating these D2-receptors, the release of glutamate from cones can be inhibited (Kamisaki *et al.*, 1991). For the latter effect a direct synaptic transmission has not been proven. It is more likely that dopamine reaches cone D2-receptors by diffusion from interplexiform or amacrine cells (Schorderet & Nowak, 1990; Masson *et al.*, 1993).

Our Parkinson's disease data have shown a parallel reduction of sensitivity to increment stimuli and to postadaptation stimuli. The effect of transient tritanopia is equal to that in normal volunteers. It therefore seems likely that the circuit involved in transient tritanopia (long wavelength cone—horizontal cell—blue cone) is not significantly affected by the dopamine deficiency, as can be expected from the lack of dopaminergic transmission within this circuit. It can be postulated, that dopamine deficiency reduces blue light sensitivity at another stage of signal processing, possibly at the level of dopaminergic interplexiform cells. A lack of inhibitory output to GABAergic horizontal cells would, in turn, increase their inhibitory effect on blue cones.

Another possible way to modify contrast sensitivity through the action of dopamine is by the influence on centre/surround inhibition. Lateral inhibition is mediated by interconnecting horizontal cells in the outer plexiform layer by inversely modifying the activity of bipolar cells. McMahon *et al.* (1989) could show that dopamine reduces the gap junctions (electrical synapses) between horizontal cells, thus reducing the size of the receptive fields and increasing the spatial resolution for low contrast values. Hence, a lack of dopamine would result in larger receptive fields at the expense of contrast sensitivity. In the inner plexiform layer dopaminergic amacrine cells bring the surround response into the rod system through synapses with rod amacrine cells (Daw *et al.*, 1990). However, it is difficult to explain why these two mechanisms should preferentially affect the perception of blue or tritan stimuli, as has been shown in our previous experiments (Haug *et al.*, 1994a,b, 1995).

Systemic application of neuroleptics is known to affect the retinal function as well as mesocortical and mesolimbic processes. Scatton *et al.* (1977) showed in rat experiments, that haloperidol and sulpiride enhance striatal and retinal dopamine turnover. van Duijn *et al.* (1985) detected an increase in visual evoked potential latency in normal volunteers exposed to a single dose of haloperidol. Stanzione *et al.* (1990) found that haloperidol delays pattern electroretinograms more than VEP in normal humans. Several electrophysiological studies in man and monkey confirmed that indeed the retinogram can be used to monitor neuroleptic action and D2 receptor activity (Bodis-Wollner, 1990; Stanzione *et al.*, 1992, 1995; Tagliati *et al.*, 1994; Stanzione, 1995).

Our data on patients on neuroleptic treatment show, in analogy to the Parkinson data, a tendency to both increased increment and postadaptation thresholds, however less conspicuous. Since all applied neuroleptics have a higher affinity to D2-receptors, the effect is most probably mediated by the above-mentioned direct action on cones. The reduced dopaminergic influence counteracts the light-induced hyperpolarization and enhances the release of glutamate from the cones (Kamisaki *et al.*, 1991).

SUMMARY AND CONCLUSIONS

Transient tritanopia is a physiological phenomenon of the human retina characterized by the momentary loss of sensitivity to blue test lights, when a yellow adaptation light is suddenly withdrawn. We used a Maxwellian view system to avoid the influence of pupil size for the presentation of a 3 deg diameter test stimulus with adjustable intensity on a concentric 10 deg heterochromatic background. In four normal volunteers we confirmed, that the effect is limited to blue test lights of <460 nm wavelength on adaptation fields of >540 nm. A maximal difference between increment threshold (superimposed on the background) and postadaptation threshold (in the otherwise dark field) was elicited, when a short stimulus of 50 msec was displayed immediately after the offset of the adaptation field and followed by a pause in illumination of at least 500 msec. Normative data were taken from 33 individuals to assess the time course of the sensitivity to a 50 msec, 440 nm test light following adaptation to 600 nm. Transient tritanopia index (TTI) was maximally 1.46 log units and gradually waned off within the first 1.5 sec of the 2.0 sec pause of background illumination. Immediately before the adaptation light was

re-established, the threshold rose again by 0.52 log units, which was considered another mechanism related to metacontrast/backward masking phenomena. Early post-adaptation thresholds showed a slight positive correlation with age, whereas increment thresholds were more stable.

The clinical study was conducted with the same optimized test conditions, allowing comparison with sex- and age-matched controls. Fifteen Parkinson patients had both elevated increment thresholds ($P < 0.001$) and postadaptation thresholds (significance levels $P < 0.01$). Fifteen patients on neuroleptic depot injections showed similar deficits of a lesser degree ($P < 0.01$ and above). By this parallel change of both thresholds the resulting transient tritanopia index (TTI) did not show pathological values.

We speculate that the general loss of blue cone sensitivity in patients with dopaminergic deficiency is due to a lack of inhibitory inputs from dopaminergic interplexiform cells via D1-receptors to GABAergic horizontal cells, which in turn increase their inhibitory effects on blue cones. A second mode of action can be assumed through D2-receptors on photoreceptors. A diminished diffusion of dopamine to these sites would result in downregulation of cone sensitivity.

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