The a-wave of the dark adapted electroretinogram in glaucomas: are photoreceptors affected?

Isabel M Velten, Matthias Korth, Folkert K Horn

Abstract

Aims—To evaluate whether the a-wave of the dark adapted flash electroretinogram (ERG) is affected by glaucomatous damage.

Methods—ERGs were recorded in 20 patients (age 33–65 years) with advanced glaucomas (primary and secondary open angle and low tension glaucomas) and 20 normals using a Ganzfeld stimulus. After 30 minutes of dark adaptation and pupil dilatation to at least 7.5 mm in diameter, luminance response functions were obtained presenting white flashes of increasing scotopic luminance (the highest flash intensity being 9.4 cd/s/m², the lowest being 5.75 log units below it) with an interflash interval of 5 seconds. For each scotopic luminance, the responses of four flashes were averaged. The a-wave's amplitude was measured at 10, 11, and 12 ms. Within the glaucoma group, correlations between the interocular differences of the a-wave's amplitude and the mean deviation of a static perimetry (Octopus 500 perimeter, program G1) were computed for all flash intensities. Between normals and glaucomas, the a-wave's amplitude was compared for all flash intensities (paired *t* test).

Results—Within the glaucoma group, the interocular differences of the a-wave's amplitudes correlated significantly with the differences of the MD for flash intensities of 9.4, 5.3, 1.7, and 0.5 cd/s/m². The a-wave's amplitude was significantly lower in the glaucoma compared with the normal group (*p* < 0.005) for flash intensities of 9.4 and 5.3 cd/s/m².

Conclusion—These electrophysiological results imply that also the outer retinal structures, especially the photoreceptors, may be affected by glaucomatous damage. (*Br J Ophthalmol* 2001;85:397–402)

Department of
Ophthalmology and
University Eye
Hospital, University of
Erlangen-Nürnberg,
Schwabachanlage 6,
D-91054 Erlangen,
Germany
I M Velten
M Korth
F K Horn

Correspondence to:
Dr Isabel M Velten,
Augenkl. mit Poliklinik
der Universität
Erlangen-Nürnberg,
Schwabachanlage 6,
D-91054 Erlangen, Germany
isabel.velten@
augen.imed.uni-erlangen.de

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The a-wave of the dark adapted ERG arising mainly from the rods,^{7,8} can be regarded as a suitable measure of the photoreceptor function. In contrast with previous investigations, the present study examined the a-wave of the dark adapted ERG using a light intensity function. The a-wave's amplitude was followed from its threshold up to high intensities lying above the intensity of the ISCEV standard⁹ bright flash. The peak amplitude of the a-wave has long been recognised as being contaminated by the intrusion of the b-wave. This may be of varying influence depending on the stimulus conditions and the nature of the process affecting retinal sensitivity.⁷ We thus used as a measure of photoreceptor function in this study the a-wave's amplitude measured at fixed times of 10, 11, and 12 ms, before interference with the b-wave can occur. Normals show a high interindividual variability in ERG responses. Thus, in this study, additionally to the comparison between the normal and glaucoma group, the interocular differences of the a-wave's amplitude were correlated with the interocular differences of the mean deviation (MD) of a static perimetry. Neglecting the interindividual variability, this intraindividual interocular comparison allows a better answer to the question of whether a relation exists between the stage of glaucoma damage and the impairment of the a-wave. The study was planned to evaluate whether differences in visual fields between the two eyes of one patient are likewise accompanied by changes in the ERG response, especially in the a-wave's amplitude. As some studies with patients with beginning or moderate open angle glaucomas did not reveal any changes in photoreceptor function^{3,4} or in photoreceptor count,¹ this study only concentrated on patients with advanced, long standing glaucomas.

Earlier studies^{3,4} found flash ERGs to be inappropriate for adequate glaucoma diagnosis, while the pattern ERG which arises mainly from the inner retinal layers, especially the retinal nerve fibre layer where glaucomatous changes occur first, was favoured for glaucoma diagnosis.^{10–13}

Thus, this study was not planned to contribute to ways of glaucoma diagnosis, rather it was the aim of this study to contribute from the electrophysiological point of view to the question of whether photoreceptors are included in advanced glaucomatous damage.

Methods

EXPERIMENTAL DESIGN

After 30 minutes of dark adaptation, flash ERGs were recorded from both eyes simultaneously in a Ganzfeld (Nicolet GS 2000) using

Histological studies revealed different results^{1,2} regarding the question whether glaucomatous damage also leads to damage of the outer retinal layers, especially the photoreceptors, or whether the glaucomatous damage remains strictly limited to the inner retinal layers. A number of electrophysiological studies^{3–6} have been performed to answer the question whether the a-wave and b-wave of the flash electroretinogram (ERG) are affected by glaucomatous damage. While some of these studies^{3,4} could not find any significant change in ERG responses related to glaucomas, others^{5,6} found significant changes in either the a-wave or the b-wave in glaucomas.

white flashes of a xenon discharge lamp. Pupils were dilated to at least 7.5 mm in diameter with 1% tropicamide and 5% phenylephrine. There was no significant difference in pupil diameter between the normals and the glaucoma group. Additionally, eye drops for local anaesthesia (oxybuprocaine hydrochloride 0.25%) and 2% methylcellulose lubrication were used before inserting a Henkes electrode (clear 20 mm, art no MW 1300, Medical Workshop bv, Netherlands). The ipsilateral earlobe served as reference and the forehead was grounded. The white flashes were presented with increasing intensity with an interflash interval of 5 seconds the highest flash intensity being 9.4 cd/s/m², the lowest being 5.75 log units below it). The lowest flash intensity was below the a-wave's threshold and above the b-wave's threshold in most subjects. Neutral density filters were used to achieve the adequate flash intensity. Each flash intensity was presented four times. An artefact rejection algorithm prevented unwanted signals like eye movements from being averaged. After amplification (2 seconds–500 Hz, 500 μ V/V), four sweeps (300 ms length) were averaged (500 Hz sampling rate) using a personal computer. Steps of 0.5 and 0.25 log units were used between two following flash intensities.

The a-wave's amplitude was measured from the baseline at fixed times of 10, 11, and 12 ms after the onset of the light stimulus (see Fig 1). These amplitudes were chosen instead of the a-wave's peak amplitude to avoid contamination of the b-wave which might influence the estimation of photoreceptor function. For this purpose, the times of 10, 11, and 12 ms were short enough in all subjects.

Within the glaucoma group, the interocular differences of the a-wave's amplitudes between both fellow eyes of one patient were correlated with the interocular differences of the MD of the static perimetry (Octopus 500 perimeter, program G1, two or three phases, see below) for all flash intensities. Additionally, the a-wave's amplitudes were compared between the normal and the glaucoma group.

Figure 1 ERG responses of one normal subject for flash intensities of 0.2, 0.5, 1.7, 5.3, and 9.4 cd/s/m². The broken line marks the time of 11 ms at which the response magnitudes were measured. This time was short enough to avoid interference of the a-wave with the b-wave.

SUBJECTS

Subjects were recruited from our glaucoma service and from hospital staff. Informed consent was obtained from each individual after explanation of the nature and possible consequences of the study according to the guidelines set by the institutional review board.

In all, 40 subjects were tested who were divided into two groups: the glaucoma group included 20 patients with advanced, asymmetric primary and secondary open angle and low tension glaucomas. The control group included 20 normals. The mean age of the glaucoma group was 56.9 (SD 9.1) versus 43.4 (11.5) years in the normal group (unpaired *t* test: *p* = 0.014). All individuals satisfied the following criteria: refractive errors less than 9 dioptres (myopic or hyperopic), no previous cataract surgery, clear optic media, open anterior chamber angle, no systemic illnesses possibly influencing the eye such as diabetes mellitus, vascular, or rheumatic diseases. The participants were between 33 and 65 years old.

All subjects underwent a full ophthalmological examination confirming a normal eye or excluding any ophthalmological diseases other than glaucoma. For both eyes in each subject, the following examinations were conducted: best refracted visual acuity, perimetry with a computerised static projection perimeter (Octopus 500 EZ, program G1, two or three phases), slit lamp examination, gonioscopy, applanation tonometry, and dilated fundus examination.

At the time of testing, the IOP was ≤ 21 mm Hg in all eyes included. As a measure for glaucoma damage, the static projection perimetry was used. The visual field indices described by Flammer *et al*¹⁴ are calculated routinely by the program G1 of the Octopus 500 EZ. Subjects performing in visual field testing with false positive and false negative responses of $>12\%$ were excluded. Normal visual fields were accepted even if the test was the first one for the subject. Abnormal fields (mean defect (MD) >2.8 dB, at least three contiguous test points 5 dB or more below the age corrected normal threshold) were accepted only if the subject had had at least two examinations with the Octopus 500-G1 perimeter.

Only patients with asymmetric or unilateral glaucomas were included in the glaucoma group. The difference in the MD had to be more than 1.5 dB between the less and the more affected eye.

For the comparison between the glaucoma and the normal group, only one eye of each individual was included. For the glaucoma patients, the eye with the more advanced glaucoma damage was chosen. For the normal group, the eye included was chosen randomly.

STATISTICAL ANALYSIS

Within the glaucoma group, the interocular differences of the a-wave's amplitudes between both fellow eyes of each patient were correlated with the interocular differences of the MD using Pearson's correlation coefficient.

Table 1 Correlation between the interocular differences of the a-wave's amplitude and the MD within the glaucoma group

Flash intensity	Correlation coefficient			p Value		
	Time at which the response magnitudes were measured					
	10 ms	11 ms	12 ms	10 ms	11 ms	12 ms
9.4 cd/s/m ²	0.730	0.743	0.758	0.001	0.001	0.001
5.3 cd/s/m ²	0.663	0.660	0.668	0.005	0.005	0.005
1.7 cd/s/m ²	0.768	0.764	0.753	0.001	0.001	0.001
0.5 cd/s/m ²	0.546	0.593	0.628	0.03	0.016	0.009
0.2 cd/s/m ²	0.236	0.287	0.368	ns	ns	ns
0.005 cd/s/m ²	0.240	0.273	0.188	ns	ns	ns

Within the glaucoma group the correlation between the interocular differences of the a-wave's amplitude and the MD between both fellow eyes of each patient was significant for flash intensities of 0.5, 1.7, 5.3, and 9.4 cd/s/m². For lower luminances, the correlation was not significant. The table shows Pearson's correlation coefficient and the p value (ns = not significant) of the correlation for each flash intensity and the a-wave's amplitudes for the three times of 10, 11, and 12 ms at which the response magnitudes were measured.

For all flash intensities, the a-wave's amplitudes were compared between the normal and the glaucoma group using the unpaired *t* test.

Results

INTEROCULAR COMPARISON WITHIN THE GLAUCOMA GROUP

Table 1 shows the results of Pearson's correlation the interocular differences of the a-wave's amplitudes and the interocular differences of the MD between both fellow eyes of each patient. The correlation was significant for flash intensities of 9.4 cd/s/m², 5.3, 1.7, and 0.5 cd/s/m². The scatter plots in Figure 2 show the correlation between the interocular differences of the a-wave's amplitude and the MD for flash intensities of 9.4, 5.3, 1.7, 0.5, and 0.2 cd/s/m².

COMPARISON BETWEEN THE NORMAL AND THE GLAUCOMA GROUP

The results of the unpaired *t* test comparing the a-wave's amplitude for all flash intensities between the normal and the glaucoma group are listed in Table 2 and Figure 3. For flash intensities of 9.4 cd/s/m² and 5.3 cd/s/m², the

Figure 2 (A-E) Scatter plots for the correlation between the interocular differences of the a-wave's amplitudes measured at a fixed time of 11 ms and the interocular differences of the MD between both fellow eyes of one patient within the glaucoma group for flash intensities of 9.4 cd/s/m² (A), 5.3 cd/s/m² (B), 1.7 cd/s/m² (C), 0.5 cd/s/m² (D), and 0.2 cd/s/m² (E). Pearson's correlation was significant for luminance times of 9.4, 1.7, and 0.5 cd/s/m² with correlation coefficients of 0.743, 0.660, 0.764, and 0.593, respectively (compare Table 2).

Table 2 Comparison of the a-wave's amplitude at 10, 11, and 12 ms between the normal and the glaucoma group

Flash intensity (cd/s/m ²)	Normal group a-wave's amplitude (μV) (mean and (SD))			Glaucoma group a-wave's amplitude (μV) (mean and (SD))			p Value		
	Time at which the response magnitudes were measured (ms)								
	10	11	12	10	11	12	10	11	12
9.4	299 (58)	331 (61)	352 (61)	235 (87)	255 (88)	165 (67)	0.006	0.005	0.004
5.3	238 (42)	273 (47)	302 (51)	165 (67)	191 (74)	214 (79)	0.004	0.004	0.004
1.7	79 (23)	95 (27)	112 (32)	64 (28)	78 (34)	92 (40)	ns	ns	ns
0.5	35 (12)	44 (14)	52 (17)	26 (12)	31 (14)	37 (16)	ns	ns	ns
0.2	23 (16)	28 (18)	34 (21)	11 (6)	14 (8)	17 (9)	ns	ns	ns

Comparing the normal and the glaucoma group, the a-wave's amplitude showed a significant difference for flash intensities of 5.3 and 9.4 cd/s/m², but not for lower luminances. The table shows the mean a-wave's amplitudes with standard deviations (SD) and the results of the unpaired *t* test for each flash intensity and for the three fixed times of 10, 11, and 12 ms at which the response magnitudes were measured.

Figure 3 The a-wave's amplitudes measured at 11 ms for all subjects in the glaucoma and the normal group for flash intensities of 0.2, 0.5, 1.7, 5.3, and 9.4 cd/s/m². For flash intensities of 9.4 and 5.3 cd/s/m², the a-wave's amplitudes differed significantly between the two study groups (*p* < 0.006, compare Table 2)

a-wave's amplitudes differed significantly between the two groups (*p* < 0.006). For all other flash intensities, there was no significant difference between the normal and the glaucoma group.

The mean age in the glaucoma group was 56.9 (9.1) versus 43.4 (11.5) years in the normal group (unpaired *t* test: *p* = 0.014). In our study with subjects between age 33 and 65, the normal group did not show a significant correlation of the a-wave's amplitude with age. We thus did not perform a correction for age although the normal and the glaucoma group showed a significant difference in age.

Discussion

Within the glaucoma group, the interocular differences of the a-wave's amplitudes correlated significantly with the interocular differences of the MD for the four highest flash intensities measured. Additionally, the a-wave's amplitudes showed a significant difference between the normal and the glaucoma group for flash intensities of 9.4 cd/s/m² and 5.3 cd/s/m².

To exclude the influence of the b-wave, the a-wave's amplitude was measured at fixed times of 10, 11, and 12 ms for all flash intensities instead of using the a-wave's peak amplitude. These times at which the response magnitudes were measured were short enough

in all patients to avoid interference of the a-wave with the b-wave. Thus, one can assume that the responses obtained can be taken as measure of photoreceptor function.^{7, 8} Unfortunately, the range of intensities available with the equipment used in the present study was not large enough to allow an analysis of the entire amplitude response function of the a-wave including stimulus levels leading to a saturation of response amplitudes around 11 ms. This would have enabled the fit of Naka-Rushton functions for a more complete description of the a-wave's behaviour using the different parameters of the equation. The significant correlation of the interocular differences of the a-wave's amplitude with the interocular differences of the MD between both fellow eyes of one patient within the glaucoma group suggests that the extent of psychophysically measurable glaucomatous damage is correlated with the extent of electrophysiologically measurable damage of photoreceptor function in advanced, long standing glaucomas. The significant difference of the a-wave's amplitude between the normal and the glaucoma group implies that in advanced primary and secondary open angle glaucomas not only the retinal ganglion cell layer, but also other retinal structures, especially the photoreceptors can be involved.

There was a significant difference in age between the normal and the glaucoma group, the glaucoma patients being significantly older than the normals. This significant difference could weaken the result of the comparison of the a-wave's amplitude between the normals and glaucomas. But no significant correlation between the a-wave's amplitude and age was found in this study including normals from 33 to 65 years. Some parameters of the ganzfeld evoked electroretinogram have been appreciated to be age dependent in the literature.¹⁵ But Weleber¹⁵ did not find any significant age correlation for dark adapted cone a-wave amplitude and scotopic a-wave amplitude from mixed rod and cone responses to bright stimuli. He suggested that for patient evaluation of the a-wave's amplitude, normal ranges derived from mean and standard deviation should be used in contrast with the b-wave which shows an age dependence and therefore needs an age correction. We thus assume that the significant difference in age between normals and glaucomas in our study should not significantly influence the result of the

comparison between the normal and the glaucoma group.

In contrast with previous investigations, this study used a light intensity function following the a-wave from low intensities below the a-wave's threshold up to high intensities lying above the intensity of the ISCEV⁹ standard bright flash. Thus, the a-wave's behaviour in normals and glaucomas could be followed over a wide range of flash intensities. In this study, correlation between the interocular differences of the a-wave's amplitude and the interocular differences of the MD was significant for the four highest flash intensities measured (0.5–9.4 cd/s/m²), but not for lower luminance levels. The normal group differed significantly from the glaucoma group for flash intensities of 5.3 and 9.4 cd/s/m², but not for lower intensities. A relatively higher variability in the a-wave's amplitudes for lower intensities (see Table 2) might be the reason.

The electrophysiologically measured photoreceptor damage could be due to either loss of photoreceptors or only to functional impairment of the photoreceptors. A differentiation between these two possibilities can be made only histologically.

Histological studies revealed different results regarding the question whether glaucomas can affect the outer retinal layers including the photoreceptors or not.

Kendell and coworkers¹ did not detect a significant loss or change of photoreceptors in primary open angle glaucoma compared with a normal control group. They did not find a detectable association between photoreceptor number and severity of glaucoma, visual field, and optic nerve fibre loss. Their study group included 14 eyes with primary open angle glaucomas, classified into four groups: four eyes with normal neural area of the optic nerve, four eyes with mild damage, and three eyes each with moderate and severe damage of the neural area of the optic nerve.

Studying the photoreceptors and retinal pigment epithelial cells in human eyes with only secondary angle closure glaucoma, Panda and Jonas² found a significantly lower photoreceptor count in the glaucomatous compared with the normal eyes. Count of retinal pigment epithelial cells did not differ significantly between the two groups. Although the pathogenesis is markedly different from open angle glaucomas, barotraumatism induced changes observed in angle closure glaucomas may also occur in eyes with open angle glaucomas. Thus, findings in angle closure glaucomas could be consistent with findings in open angle glaucomas. Two possible mechanisms may lead to a photoreceptor damage or loss: (1) intraocular pressure acting directly on the receptors, (2) diminished blood supply to the photoreceptors.

A decreased choroidal thickness in eyes with secondary angle closure glaucoma was described by Kubota *et al.*¹⁶ This suggests a reduced choroidal perfusion, an observation consistent with a lack of autoregulation of the choroidal blood circulation in glaucomas as already reported.^{17–19} This reduced choroidal

perfusion with secondary photoreceptor dysfunction in long standing glaucomas could be one explanation for the ERG changes, especially changes of the a-wave as reported in this study. Glaucoma induced horizontal cell alterations in human retinas were described by Janssen *et al.*²⁰

Several electrophysiological studies have focused on the question whether outer retinal layers are affected by glaucomatous damage or not. Mehafeey *et al.*²¹ found significant electro-oculogram changes in patients with ocular hypertension and primary open angle glaucoma suggesting changes of the retinal pigment epithelium due to long standing glaucomas or long term elevations in intraocular pressure. Investigations with flash ERGs in glaucomas performed so far have led to contradictory results. The retinal responses from flash ERGs are known to originate mainly from the outer retinal layers, while the oscillatory potentials originate from the inner plexiform layer, and the scotopic b-wave from the on-bipolar cells. The a-wave of the human dark adapted electroretinogram was found to originate almost exclusively from the cones and rods.^{7 8 22}

The first major study of flash electroretinograms in glaucomas was performed by Leydhecker in 1950.³ He investigated patients with primary open angle and angle closure glaucomas and did not find any correlation between visual function and ERG responses. The technique used was a white light flash of 20 lux and 0.04 second duration after dark adaptation of the patient for 5 minutes. Francois⁴ found normal flash ERG responses in open angle glaucomas except those patients with accompanying retinal alterations such as in some secondary open angle glaucomas. Fazio *et al.*⁶ detected significant changes in a group of 14 patients with advanced primary open angle glaucomas with a normal group in several ERG parameters. In general, implicit times were longer and amplitudes were smaller in the glaucoma group (significant differences for photopic a-wave implicit time, dark adapted bright flash a-wave amplitude, and dark adapted bright flash a-wave and b-wave implicit times). Vaegan *et al.*²³ investigated flash ERG changes in patients with simple optic atrophy (anterior ischaemic optic neuropathy, trauma, and hereditary optic atrophy) and glaucomas. In patients younger than 55 years they found significant glaucomatous ERG changes such as reduction of oscillatory potentials, delayed implicit times, and reduced amplitude of the a-wave and b-wave which increased with disease severity. Compared with changes from simple optic atrophy, the glaucomatous changes were significantly larger.

Changes in the oscillatory potentials in glaucomas also were described by Gur *et al.*²⁴ A decreased scotopic b-wave was found by Korth *et al.*²⁵ indicating glaucomatous changes of the on-bipolar cells. The scotopic and photopic flash electroretinograms of the macaque after retinal ganglion cell loss from experimental glaucoma were investigated by Frishman *et al.* and Viswanathan *et al.*^{26 27} who used red flashes projected on a blue background. In scotopic

ERGs, they found a sensitive negative component to be reduced or absent in eyes with experimental glaucomas. The photopic negative responses were significantly reduced when visual sensitivity losses were mild.

The results of the present study suggest that outer retinal structures, especially the photoreceptors can be involved in glaucomatous damage.

Further studies should answer the question whether the a-wave's amplitude is correlated with the duration of the glaucoma, with the maximum intraocular pressure before treatment, and whether a relation can be found between the ERG changes and the subtype of glaucoma. These answers could contribute to the understanding of glaucomas.

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