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ET-1 plasma levels, choroidal thickness and multifocal electroretinogram in retinitis pigmentosa

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ABSTRACT

Aim: To assess the relationship between both photoreceptor function and choroidal thickness and endothelin-1 (ET-1) plasma levels in patients with early stage retinitis pigmentosa (RP).

Main methods: We compared 24 RP patients (14 males and 10 females), 25 to 42 years of age (mean age: 34 ± 7 years) with 24 healthy controls (12 males and 12 females) aged between 28 and 45 years (mean 36 ± 6.8 years). All patients underwent visual field test, electroretinogram and multifocal-electroretinogram and choroidal thickness measurement by using spectral domain optical coherence tomography.

Key findings: RP patients had a visual acuity of 0.95, a mean defect of the visual field of −7.90 ± 1.75 dB, a pattern standard deviation index of 6.09 ± 4.22 dB and a b-wave ERG amplitude of 45.08 ± 8.24 μV. Notably RP subjects showed significantly increased ET-1 plasma levels and reduced choroidal thickness compared with controls: respectively, 2.143 ± 0.258 pg/ml vs. 1.219 ± 0.236 pg/ml; $p < 0.002$ and 226.75 ± 76.37 μm vs. 303.9 ± 39.87 μm; $p < 0.03$. Spearman's correlation test highlighted that the increase of ET-1 plasma levels was related with the decrease of choroidal thickness ($r = -0.702$; $p < 0.023$) and the increase of implicit time in both ring 2 ($r = -0.669$; $p < 0.034$) and ring 3 ($r = -0.883$; $p < 0.007$) of mfERG.

Significance: Increased ET-1 plasma levels may play a key role in the impairment of retinal and choroidal blood flow due to the vasoconstriction induced by ET-1. This could lead to worsening of the abiotrophic process of the macular photoreceptors.

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Introduction

Endothelin-1 (ET-1), the most potent and long-acting vasoconstrictor of small and large vessels (Masaki et al., 1991) was first isolated from the culture supernatant of porcine aorta endothelium cells in 1988 (Yanagisawa et al., 1988). It is mainly synthesized and released by endothelial cells of the arterial, venous and lymphatic vessels and is able to modulate the secretion of renin, vasopressin and aldosterone which play an important role in the regulation of vascular tone (Simonson and Dunn, 1990). ET-1 binding sites have been identified in many ocular tissues, such as iris, ciliary processes and both choroidal vasculature and retinal vasculature (MacCumber et al., 1991).

ET-1 system plays a key role in both normal and pathological processes which may also involve the eye; indeed several studies have found increased ET-1 plasma levels in some ocular diseases such as glaucoma (Sigiyama et al., 1997), thanks to its ability to reduce both ocular blood flow and retinal blood flow, leading to ischemic damage to optic nerve head and retinal ganglion cells (Polak et al., 2003), and retinitis pigmentosa (RP) (Cellini et al., 2002).

RP is an inherited, degenerative retinal disorder characterized by bone spicule-shaped pigment deposits in the retina, attenuated retinal blood vessels and a pale, waxy optic nerve head with degeneration, atrophy and finally loss of photoreceptors and retinal pigment epithelium (RPE), leading to progressive visual impairment (Li et al., 1995). Furthermore visual field contraction and abnormalities in the electroretinographic recording are characteristic features of the disease (Heckenlively et al., 1988). Recently, a reduced choroidal thickness in RP patients has been demonstrated by using spectral-domain optical coherence tomography (SD-OCT) (Dhoot et al., 2013), whereas hemodynamic studies have shown the relationship between the increase of ET-1 plasma levels and the decrease of both retinal blood flow and choroidal blood flow not only in the advanced RP stages but also in the early stages (Cellini et al., 2010) even before the appearance of any ophthalmoscopic signs.

The purpose of this study was to assess the choroidal thickness and the photoreceptor dysfunction of early RP patients in order to search for a possible correlation with ET-1 plasma levels.

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Materials and methods

Patients

A total of 24 patients (14 males and 10 females), aged 25 and 42 years (mean 34 ± 7 years), who were affected by early stage RP were enrolled and compared with 24 age- and sex-matched healthy controls (12 males and 12 females), aged between 28 and 45 years (mean 36 ± 7 years). The tenets of the Declaration of Helsinki were followed and, after a full explanation of the aim of the study and of the procedures, all the participants signed written informed consent. This study was reviewed and approved by the Institutional Ethics Committee of the S. Orsola-Malpighi Hospital.

Clinical examination

RP diagnosis is usually based on detection of abnormalities of the visual field, attenuation of the electroretinogram, and a pale optic nerve head with narrowed retinal blood vessels and accumulation of bone spicule-shaped pigment deposits in the peripheral retina at the ophthalmoscopy. We included young RP patients with preserved visual function and excluded those who had systemic diseases, were taking any medications or who had advanced posterior subcapsular cataract and macular cystoid edema.

The diagnostic criteria for the early stage of RP are those described by Hamel (2006): night blindness, peripheral visual field defects, normal or subnormal visual acuity, color vision and life habits, modest attenuation of retinal arterioles, normal or fainly pale optic disk, absent or rare peripheral bone spicule-shaped pigment deposits and a decrease in maximum ERG amplitude. All participants underwent a complete ophthalmological evaluation, including visual acuity, Goldmann applanation tonometry and slit lamp examination of anterior and posterior segment. Visual field test, standard ERG (ERG), multifocal ERG (mfERG) and choroidal thickness measurement were also performed.

Visual field test

Visual field test was performed by using standard automated perimetry (SAP) with the Humphrey 740 field analyzer 30.2 full threshold program (Humphrey Instruments Inc., San Leandro, CA, U.S.A.). Calculation of mean defect (MD) and pattern standard deviation (PSD) for each 30.2 visual field were obtained using Humphrey STATPAC software.

Electroretinogram stimulus and recording

Electroretinogram was recorded using Retimax Plus (CSO, Florence, Italy). After pupil dilation with 1% tropicamide and topical anesthesia of the cornea with 0.4% oxybuprocaine hydrochloride, HK-Loop ERG electrodes, a ground electrode and the reference electrodes were applied, respectively to the ocular surface, to the forehead and to the temporal region. Electrical impedance was smaller than 5 kω for all electrodes. ERGs were recorded from both eyes simultaneously, according to International Society for Clinical Electrophysiology of Vision (ISCEV) standards (Marmor et al., 2009), by using a standard flash strength of 2.5 $cd \cdot s \cdot m^{-2}$. Band-pass filter was between 0.3 Hz and 300 Hz with an amplification of 5 *k* while artifactual signals were automatically removed. The amplitude of b-wave was measured from the baseline and was expressed in microvolts (μV).

MfERG stimulus and recording

Multifocal electroretinogram was performed using Retimax Plus (CSO, Florence, Italy). The arrangement of the electrodes was the same we used to perform ERG. MfERG was recorded monocularly using a 61-hexagon stimulus according to the ISCEV guidelines (Hood et al., 2012), with a 21-inch video stimulating display (CRT monitor, 75-Hz frame rate, cutoffs: 10–100 Hz) subtending 30° on either side of fixation. The room light was on during stimulation and the screen–patient distance was 28 cm. The radius of the central hexagon was 2° and a red central-fixation cross 2 mm in diameter was used. During stimulation, each element was either black or white (93% contrast) and the mean luminance was 51.8 $cd \cdot m^{-2}$. The mean responses, assessed by the analysis of five concentric stimulus rings, were passed through a band-pass filter at between 10 Hz and 300 Hz.

The amplitude of P1 wave of each ring was expressed in microvolts (μV) and the implicit time in milliseconds (ms) (Fig. 1).

SD-OCT image acquisition and analysis

SD-OCT is a noninvasive, widespread technique that allows in vivo cross-sectional high resolution visualization of retinal structures and choroid with a fast scanning speed (Ruggeri et al., 2007). However, to enhance the quality of the images and to provide many details of the architecture of the choroid, a new technique called enhanced depth imaging (EDI) has been developed in the recent years and described elsewhere (Spaide et al., 2008). We selected the horizontal scan running directly through the center of the fovea of both eyes of each patient by using spectral-domain optical coherence tomography (Heidelberg Engineering GmbH, Heidelberg, Germany) with the EDI technique. Choroidal thickness was measured manually and was defined as the vertical distance from the hyperreflective line of the retinal pigment epithelium–Bruch's membrane complex to the innermost hyperreflective line of the choroidal scleral interface, exactly below the foveola. The values were expressed in micrometers (μm) (Fig. 1).

Endothelin-1 determination

For ET-1 measurements the plasma samples were drawn from the antecubital vein and collected in a container with EDTA, cooled and stored in ice. Subsequently, the samples were centrifuged at 4 °C and frozen at −25 °C. After centrifugation the extraction was performed using a Sep-column containing C-18 (Peninsula Laboratories, Belmont, CA, USA) and ET-1 concentration was determined by using a commercial radioimmunoassay (RIA) kit (Peninsula Laboratories, Belmont, CA, USA), after that samples and standards were firstly incubated with rabbit anti-ET-1 serum for 24 h at 4 °C. A second 24 h incubation was performed after the addition of an iodinated tracer [^{125}I]-ET-1. Free and bound radioligands were separated with centrifugation and radioactivity in the precipitate was counted with an automatic gamma-counter. ET-1 concentration was expressed in picogram/milliliter (pg/ml).

Statistical analysis

All data were expressed as the mean ± standard deviation (SD). The statistical analysis was performed with MedCalc 10.9.1 statistical program (MedCalc Software, Ostend, Belgium), to assess the differences between RP patients and controls by using the Wilcoxon rank-sum test. Spearman's correlation test was used to evaluate the relationship between abnormalities in both P1 amplitude and implicit time and choroidal thickness and the association between ET-1 plasma levels and both choroidal thickness and mfERG parameters. *p* values less than 0.05 were regarded as being statistically significant.

Results

Best corrected visual acuity and intraocular pressure did not differ significantly between RP patients and controls, whereas there was a significant difference with regard to MD ($p < 0.006$), PSD ($p < 0.001$) and both b-wave amplitude and a-wave ERG amplitude ($p < 0.002$ and $p < 0.019$, respectively). Furthermore RP patients showed significantly

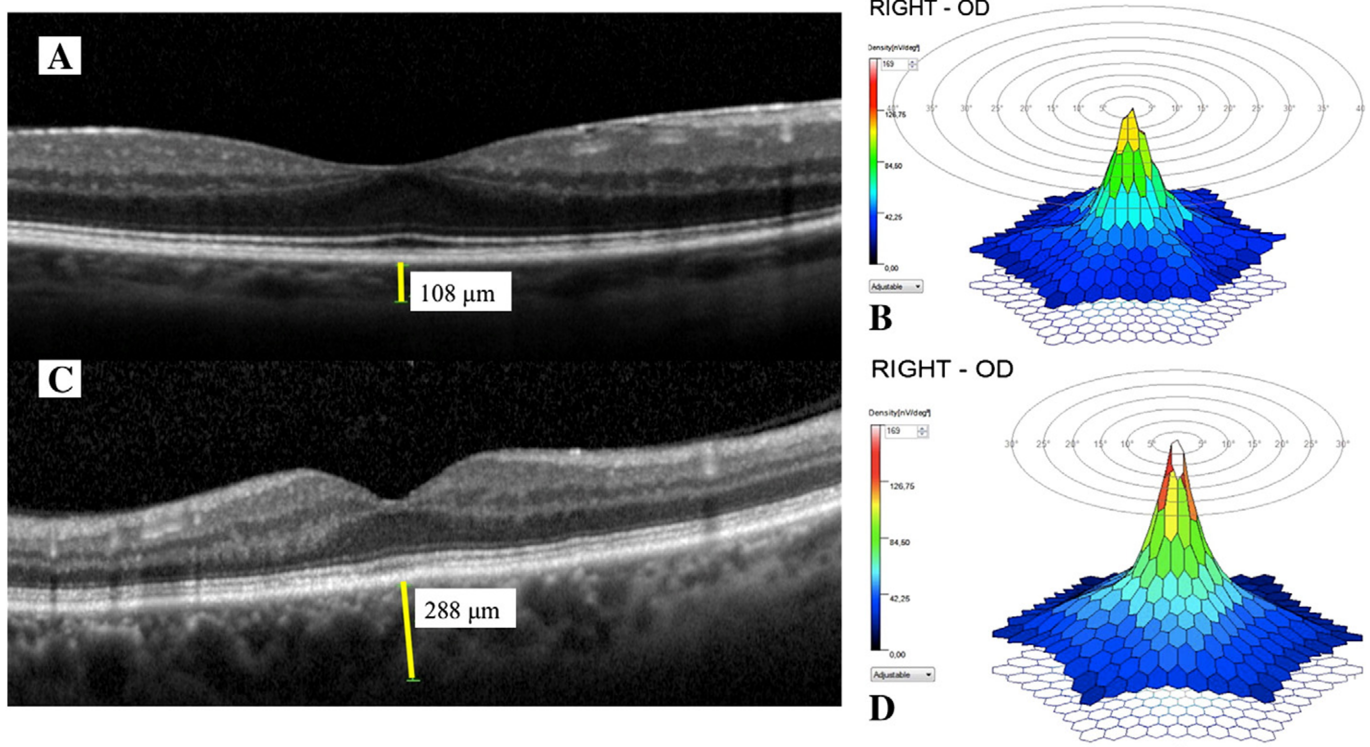

Fig. 1. Representative enhanced depth imaging optical coherence tomography scans of 2 eyes and the corresponding multifocal ERG images: (A–B) patient with retinitis pigmentosa and (C–D) control subject. There is a marked choroidal thickness difference between the 2 patients (108 vs. 288 μm, respectively). Choroidal thickness was measured as the distance between the hyperreflective lines of the retinal pigment epithelium–Bruch's membrane complex to the innermost hyperreflective line of the choroid–sclera junction. MfERG show attenuated paracentral responses in retinitis pigmentosa compared with a healthy subject.

higher ET-1 plasma levels and lower choroidal thickness compared with healthy subjects: respectively, 2.143 ± 0.258 pg/ml vs. 1.219 ± 0.236 pg/ml ($p < 0.002$) and 226.75 ± 76.37 μm vs. 303.9 ± 39.87 μm ($p < 0.03$) (Table 1).

No significant correlation between standard ERG and plasmatic ET-1 levels ($r = -0.511$; $p < 0.131$) was observed.

Finally data obtained by mfERG demonstrated that RP subjects had a statistically significant decrease of P1 amplitude in rings 2, 3, 4 and 5 compared with controls, respectively ($p < 0.01$), ($p < 0.027$), ($p < 0.002$) and ($p < 0.007$) and an increase of P1 implicit time in both ring 2 ($p < 0.018$) and ring 3 ($p < 0.001$) (Table 2).

Spearman's correlation test highlighted that the increase of ET-1 plasma levels was related with the decrease of choroidal thickness ($r = -0.702$; $p < 0.023$; Fig. 2) and the increase of implicit time in both ring 2 ($r = -0.669$; $p < 0.034$) and ring 3 ($r = -0.883$; $p < 0.007$) of mfERG. Notably we also found a positive correlation between the decreased choroidal thickness and the reduction of P1 amplitude in both ring 2 ($r = 0.787$; $p < 0.037$) and ring 3 ($r = 0.810$; $p < 0.001$), whereas, as regards rings 1, 4 and 5, no statistically significant correlation was reported (Table 3).

Table 1
Demographic and ocular parameters and ET-1 plasma levels in patients with retinitis pigmentosa and in healthy controls.

	Controls	Retinitis pigmentosa	$p < 0.05$
Age, years	36.0 ± 6.8	33.8 ± 7.3	0.155
Visual Acuity, decimals	0.97 ± 0.04	0.95 ± 0.07	0.235
SAP-PSD, dB	1.98 ± 0.98	6.09 ± 4.22	0.001
SAP-MD, dB	−1.95 ± 0.83	−7.90 ± 1.75	0.006
ERG b-wave, μV	65.36 ± 9.84	45.08 ± 8.24	0.002
ERG a-wave, μV	38.16 + 5.57	28.13 + 5.77	0.019
ET-1, pg/ml	1.219 ± 0.236	2.143 ± 0.258	0.002
Choroidal thickness, μm	303.9 ± 39.87	226.75 ± 76.37	0.023

Note: Values are presented as means ± SD; $n = 24$ per group.

Discussion

RP includes a group of hereditary disorders with variable clinical presentation and wide range of severity, age of onset and progression and is characterized by progressive visual impairment, visual field loss and abnormal ERG responses because diffusely involves photoreceptors and RPE function.

Our results show that early stage RP patients with preserved central visual acuity have decreased P1 amplitude, increase in P1 implicit time, thinner subfoveal choroidal thickness and higher ET-1 plasmatic levels compared with healthy subjects.

Both Cellini et al. (2002) and Vingolo et al. (2010) demonstrated higher levels of ET-1 plasma concentration in RP subjects compared with healthy patients, whereas Ohguro and associates found that there were significantly lower ET-1 plasmatic levels than those of controls (Ohguro et al., 2010). Different disease heterogeneity, stages,

Table 2
Multifocal ERG characteristics in patients with retinitis pigmentosa and in healthy controls.

Characteristic	Controls	Retinitis Pigmentosa	$p < 0.05$
P1 amplitude, μV			
Ring 1	0.94 ± 0.35	0.61 ± 0.79	0.432
Ring 2	0.67 ± 0.34	0.33 ± 0.23	0.010
Ring 3	0.56 ± 0.17	0.27 ± 0.23	0.027
Ring 4	0.53 ± 0.15	0.17 ± 0.22	0.002
Ring 5	0.50 ± 0.07	0.15 ± 0.19	0.007
P1 implicit time, ms			
Ring 1	35.44 ± 5.92	38.47 ± 2.96	0.129
Ring 2	37.19 ± 1.31	41.04 ± 2.32	0.018
Ring 3	35.76 ± 0.82	40.29 ± 1.94	0.001
Ring 4	34.14 ± 3.85	34.48 ± 3.21	0.238
Ring 5	35.60 ± 1.51	36.07 ± 2.07	0.467

Note: Values are presented as means ± SD; $n = 24$ per group.

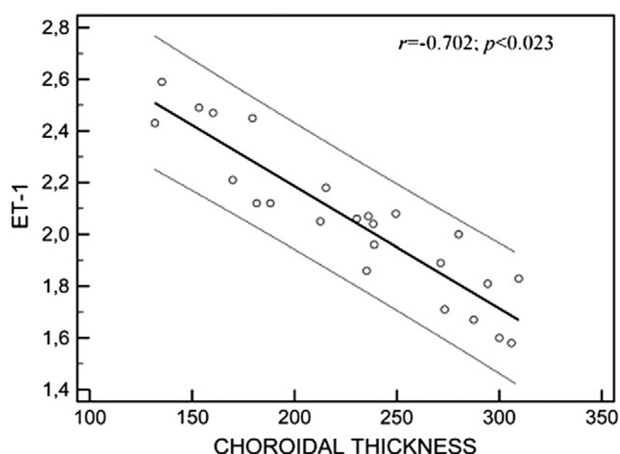

Fig. 2. Scatterplot showing the correlation between ET-1 plasmatic levels (picogram/milliliter) and subfoveal choroidal thickness (micrometers) in patients with retinitis pigmentosa (Spearman's correlation coefficient, $r = -0.702$; $p < 0.023$).

race, sample size and the method used for the ET-1 determination may justify contrasting results.

The thinnest choroidal thickness values we measured in early stage RP patients compared with controls ($p = 0.023$), by using EDI SD-OCT, are in agreement with those already demonstrated by Dhoot et al. (2013) with the same objective technique.

Several previous hemodynamic studies showed a reduction in both choroidal blood flow and retinal blood flow in RP, by using color Doppler imaging and laser Doppler flowmetry (Langham and Kramer, 1990; Akyol et al., 1995; Cellini et al., 1997; Schmidt et al., 2001; Falsini et al., 2011; Grunwald et al., 1996) and in addition, other authors found a positive correlation between increased ET-1 plasma concentration and abnormalities in the microcirculation not only in the eye, but also in the whole body (Cellini et al., 2010; Konieczka et al., 2012). Notably we reported a negative association between choroidal thickness and ET-1 ($r = -0.702$; $p < 0.023$) and hypothesize that the reduction of choroidal thickness may be determined by the vasoconstrictor effect of ET-1 which could cause choroidal vascular abnormalities and blood flow impairment with a resulting relative ischemia leading to worsening of the abiotrophic process of the macular photoreceptors.

The reason why ET-1 is increased in RP patients is not well understood. Indeed ET-1 is mainly produced by vascular endothelial cells but also different kind of cells may secrete ET-1 when they are under stress conditions, such as hypoxia and oxidative stress. It has been widely suggested that oxidative stress is a typical finding in RP and possibly contributes to its pathogenesis (Martínez-Fernández de la Cámara et al., 2013).

Furthermore some authors have hypothesized a primary vascular dysregulation syndrome (Flammer et al., 2013) to explain all the signs and symptoms both in the eye and in the body of RP patients. Finally the term retinitis refers to an inflammatory component (Yoshida et al., 2013a; Yoshida et al., 2013b) which could contribute to a microvascular dysfunction. Thus oxidative stress, vascular dysfunction and inflammation interact to enhance ET-1 production and secretion. Increased ET-1 plasmatic levels may lead to unstable ocular blood supply, by altering the regulation of retinal and choroidal blood flow and this, in turn, leads to an increase in free radicals and chronic oxidative stress which may stimulate cells to secrete more ET-1. From an accurate analysis of the data reported in literature and from our study results we suppose that the increase of ET-1 plasmatic levels in RP patients may be a consequence of the pathogenetic elements of the disease but also a potential modifying factor able to modulate the manifestation and/or the progression of the disease itself.

Table 3
Correlation between the amplitude of P1 in each of the five rings of mfERG and subfoveal choroidal thickness.

P1 amplitude, μV	Choroidal thickness, μm	$p < 0.05$
Ring 1	r = 0.043	0.906
Ring 2	**r = 0.787**	**0.037**
Ring 3	**r = 0.810**	**0.001**
Ring 4	r = 0.492	0.149
Ring 5	r = 0.104	0.774

Multifocal ERG, described for the first time by Sutter and Tran (1992), allows recording ERG waves in response to a series of stimuli presented in different points of the visual field and provides a simultaneous estimation of the functionality of each retinal area and thus alterations of mfERG may constitute an early indication of local retinal damage to the cone system. The recordings show the activity of the outer retina, especially photoreceptors and bipolar cells. Indeed we demonstrated that RP subjects, compared with healthy controls, show abnormalities in P1 amplitudes in each ring, with the exception of ring 1, and also that the reduction of P1 amplitude in both ring 2 and ring 3 was positively related to the thinning of the choroid; respectively ($r = 0.787$; $p < 0.037$) and ($r = 0.810$; $p < 0.001$). Furthermore, our patients had a significant increased implicit time in both ring 2 and ring 3 compared with controls and this data was very well related to the increase in ET-1 plasma levels. Indeed Kobayashi et al. (2005) demonstrated that ET-1 increases the intracellular Ca^{2+} concentration in glial and neuronal cells through ET-A receptors, thereby favoring the glutamate-induced death of retinal neurons, especially amacrine cells, which have neural connections with bipolar, horizontal and retinal ganglion cells and play a key role in the modulation of the activities of these cells. For this reason the glutamate neurotoxicity is enhanced by the increase of ET-1. The death of amacrine cells may lead to abnormal neural transmission and explain the increase of implicit time in mfERG. These functional changes are statistically more significant in both ring 2 and ring 3 because of the anatomical distribution of bipolar cells in the macula, which are poor in the foveal region and become more dense toward the parafovea and perifovea (Miyake, 1998).

From our results it is worth noting that mfERG findings may not be simply explained by a primary photoreceptor degeneration but may be influenced by plasmatic ET-1 levels. Indeed we suppose a mechanism of photoreceptor ischemia due to reduced choroidal blood flow, caused by increased ET-1 plasmatic levels in RP eyes, leading to abnormal electrophysiological responses.

This study has some limitations. First, the sample size was small because participants were accurately selected among young healthy RP patients, to limit confounding factors, such as age and systemic diseases which could affect plasmatic ET-1 levels. It is likely that results may be more heterogeneous by considering a wider RP population. Second, we did not evaluate intraocular ET-1 concentration; indeed ET-1 plasma levels obtained in our study might not reflect the intraocular activity of this peptide.

Conclusions

Our study suggests that increased ET-1 plasma levels may play a key role in the impairment of choroidal blood flow and thickness and may favor glutamate-induced toxicity to retinal cells leading to worsening of the abiotrophic process of the macular photoreceptors and to abnormalities in neural connections.

Although our results require further confirmation and investigation, this study might provide reasonable data about the possibility to use antagonists of ET-1 with the purpose of improving the ocular blood flow and reducing the glutamate neurotoxicity to ameliorate the function of the macular photoreceptors and enhance survival of cells.

Conflict of interest statement

Authors do not have a financial relationship with any organization. The authors have full control of all primary data and they agree to allow Life Sciences to review their data if requested.

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