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CLINICAL INVESTIGATION

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Neural conduction in the visual pathways in ocular hypertension and glaucoma

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Abstract ● Background: The aim of our work was to evaluate neural conduction in visual pathways in subjects with ocular hypertension and glaucoma. ● Methods: We assessed simultaneous recordings of pattern electroretinograms (PERG) and visual evoked potentials (VEP) in 16 subjects with ocular hypertension (OHT), in 16 subjects with primary open-angle glaucoma (POAG) and in 15 age-matched controls. The visual stimuli were checkerboard patterns (the check edges subtend 15 min of visual arc; contrast 70%) reversed at the rate of 2 reversals/s. ● Results: In OHT and POAG patients we found PERG and VEP latencies signficantly longer than in controls. The P50-N95 PERG amplitudes were significantly reduced in OHT and POAG eyes. VEP amplitudes were significantly reduced in POAG eyes, while in OHT they were similar to controls. The retinocortical time (RCT; difference between VEP P100 latency and PERG P50 latency) was longer in POAG patients than in controls; no differences between patients with OHT and controls were observed. Moreover, we observed that in POAG the longer RCT was inversely related to the PERG amplitude. ● Conclusion: Our results suggest that involvement of the innermost retinal layers in POAG is accompanied by slowed neural conduction in the visual pathways.

Introduction

The clinical diagnosis of glaucoma is commonly made in presence of intraocular pressure (IOP) above 21 mm Hg, characteristic optic nerve head cupping and characteristic visual field defects.

Histological studies in monkeys and humans with chronic open-angle glaucoma found a loss of retinal neurons, in particular with larger axons. This loss correlated with enlargement of the optic nerve head cup [44–46].

Retinal and optic nerve functions can be assessed by recordings of electroretinographic signals evoked by flash or patterned stimuli (flash or pattern ERG) and cortical potentials evoked by patterned stimuli (visual evoked potentials, VEPs).

Maffei and Fiorentini, after section of the optic nerve in cats and monkeys [30–32], observed a decrease in amplitude, and eventually the disappearance of the electroretinographic signal evoked by pattern stimuli, while the electroretinographic signal evoked by flash stimuli was preserved. The electrophysiological changes were related to ganglion cell degeneration [21, 53], and therefore the pattern ERG (PERG) was related to the bioelectric activity of the innermost retinal layers.

By comparing the VEP peak latency (P100) and the PERG peak latency (P50) it is possible to obtain an index of postretinal neural conduction. We call the difference between VEP P100 latency and PERG P50 latency the retinocortical time (RCT), following Celesia et al. [9, 10].

Using simultaneous recordings of PERG and VEP, an increase in latency of PERG and VEP and unchanged RCT were observed in patients with maculopathies, suggesting an increase in latency only at the retinal level [9].

Table 1 Clinical population profile

Group	N	M/F	Age (years)	VA	IOP	C/D
Controls	15	8/7	50.6±4.4	10/10	14.31±1.2	0.25±0.05
OHT	16	9/7	52.2±5.3	10/10	24.56±1.31	0.25±0.05
POAG	16	8/8	52.2±5.3	10/10	25.87±1.86	0.69±0.13

(*OHT* patients with ocular hypertension, *POAG* patients with open-angle glaucoma, *VA* best corrected Snellen visual acuity in all subjects, *IOP* intraocular pressure in mm Hg (group mean of mean of different measures in same subject), *C*/D mean cup to disc ratio; ±=1 SD of mean)

Patients with optic nerve demyelination presented normal PERG, delayed VEP and prolonged RCT, suggesting a delay in the postretinal visual pathways [10].

Several studies performed in cats, monkeys and humans with ocular hypertension or glaucoma showed a normal flash-ERG [8, 15, 17, 19, 20, 29, 34, 40, 48, 54], reduced PERG [1, 3, 16, 18, 27, 28, 33–36, 39, 41, 48, 55–58] and delayed VEP [2, 3–7, 24, 33, 37, 49, 52].

In the light of these results the aim of our work was to evaluate with an objective test:

1. The bioelectrical retinal activity in normal subjects and in OHT and POAG patients
2. The neural conduction between retina and visual cortex in OHT and POAG patients

Our goal was to assess whether a correlation exists between the involvement of retinal layers caused by ocular hypertension and neural conduction in postretinal visual pathways.

Materials and methods

Simultaneous recordings of PERG and VEP were carried out on 47 subjects: 15 control subjects (C) with normal IOP (15 eyes), 16 patients with ocular hypertension (OHT; 16 eyes), and 16 patients with primary open-angle glaucoma (POAG; 16 eyes). Informed consent was received from all patients involved in the study.

The control subjects had IOP <21 mm Hg, normal visual acuity, normal visual field (Goldmann and Humphrey 24-2 perimetry), and no ocular or neurologic problems. Their mean age (±SD) was 50.6±4.4 years. They were age-matched to the OHT and POAG patients.

The OHT patients had IOP >21 mm Hg, no optic nerve head cupping at the ophthalmoscopic examination (cup/disc ratios <0.3) and normal visual field. The mean age was 52.2±5.3 years.

The POAG patients had IOP >21 mm Hg, characteristic optic nerve head cupping (cup/disc ratio >0.5) and characteristic visual field defects. The mean age was 52.1±4.7 years.

Since the relative amplitude of visual field loss influences the PERG response in glaucoma patients [36, 56, 58], only POAG patients with typical arcuate visual field loss which did not involve the area tested by the visual stimuli (see below) took part in our study. The POAG patients were on pharmacological treatment with beta-blockers only; miotic or mydriatic drugs were never used.

The observed characteristics of all subjects are reported in Table 1.

The subjects under examination were seated in a semi-dark room acoustically isolated in front of the display that was surrounded by a uniform field of luminance of 5 cd/m^2. The subjects were informed of the type of examination of its diagnostic uses.

Prior to the experiment, each subject was adapted to the ambient room light for 10 min and the pupil diameter was about 5 mm.

VEP and PERG were recorded using the following method. The visual stimuli were checkerboard patterns (contrast 70% [50], mean luminance 110 cd/m^2) generated on a TV monitor and reversed in contrast at the rate of 2 reversals/s. At the viewing distance of 114 cm the check edges subtended 15′ of visual angle and the screen of the monitor subtended 12.5°. The refraction of all subjects was corrected for the viewing distance.

It is known that VEP response is initiated by retinal neurons lying within 2° of the fovea, while the PERG is obtained from a larger retinal area. In accordance with several studies, we used 15′ of visual angle because this smaller size is considered "optimal to stimulate the fovea" also in pattern electroretinography [11, 51].

The stimulation was monocular, the other eye being occluded.

PERG recordings

The bioelectrical signal was recorded by means of platinum hook electrodes inserted into the external corner of the inferior eyelid. Electroretinograms were derived bipolarly between the tested (active electrode) and the patched (reference electrode) eye using the method described by Fiorentini et al. [16]. Local anesthesia was provided by application of novesine 0.4%. The ground electrode was on the left arm. The interelectrode resistance was kept below 3 kΩ. The signal was amplified (gain 50000), filtered (band pass 1–30 Hz) and averaged with automatic rejection of artifacts (200 events free from artifacts were averaged for every trial) using BM 6000 equipment (Biomedica Mangoni, Pisa, Italy). The analysis time was 250 ms.

The transient PERG response is characterized by a number of waves with three consecutive peaks of negative, positive and negative polarity, respectively. In normal subjects and in the conditions of our experiment, these peaks have the following mean latencies: 35, 50 and 95 ms.

VEP recordings

Cup-shaped of silver–silver chloride electrodes were fixed with collodion in the following in the following positions: active electrode at Oz, reference electrode at Fpz, ground on left arm.

The interelectrode resistance was kept below 3 kΩ. The bioelectric signal was amplified (gain 20000), filtered (band-pass 1–100 Hz) and averaged (200 events free from artifacts were averaged for every trial) using BM 6000 equipment. The analysis time was 250 ms.

The transient VEP response is characterized by a number of waves with three subsequent peaks of negative, positive and negative polarity, respectively. In normal subjects and in the conditions of our experiment, these peaks have the following mean latencies: 75, 100 and 145 ms.

In the recording session, simultaneous PERG and VEP were recorded at least twice and the resulting waveforms were superimposed to check the repeatability of the results.

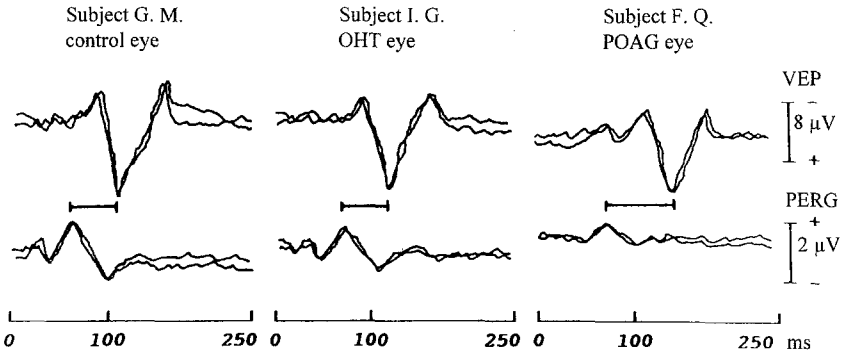

Fig. 1 Layout of simultaneous recordings of VEP and PERG of subjects G.M. (control eye), I.G. (OHT eye) and F.Q. (POAG eye). OHT and POAG eyes showed VEP P100 latency and PERG P50 latency longer than control eye. PERG and VEP amplitudes were reduced in POAG eyes. Retinocortical time (difference time between VEP P100 latency and PERG P50 latency, ⊢—⊣) in POAG eyes was longer than in control eyes, while in OHT eyes it was similar to control eyes

We accepted PERG and VEP signals with signals-to-noise ratio >2. The noise was measured by recording the bioelectrical signals while a card was held in front of the monitor, and noise below 0.1 μV (mean 0.085 μV) was observed in all subjects tested.

For all PERG and VEP the peak latency and the peak amplitude of each of the waves were measured directly on the displayed records by means of a pair of cursors.

Results

In the analysis of PERG records we evaluated the P50 latency and the P50-N95 amplitude. In the analysis of VEP records we evaluated the P100 latency, the temporal difference N75/N145 and the N75-P100 amplitude. The differences between the control, OHT, and POAG eyes were statistically evaluated with one-way analysis of variance for repeated measures. Examples of simultaneous PERG and VEP recordings from a normal subject, OHT and POAG patients are shown in Fig. 1.

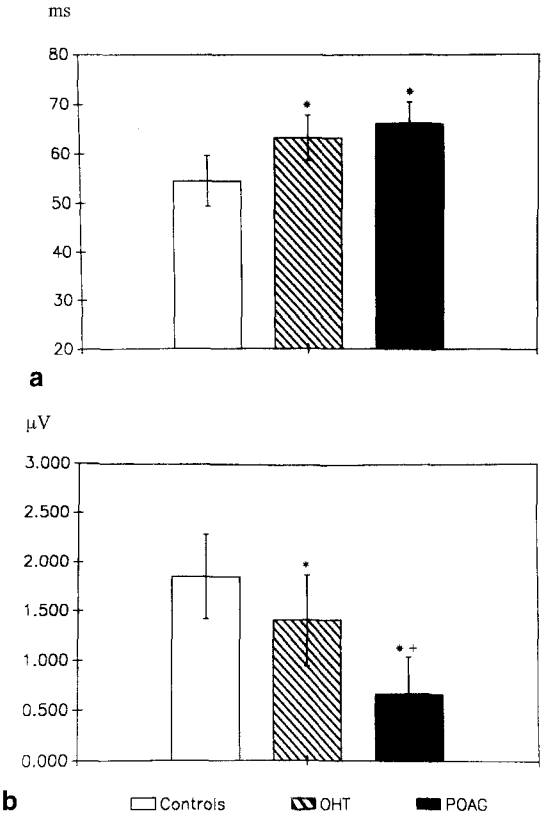

Fig. 2 Bar charts of mean values of PERG parameters. **a** P50 latency. **b** P50–N95 amplitude). The *vertical lines* represent one (±) standard deviation. * $P<0.01$ vs controls; + $P<0.01$ vs OHT

PERG recordings

The mean data are presented in Fig. 2.

In the control eye the parameters of PERGs (P50 latency and P50–N95 amplitude) were within the following limits observed in our normal subjects [38]: mean value ± 1SD for P50–N95 amplitude, and mean value ± 3SD from P50 latency. No difference was found between control eyes and our normal subjects.

P50 latency was significantly higher in OHT and POAG eyes than in the control eyes (OHT vs C: $F_{1,29}=25.22$, $P<0.01$; POAG vs C: $F_{1,29}=48.43$, $P<0.01$) and was similar in POAG and OHT eyes ($F_{1,30}=3.66$, $P=0.065$).

The P50–N95 amplitude was significantly lower in OHT and POAG eyes than in control eyes (OHT vs C: $F_{1,29}=7.63$, $P=0.01$; POAG vs C: $F_{1,29}=67.34$, $P<0.01$) and was lower in POAG than OHT eyes $F_{1,30}=25.14$, $P<0.01$).

VEP recordings

The mean data are presented in Fig. 3.

In the control eyes the parameters of VEPs (P100 latency, time difference N75/N145, N75–P100 ampli-

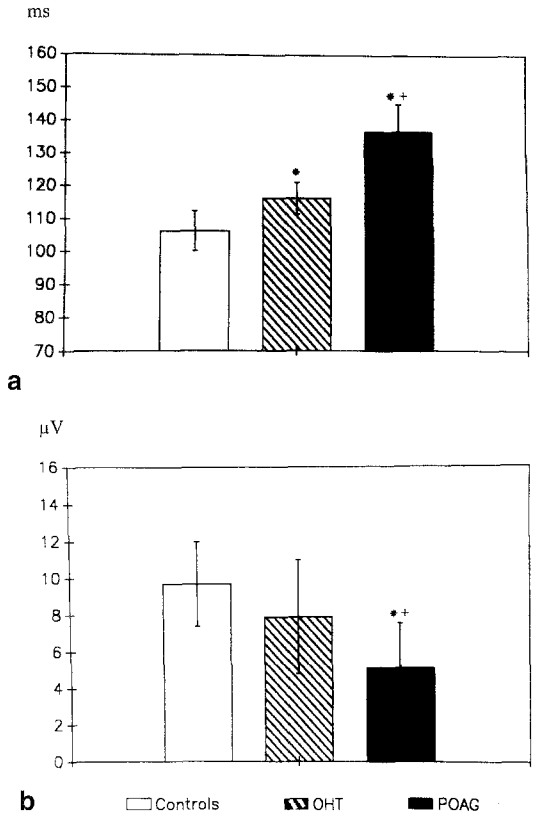

Fig. 3 Bar charts of mean values of VEP parameters. **a** P100 latency. **b** N75–P100 amplitude). The *vertical lines* represent one (±) standard deviation. * $P<0.01$ vs controls; + $P<0.01$ vs OHT

tude) were within the following limits observed in our normal subjects [38]: mean value ± 1SD for N75–P100 amplitude, mean value ±3SD for P100 latency and for time difference N75/N145. No difference was found between control eyes and our normal subjects.

P100 latency was significantly higher in OHT and POAG eyes than in control eyes (OHT vs C: $F_{1,29}=26.9$, $P<0.01$; POAG vs C: $F_{1,29}=135.38$, $P<0.01$) and was significantly higher in POAG than OHT eyes ($F_{1,30}=73.02$, $P<0.01$).

The N75–P100 amplitudes of the OHT patients were comparable to the controls ($F_{1,29}=3.37$, $P=0.07$); the POAG eyes showed reduction in amplitude compared to the control and OHT eyes (POAG vs C: $F_{1,29}=28.83$, $P<0.01$; POAG vs OHT: $F_{1,30}=7.99$, $P<0.01$).

The time difference N75/145 was similar in the three groups.

Retinocortical time

The mean data are presented in Fig. 4.

In the control eyes the RCT was within the following limits observed in our normal subjects [38]: mean values ± SD. No difference was found between control eyes and our normal subjects.

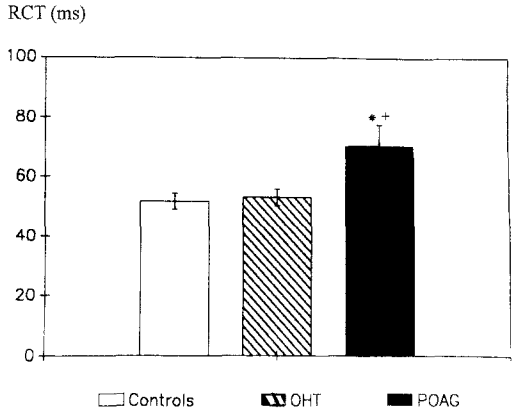

Fig. 4 Bar charts of mean values of retinocortial time. The *vertical lines* represent one (±) standard deviation.* $P<0.01$ vs controls; + $P<0.01$ vs OHT

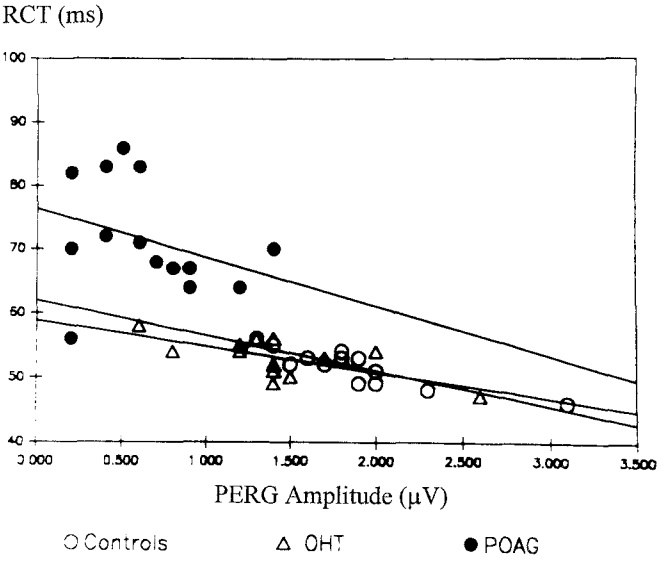

Fig. 5 Retinocortical time plotted against P50–N95 PERG amplitude in controls and in OHT and POAG patients. Least-squares regression analysis: see Table 2

RCT was significantly higher in POAG eyes than in control and OHT eyes (POAG vs C: $F_{1,29}=90.4$, $P<0.01$; POAG vs OHT: $F_{1,30}=82.24$, $P<0.01$); no difference was found between OHT and control eyes ($F_{1,29}=1.76$, $P=0.195$).

We observed that RCT was inversely related to the PERG amplitude (Fig. 5); we found no correlation between P50 latency and RCT. Regression analysis is reported in Table 2.

Table 2 Regression analyses and correlation

Statistics	Group	*n*	*r*	*t*	*P*
P50–N95 amplitude vs RCT	Controls	15	−0.851	5.846	0.000
	OHT	16	−0.665	3.333	0.005
	POAG	16	−0.798	4.961	0.000
P50 latency vs RCT	Control	15	−0.093	0.336	0.742
	OHT	16	−0.346	1.378	0.190
	POAG	16	−0.007	0.027	0.979

Discussion

In agreement with the results of previous studies [36, 39, 41, 57], we found a modified electroretinographic response evoked by patterned stimuli in OHT patients.

Since it is known that the PERG reflects the bioelectric activity of the innermost retinal layers, our results suggest that the IOP elevation produces a functional early involvement of the innermost retinal layers. That electrophysiological alterations are present in OHT patients (without characteristic optic nerve head cupping and characteristic visual field defects), suggests that the functional impairment may precede the enlargement of the optic nerve head cup and the defects of the visual field.

Our POAG patients showed impaired PERG (delayed latencies and reduced amplitudes), in agreement with previous electrophysiological studies [1, 3, 16, 27, 33, 35, 41, 56, 58].

POAG patients presented an enlargement of the optic disc cup (mean ratio cup/disc 0.69) ascribed to a loss of ganglion cells and their fibers [44, 47]. The loss of ganglion cells is directly related to the reduction in amplitude of the PERG signals, as has been observed experimentally with monkeys in which monocular glaucoma was induced by laser photocoagulation of the trabecular meshwork [26].

Although the pattern electroretinogram originates in the ganglion cell layer, the preganglionic retinal elements of the central retina could not be excluded with their contribution to the impaired PERG response. In fact, Falsini et al. [14] using focal ERG, which represents a more sensitive way of testing, layer by layer, the function of the central retina [42, 43], observed, in patients with glaucoma, damage of the outer retinal layers and even of the photoreceptors secondary to the pressure damage. This damage has also been shown by a reduction in amplitude of 30-Hz flicker VEP [22, 23] and delayed recovery of VEP after photostress [37].

Our data show that POAG patients display delayed VEP peak latencies and longer RCT, while OHT patients display delayed VEP peak latencies but unchanged RCT.

It is unlikely that RCT (expressed as the difference between the VEP P100 latency and the PERG P50 latency) represents the real transit time of neural conduction between retina and visual cortex; we do not believe that the bioelectrical signal takes 50 ms to travel from retina to visual cortex in normal subjects.

Marx et al. [35] suggest assessing neural conduction in the postretinal visual pathways by the evaluation of the time difference between the positive latency of the PERG (P50) and the first negative component of the VEP (N75). They termed this measure, which is much shorter than the RCT of Celesia et al. [9, 10], the "latency window".

Nonetheless, the data observed in patients with maculopathies and optic nerve demyelination [9, 10] suggest that RCT could be considered an index of neural conduction in the postretinal visual pathways.

The longer RCT and the delayed VEP peak latencies observed in POAG patients could be ascribed to impaired neural condition in the optic nerve and in whole postretinal visual pathways as a consequence of the dysfunction of the innermost retinal layers. This derives from the correlation between the longer RCT and the reduction in amplitude of PERG.

Our data might appear in contrast with those of Marx et al. [35]. They found no statistical difference between the control and "early glaucoma" groups, evaluating the latency window; nonetheless, 15/26 patient eyes presented an abnormal latency window. In addition Marx et al. [35] included patients with early glaucoma in their study, while in our study the POAG patients cannot be classified as "early glaucoma" because of the optic nerve head cupping (cup/disc ratio >0.5) and the visual field defects.

Available data on the effects of glaucoma at the level of the dorsal lateral geniculate nucleus (dLGN) may offer an explanation for the electrophysiological abnormalities we found. A histological study in experimental glaucoma by Dandona et al. [13] showed reduced axonal transport to the LGN in monkeys with chronic IOP elevation and damage, particularly regarding the magnocellular layers of the LGN. In addition, Chaturvedi et al. [12] on autopsy section of the LGN of five patients with a documented history of glaucoma, observed a significant loss of magnocellular tissue compared to controls, while there was no statistical difference in the parvocellular layer.

The histological changes at the dLGN level could be a cause of functional changes in those cells which produce the visual evoked response; this is likely to be related both to the increase in RCT and to the delayed VEP observed in POAG patients.

In OHT and POAG patients, the VEP recorded showed P100 latency longer than in controls; the amplitudes were reduced in POAG patients but not in OHT patients. These electrophysiological changes were previously attributed to selective reduced functionality of the inner retinal layers [2–7, 24, 33, 36, 37, 49, 52].

Our results suggest that the impaired VEP observed in the POAG patients could be ascribed both to reduced

functionality of the inner retinal layers (delayed PERG) and to slowed neural conduction in the visual pathways (delayed RCT), while in OHT patients the delayed VEP could be attributed to functional impairment of the retinal layers only (delayed PERG with unchanged RCT).

In conclusion, our results suggest that in POAG patients retinal involvement is accompanied by slowed neural conduction in the postretinal visual pathways.

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