Oscillatory Potentials in Diabetic Retina without Retinopathy

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Abstract

***Purpose*:** To study recordings of oscillatory potentials (OPs) of the electroretinogram (ERG) in diabetic eyes that have no visible fundus alterations, to ascertain whether changes in sensitivity are evident when compared with recordings from age-matched controls.

***Methods*:** OPs of the ERG were measured from 68 eyes of 34 patients with diabetes without retinopathy and from 30 eyes of 15 normal subjects.

***Results*:** A reduction in the amplitude of each oscillatory potential, as well as delayed implicit time of each oscillatory potential peak could be found in diabetic patients without retinopathy although not all significant. Decrease in the amplitude of OP1 and summed OP (OP-sum) and also delayed the implicit time of OP1 were seen between diabetic patients with no observable diabetic retinopathy.

***Conclusion*:** Patients with diabetes without retinopathy show prolonged latencies in OPs recordings and decreased in amplitudes of OP-1 and OP-sum. This indicates an alteration in inner retinal sensitivity or ischemic change of overall retinal layer that can be explained by an impaired rod-cone interaction.

***Keywords*:** oscillatory potential, electroretinogram, diabetic retinopathy

***Iranian Journal of Ophthalmology** 2008;20(1):20-24*

Introduction

The electroretinogram (ERG) has been used for decades to uncover the mechanisms of retinal physiology and their alterations in disease. Electroretinographic oscillatory potentials (OPs) are high frequency oscillatory components superimposed on the b-wave of the flash ERG and are thought to reflect inner retinal activity.[1–4] In patients with diabetes mellitus, an alteration of OP amplitude has been most commonly reported, even in the absence of retinal vascular changes[5–8] and a reduction in amplitude has been proposed to predict the development of proliferative retinopathy.[9–12] In addition, there are also reports of prolonged latencies in some of the OPs before the reduction in amplitude.[7,8,12–14]

OPs in addition to being as sensitive indicators of disease in diabetic retinopathy[9] and, as such, have now been studied in a variety of diseases such as glaucoma, [15-17] vascular occlusions[18–20], and congenital eye diseases.[21]

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Received: April 28, 2007
Accepted: August 27, 2007

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It has been proposed that recording OPs may serve as a prognostic test in diabetic retinopathy. However, it has not been clarified whether this electrofunctional parameter can also be used to predict the onset of early stages of diabetic retinopathy in patients who initially present with normal fundi. So, in this study we investigated the role of electroretinographic OPs in predicting the onset of non-proliferative diabetic retinopathy.

Materials and Methods

Patient selection

Thirty four patients (19 males and 15 females) were recruited for the study from a wider group of diabetic patients. The inclusion criteria were: confirmed diabetes with more than 5 years duration; absence of cardiovascular, neurological or concurrent ocular diseases and normal fundi at fluorescein angiography. An informed consent was obtained from each patient and the study was approved by the Medical Ethics Committee of Tehran University of Medical Sciences. Patients underwent a complete ophthalmological examination, involving best corrected distance visual acuity (VA), slit-lamp observation, direct and indirect ophthalmoscopy using a three-mirror contact lens, and scotopic electroretinographic registration including OPs. On clinical examination all patients had normal fundi. The control group consisted of 15 age matched healthy volunteers.

Methods

Stimulus-generating apparatus and ERG recording protocols were established according to International Society for Clinical Electrophysiology of Vision (ISCEV). Conventional a- and b-waves were evoked prior to OP recording with a Ganzfeld. The scotopic ERG was recorded after 30min of dark adaptation and the photopic ERG after 5min of adaptation to a steady white light of 800lux. The stimulus used was a white flash of 1.33 cd/s/m^2, at 0.1 flash/sec for rod-dominated responses, and 30 Hz flicker and 1flash/sec for cone-dominated responses. Steady background illumination was not used during the scotopic ERG recording. Sets of neutral filters (Kodak Wratten, neutral density at -3.0–0.0 Ulog) were used to reduce the intensity of the stimulus. The band pass filter was set at 1–100Hz and a fixed 5000 x gain conventional amplification was applied.

Photopic OPs were recorded according to the methods normally used in our laboratory. A stimulus flash of 2.6 cd/s/m^2 at 3 Hz frequency was delivered with a Ganzfeld immediately after a complete light adaptation of 5min. No adapting background illumination was used during OP recording. The band pass filter was set at 1–1000 Hz and the amplification at 10000 x gain. A personal computer was used for acquisition, recording and processing of data. The digital filter was set at 70–160 Hz: the amplitudes of the first four wavelets were measured from peak to peak and then combined to obtain 'summed OP amplitudes'. The acquisition system rejected the first response. We used the first three nodes, denoted OP-1, OP-2, and OP-3, and the individual three nodes were also summed, OP-sum.

The cornea was anaesthetized with tetracaine eye drop. A Henkes' corneal contact lens was used as the active monopolar electrode, while skin electrodes on the forehead served as reference electrodes. Pupils were maximally dilated (5mm) with tropicamide.

Statistical analysis

Data were expressed as mean values±SD. The Student's test was used to compare data between groups, The Pearson (R) correlation test was calculated to determine whether there were significant relationships between variables. The data were analyzed using SPSS version 13, and a p value < 0.05 was established for significance.

Results

Through March 2003 to December 2006, 34 diabetic patients with normal fundi and mean age of 54.62±10.8 years (range 7-38) were included in the study. The duration of disease and the age of patients at disease onset were 7.8±2.4 and 36±7 years, respectively. Table1 summarizes the demographic and ERG data of diabetic patients and normal subjects. Three of the parameters under consideration differed significantly between the groups: first; OP_1 implicit time in diabetic patients was significantly higher in patients compared to controls (p =0.02).

Table1: The demographic and ERG data of diabetic patients and normal subjects.

	Diabetic patients (No=34)	Normal controls (No=15)	p value
Age (years)	54.6±10.8	48.8±11.8	> 0.05
Gender (M:F)	15:19	10:5	0.146
Duration of diabetes (years)	7.8±2.4		
OP_1 amp (μV)	13.22±6.67	23±12.12	0.05
OP_2 amp (μV)	18.84±10.19	23.51±6.9	0.410
OP_3 amp (μV)	9.77±7.01	15.20±0.00	0.506
OP_1 it (msec)	33.30±2.93	29.61±2.63	0.02
OP_2 it (msec)	39.38±4.43	36.46±3.35	0.251
OP_3 it (msec)	45.00±5.20	44.00±0.00	0.860
OP-sum(msec)	28.98±17.26	64.90±22.81	0.000

amp: amplitude, it: implicit time

Second; in patients group OP_1 amplitude was lower in patients than controls with near to significant level (p=0.050). There were no significant difference between OP_2 (p=0.410) and OP_3 amplitudes (p=0.506) in diabetic patients and controls. Third; the OP-sum amplitudes were significantly low compared to controls (p<0.000). In other factors, the differences between two groups were not significant (Table 1).

Discussion

The OPs are four to six wavelets in the ERG that are present on the rising phase of the b-wave.[22] Which specific cells in the retina are responsible for the OPs is still being debated. It has been suggested that OPs are generated by the amacrine cells, because their retinal depth is shown to be similar to that of the amacrine cells[4] and pharmacologic studies[23] showing that dopamine[4], γ-aminobutyric acid (GABA), and glycine blockers[24] all diminish the OPs.

Clinical examinations often focus on the visualization of retinal lesions in diabetic patients, however electrophysiologic changes have been shown to occur before the onset of clinically evident retinopathy.[14, 25–27] Thus, an electrophysiological assessment of retinal function could be an extremely valuable monitoring metric for retinal health in diabetic patients. A reduction in the a-wave amplitude has been demonstrated in patients with type 1 diabetes without clinical indices of retinopathy.[25,28–30] Delays in the a-wave implicit times have also been reported in diabetic patients compared with control subjects.[31] However, the most consistently reported index of disease in diabetes is the OP. It has been repeatedly reported that the OPs have reduced amplitudes in diabetes.[11,12,25] Abnormalities in the OPs are of great interest in the assessment of diabetic retinopathy, because OP abnormalities have been shown to predict onset as well as progression of diabetic retinopathy,[11,26] but which abnormalities in the OP are predictive, is not clear. It has been independently reported that the peaks of OPs are reduced in amplitude[8,12,26,27] and delayed.[14,31]

Description of these changes could help our understanding of the pathophysiology of diabetic retinopathy (DR) as well as provide the foundation for the design of new screening tests for diabetic patients. Sakai et al.[27] previously reported that OPs become delayed soon after the onset of elevated blood sugar in an animal model of diabetes and before the onset of vitreous fluorophotometric changes. In our work, we found that OP_1 are delayed compared to other parameters. Numerous studies point to the OPs as the most sensitive

electrophysiologic indicator of DR.[12,14,25,26,32] Holopigian et al.[8] reported that the b-wave is as sensitive an indicator of DR as the OPs. In a study on rats Hancock and Kraft[33] reported that the b-wave implicit time was unchanged, but the b-wave amplitude was significantly reduced in diabetic animals. The reduction in the sensitivity and amplitude of the b-wave could, by themselves, account for the appearance of the delay in the a-wave, because these two components of the ERG have opposite electrical signs.[33] The reductions of the a- and b-wave amplitudes may, in part, be due to an aging effect. A similar effect has been previously observed in mouse[34] and human ERGs.[35,36] Typical clinical ERG recordings measure the OP with a series of four bright white flashes presented at 15-second intervals; the first response is discarded.[37] We used a similar paradigm, but extended the stimulus to 20 flashes to observe the stability of the OP kinetics.

It has been repeatedly reported that OPs are delayed and reduced in amplitude in diabetes. In the current study, we showed that the implicit time of the OP_1 was involved significantly but amplitude of the OP_1 involved not significantly. OP-sum was significantly lower in patients group compared to normal controls. Summed amplitudes of OPs are reduced with age[38] and duration of diabetes.[10,38] A reduction in the amplitude of each oscillatory potential, as well as delayed implicit time of each oscillatory potential peak could be found in diabetic patients without retinopathy although not significant. However, the timing of the OPs is dependent on the stimulus intensity and future studies of OPs should consider this relationship. If a delay in the OP timing is suspected, it is important that the stimulus intensity be considered, because a false appearance of a delay could be given by a lesser light intensity stimulus, resulting in a smaller amplitude OP. For example, the presence of nonretinal disease, such as a cataract or corneal lesion, would reduce retinal illumination and produce a smaller OP having a slower time course. In such a situation, a slower OP would be due to decreased photon count at the retina and not to a change in retinal function.

Conclusion

In summary, patients with diabetes without retinopathy show prolonged latencies in OP_1 recordings. This indicates an alteration in inner retinal sensitivity that can be explained by an impaired rod-cone interaction. Subnormal OP amplitudes are not proof of real concomitant visible vascular damage, but may reflect a predisposition to functional disorder. A study with follow up of patients who have decreased OP amplitude is suggested in diabetic patients without DR, because eyes with reduced OP amplitude have a greater probability of developing DR.

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