Reduction on OFF-responses of Electroretinogram in Monkeys with Long-term High Intraocular Pressure

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Abstract

Background: There are ON- and OFF-pathways in the normal vertebrate retina. Short- and long-flash electroretinogram (ERG) are suitable methods to observe the function of ON- and OFF-pathways *in vivo*, respectively. It is clear that high intraocular pressure (IOP) might cause dysfunction of cone-dominated photopic negative response (PhNR) in monkeys with high IOP in ON-pathway. However, whether cone-dominated OFF-responses are also affected is less known. The aim of this study was to observe photopic OFF-responses of ERG in monkeys with high IOP.

Methods: Nine monkeys were involved in the experiment from January 2006 to December 2016. High IOP was induced in the right eye by laser coagulation of the mid-trabecular meshwork in five monkeys. Six years after the laser coagulation, both short- and long-flash of the photopic ERG were recorded. Stimulus light was red flashes superimposed on a blue background. Four normal monkeys were examined under the same ERG protocols as controls. Paired *t*-test was used to compare the difference of each ERG parameter between the lasered eye and the fellow eye. Analysis of variance (ANOVA) with Tukey adjustment was adopted to calculate the differences among the lasered eye, the fellow eye, and the eyes of normal monkeys.

Results: The mean amplitude of a-wave (11.73 ± 2.05) and PhNR (8.67 ± 2.44) in lasered eyes was significantly lower than that of a-wave (21.47 ± 3.15) and PhNR (22.05 ± 3.42) in fellow eyes ($P = 0.03$ and $P = 0.01$, respectively) in response to short flash. The mean amplitude of d-wave (1.60 ± 0.59) and i-wave (3.13 ± 0.64) was significantly reduced in the lasered eyes than that of d-wave (4.01 ± 0.56) and i-wave (8.79 ± 1.75) in the fellow eyes ($P = 0.02$ and $P = 0.02$, respectively) in response to long flash.

Conclusions: Reduced OFF-responses are recorded in monkeys with high IOP when dysfunction of photoreceptor is involved. The reduced OFF-responses to long-flash stimulus show evidence of anomalous retinal circuitry in glaucomatous retinopathy.

Key words: Electroretinogram; OFF-responses; Monkey; Intraocular Pressure; Retinal Pathway

INTRODUCTION

Glaucoma is characterized by chronic damage of optic nerve that leads to eventual blindness. High intraocular pressure (IOP) is a major risk factor for the incidence of glaucoma. High IOP may result in the degenerative optic neuropathy and the damage of retina in glaucoma patients[1] and in monkey glaucoma model.[2] Histological studies[2] and optical coherence tomography (OCT) images[3,4] have revealed degeneration of retinal nerve fiber layer and loss of retinal ganglion cells (RGCs). The functional and structural abnormalities of photoreceptor cells under high IOP are also noticed in glaucoma patients[5] and in primate glaucoma model.[2,4]

There are ON- and OFF-pathways in the normal vertebrate retina. Short- and long-flash electroretinogram (ERG) are suitable methods to observe the function of ON- and OFF-pathways *in vivo*, respectively. Photopic ERG ON-responses are obtained when short-duration stimuli are used under light-adapted condition. Photopic ERG

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OFF-responses are obtained when long-duration stimuli are used under light-adapted condition after light offset. In photopic ON-responses, the photopic negative response (PhNR) is an indicator of retinal function in early glaucomatous optic neuropathy because PhNR was greatly reduced in eyes with experimental glaucoma and in human glaucoma. Therefore, it is clear that high IOP might cause dysfunction of cone-dominated PhNR in ON-pathway. However, whether cone-dominated OFF-responses are also affected is less known.

The purpose of this study was to observe the changes of full-field flash ERG to light ON- and OFF-stimuli in monkeys with high IOP to test the hypothesis whether OFF-responses of photopic ERG are suppressed under long-term high IOP.

Methods

Ethical approval

All procedures in this study were approved by the Animal Care and Use Committee at the Capital Medical University (No. 2011-D-0008) and were performed in accordance with the Association for Research in Vision and Ophthalmology (ARVO) Statement for the Use of Animals in Ophthalmic and Vision Research.

Study subjects

Five male cynomolgus monkeys (*Macaca fascicularis*) were involved as experimental group. At the ERG examination, the age of the five monkeys was 13 years and body weight was in the range of 5.7–7.5 kg. All the five monkeys were purchased from the Academy of Military Medical Science (No. SCXK- [Military] 2012-0019) and kept in the Department of Experimental Animals of the Capital Medical University at the age of 4 years. High-IOP monkey model was made at 6 years prior to this study. Laser coagulation of the mid-trabecular meshwork was applied to induce ocular hypertension in the right eye (OD) of each monkey. In addition, four normal rhesus monkeys were also examined under the same ERG protocols to serve as normal controls. The age of the four normal monkeys was in the range of 4–6 years, and the body weight was in the range of 6.3–7.2 kg. All monkeys were kept in the environment of alternating 12-h dark and 12-h light cycles (100 lux).

Induction of high intraocular pressure

Monkeys were anesthetized with intraperitoneal injection of 10% ketamine (4 ml/kg) and intramuscular injection of Sumianxin-II (0.1 ml/kg; The Munitions University of Peoples Liberation Army, Changchun, Jilin, China). The main ingredients of Sumianxin-II contain xylazine haloperidol and dihydroetorphine hydrochloride. After anesthesia, the monkeys were fixed in front of the slit-lamp microscope. The OD of each monkey was selected to make high IOP model. A drop of 1% pilocarpine on hydrochloride (FREDA, Jinan, Shandong, China) was used to constrict the pupil of the eye. The right cornea was placed with a gonioscope (Ocular Instruments, Bellevue,

Washington, USA) that was specially designed for monkeys. The mid-trabecular meshwork was coagulated by Novus Spectra® (Lumenis Ltd., Beijing Office, South Tower Kerry Centre, Beijing, China) with 532 nm laser facility. The number of burns was 60 to 150 over the 270° midportion of the trabecular meshwork at the first coagulation. Based on a previous study, laser parameters were set as follows: laser power, 1000–1500 mW; spot size, 50 μm; and exposure duration time, 0.5 s. Two weeks after the first coagulation, laser coagulation was re-applied to the remaining 90° midportion of the trabecular meshwork if IOP was below 30 mmHg (1 mmHg = 0.133 kPa). According to previous literatures, repeated laser coagulation of the mid-trabecular meshwork results in the elevation of IOP that can be maintained for many years. However, the elevated IOP might decrease gradually even without any treatment due to factors such as self-regulation. To achieve a sustained elevated IOP, additional laser coagulation was applied occasionally if IOP was below 30 mmHg during the experimental period. Some monkeys received additional laser coagulation one or two times during the 6 years. The number of laser coagulation during the period was no more than four times. As high IOP had been maintained more than 6 years, we designated the lasered OD as glaucomatous eye and the untreated left eye (OS) as the fellow eye. The measurement of IOP was performed with a Tonovet tonometer (Icare Finland Oy, Espoo, Finland). Three averaged values were referred as the final value of IOP.

Electroretinography

After administration of anesthesia, each monkey was prepared for electroretinography. Both corneas of eyes were instilled with a drop of 0.5% proparacaine hydrochloride. Pupils of the two eyes were dilated with a drop of 1% cyclopentolate hydrochloride (Cyclomydril, Alcon, Fort Worth, TX, USA). Both eyes were placed with Burian-Allen bipolar electrode (Hansen Laboratories, Coralville, IA, USA). The ground electrode was a needle electrode that penetrates into the skin of the left forearm. All monkeys were examined with the Espion Visual Electrophysiology System from Diagnosys, LLC (Littleton, MA, USA). Our ERG protocol was designed according to the standard documents recommended by the International Society for Clinical Electrophysiology of Vision.[6]

A ganzfeld stimulator ColorDome that created full-field stimulation was placed above the center of the two eyes so that ERG signals from two eyes were recorded simultaneously. Before stimuli with red flashes, monkeys were adapted to a blue background (luminance: 30 cd/m²) for 10 min to suppress rod responses. The stimulus parameters of short- and long-flash red on blue background were designed based on previous studies. A protocol of two steps was created and automatically run sequentially. Step 1 was short-duration (4 ms) red flash light, with stimulus intensity of 1 cd·s·m⁻². Responses recorded by step 1 were designated as short-flash responses. Step 2 was long-duration (200 ms) red light, with stimulus luminance of 125 cd/m. Responses recorded by step 2 were

designated as long-flash responses. Sweep time was 250 ms for short flashes in step 1 and 500 ms for long flashes in step 2. Twenty sweeps were averaged. The inter-sweep delay was all set to 20 s. Sample frequency was 1000 Hz. The low- and high-frequency cutoffs used for ERG recordings were set at 0.15 Hz and 300 Hz, respectively. To ensure that the recorded signal is stable and repeatable, the software created by the Espion manufacturer can automatically perform baseline removal and auto-zeroing. The essential principle is based on removing a sloping direct current (DC) drift from the result by fitting a straight line through result and subtracting it. To do this, the software measures the signal over a period and then takes the average value of this signal during this time and subtracts it from the entire sweep. If long-duration stimuli are used, trend removal is used.

To analyze and measure the value of ERG, we used the principles and methods reported in literature[7] and in our previous studies.[4,8,9] The implicit time (IT) of a- and b-waves was measured from the start of the stimulus to the peak of the a- and b-waves. The amplitude of a-wave was measured from baseline to the trough of a-wave. The amplitude of b-wave was measured from the trough of a-wave to the peak of b-wave. Two major components were noted after the offset of long-flash stimulus. The first positive peak was labeled as d-wave and the second positive peak was labeled as i-wave. As it was difficult to determine the trough of the d-wave, especially in eyes with disease, the amplitude of the d-wave was measured from the stimulus offset (at 200 ms after stimulus start) to the first positive peak. The amplitude of the i-wave was measured from the trough of d-wave to the peak of i-wave. IT of d-wave and i-wave was measured from the stimulus offset (at 200 ms after stimulus start) to the peaks of the d- and i-waves, respectively. Inter-peak time (IPT) of d-wave and i-wave was measured from the peak of d-wave to the peak of i-wave [Figure 1].

Statistical analysis
Difference of each ERG parameter obtained from the lasered eye and the fellow eye was compared by means of the paired *t*-test. One-way analysis of variance (ANOVA) with Tukey adjustment was adopted to calculate the differences among the lasered eye, the fellow eye, and the eyes of normal monkeys. SPSS software (version 17.0, Chicago, IL, USA) was used for the analyses of all the ERG data that were expressed as mean ± standard error (SE). The statistical significance level was set at $P < 0.05$.

RESULTS

Characteristics of short-flash electroretinogram
Figure 1a and 1b are sample traces of short-flash ERG in a monkey with high IOP in OD. The waveform of the short-flash ERG in the fellow eye shows a deep negative wave following the b-wave, which was designated as PhNR [Figure 1a]. The decreased amplitude of a-wave and flat PhNR around the baseline was noticed in the lasered eye [Figure 1b]. The mean amplitude of a-wave
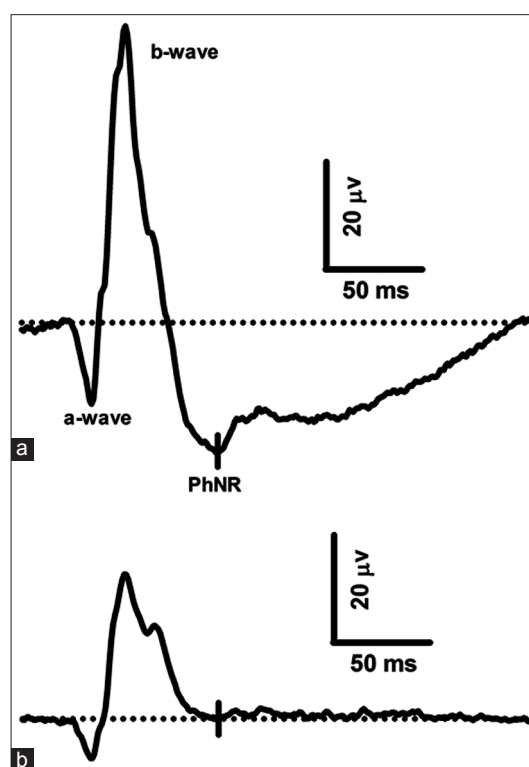

Figure 1: Sample traces of short-flash ERG in a monkey with high IOP in the right eye. The dotted line on the horizontal axis is baseline. (a) Fellow eye (*n* = 5, OS); (b) lasered eye (*n* = 5, OD). ERG: Electroretinogram; IOP: Intraocular pressure; PhNR: Photopic negative response; OD: Right eye; OS: Left eye.

(11.73 ± 2.05) and PhNR (8.67 ± 2.44) in lasered eyes was significantly lower than that of a-wave (21.47 ± 3.15) and PhNR (22.05 ± 3.42) in fellow eyes ($P = 0.03$ and $P = 0.01$, respectively) [Figure 2 and Table 1]. There is no statistical difference of b-wave between the lasered eyes (52.96 ± 9.40) and fellow eyes (80.88 ± 12.92, $P = 0.12$) [Figure 2 and Table 1].

Characteristics of long-flash electroretinogram
The waveform of the long-flash ERG shows a negative plateau between the b- and d-waves in the fellow eye [Figure 3a]. The decreased amplitude of a- and d-waves was recorded, and the elevated plateau above the baseline was noticed in the lasered eye [Figure 3b]. Reduced amplitude of d- and i-waves was found in each lasered eye. The mean amplitude of d-wave (1.60 ± 0.59) and i-wave (3.13 ± 0.64) was significantly reduced in the lasered eyes than that of d-wave (4.01 ± 0.56) and i-wave (8.79 ± 1.75) in the fellow eyes ($P = 0.02$ and $P = 0.02$, respectively) [Figure 4 and Table 1]. There were no statistically significant differences in the mean amplitude of the b-wave between the two eyes ($P = 0.10$) [Figure 4 and Table 1].

For both flash durations, no statistical differences were found in the mean IT of the a-wave ($P = 0.76$), b-wave ($P = 0.16$), and PhNR ($P = 1.00$) in response to the short-flash and a-wave ($P = 0.78$), b-wave ($P = 0.15$), d-wave ($P = 0.29$), and i-wave ($P = 0.25$) in response to the long-flash between the lasered eyes and fellow eyes [Table 2]. There was statistical

difference in mean IPT of d-wave and i-wave between the lasered eyes (61.80 ± 5.95) and the fellow eyes [52.60 ± 2.98, $P = 0.04$, Table 2].

As expected, no significant differences were found statistically in mean amplitude between the two eyes in the a-wave ($P = 0.29$), b-wave ($P = 0.61$), and PhNR ($P = 0.96$) in response to the short flash or in the a-wave ($P = 0.88$), b-wave ($P = 0.99$), d-wave ($P = 0.80$), and i-wave ($P = 0.10$) in response to long flash. There were no differences in IT in the a-wave ($P = 1.00$), b-wave ($P = 0.72$), and PhNR ($P = 1.00$) in response to the short flash or in the a-wave ($P = 1.00$), b-wave ($P = 1.00$), d-wave ($P = 0.42$), i-wave ($P = 0.43$), and IPT of d-wave and i-wave ($P = 0.42$) in response to long flash in the normal monkeys.

DISCUSSION

The ON and OFF channels are basic functional elements in parallel processing in the visual system in vertebrates including primates.[10] The majority of cones in the central retina connect with at least two bipolar cells, one of which is ON and the other is OFF. The ON and OFF bipolars in turn connect with ON and OFF RGCs, respectively. The
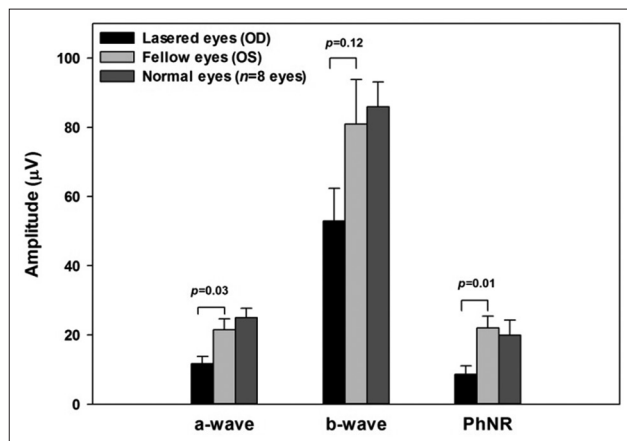
axons of the ganglion cells project to the lateral geniculate nucleus of the thalamus in the brain, and then optic tract containing information from ON and OFF channels projects to the visual cortex. There are evidences which suggest that the cortical OFF-potentials in visual cortex are reduced in early glaucoma patients,[11] the ON- and OFF-pathways from the retina to the superior colliculus were disrupted in mice with sustained ocular hypertension,[12] and elevated IOP decreases response sensitivity of inner retinal neurons in experimental glaucoma mice.[13] However, it is still less known whether cone-dominated OFF-responses in the retina are affected under long-term high IOP. The present results
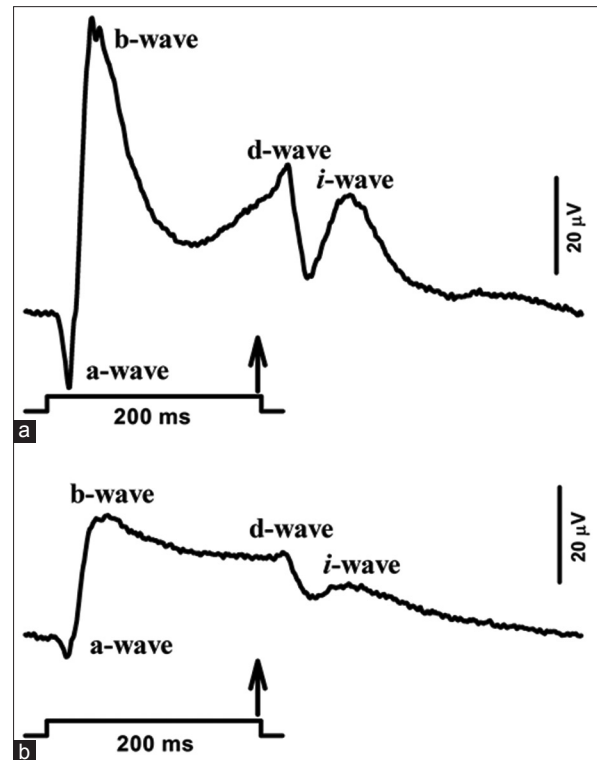
Figure 3: Sample traces of long-flash ERG in the same monkey with high IOP in the right eye. The up arrow on the horizontal axis (at 200 ms) indicates stimulus offset. (a) Fellow eye ($n = 5$, OS); (b) Lasered eye ($n = 5$, OD). ERG: Electroretinogram; IOP: Intraocular pressure; OD: Right eye; OS: Left eye.

Figure 2: Mean amplitude of the photopic ON-response components in lasered monkeys ($n = 5$ eyes) and normal monkeys ($n = 8$ eyes). OD: Right eye; OS: Left eye.

Table 1: Mean amplitude (μV) in monkeys with high IOP and normal monkeys

ERG Parameters	High IOP, $n = 5$ eyes		t	P	Normal monkeys, $n = 8$ eyes
	OD	OS			
Short flash (μV)					
a-wave	11.73 ± 2.05 (5.69–17.02)	21.47 ± 3.15 (15.27–33.35)	−2.59	0.03	24.99 ± 2.71
b-wave	52.96 ± 9.40 (32.42–81.03)	80.88 ± 12.92 (45.53–126.00)	−1.75	0.12	85.90 ± 7.24
PhNR	8.67 ± 2.44 (1.69–15.54)	22.05 ± 3.42 (15.59–34.03)	−3.19	0.01	19.95 ± 4.38
Long flash (μV)					
a-wave	4.06 ± 0.71 (2.34–6.67)	8.81 ± 1.65 (6.06–15.20)	−2.64	0.03	10.79 ± 1.27
b-wave	26.93 ± 4.69 (12.83–40.81)	45.37 ± 8.61 (20.34–73.17)	−1.88	0.10	37.01 ± 2.86
d-wave	1.60 ± 0.59 (0.32–3.77)	4.01 ± 0.56 (2.20–5.68)	−2.97	0.02	6.92 ± 0.91
i-wave	3.13 ± 0.64 (2.10–5.44)	8.79 ± 1.75 (5.23–15.29)	−3.03	0.02	8.51 ± 1.35

Data are presented as mean ± SE (range). SE: Standard error; ERG: Electroretinogram; IOP: Intraocular pressure; PhNR: Photopic negative response; OD: Right eye; OS: Left eye.

Table 2: Mean IT (ms) and IPT (ms) in monkeys with high IOP and normal monkeys

ERG Parameters	High IOP, $n = 5$ eyes		t	P	Normal monkeys, $n = 8$ eyes
	OD	OS			
Short flash (ms)					
a-wave	15.80 ± 0.49 (15–17)	15.60 ± 0.40 (15–17)	0.32	0.76	15.25 ± 0.31
b-wave	35.60 ± 0.81 (34–38)	34.00 ± 0.63 (33–36)	1.55	0.16	32.00 ± 0.33
PhNR	85.00 ± 0.00 (85–85)	85.00 ± 0.00 (85–85)	0.00	1.00	84.38 ± 0.38
Long flash (ms)					
a-wave	19.60 ± 0.60 (18–21)	19.80 ± 0.37 (19–21)	−0.28	0.78	19.25 ± 0.31
b-wave	40.00 ± 0.00 (40–40)	39.00 ± 0.63 (37–40)	1.58	0.15	38.50 ± 0.50
d-wave	221.00 ± 0.55 (220–223)	222.60 ± 1.29 (219–225)	−1.14	0.29	223.00 ± 0.53
i-wave	282.80 ± 5.61 (267–300)	275.20 ± 2.35 (269–282)	1.25	0.25	276.75 ± 1.90
IPT	61.80 ± 5.95 (46–80)	52.60 ± 2.98 (44–59)	2.79	0.04	53.75 ± 2.40

Data are presented as mean ± SE (range). SE: Standard error; ERG: Electroretinogram; PhNR: Photopic negative response; IOP: Intraocular pressure; IPT: Inter-peak time between d-wave and i-wave; PhNR: Photopic negative response; IT: Implicit time; OD: Right eye; OS: Left eye.
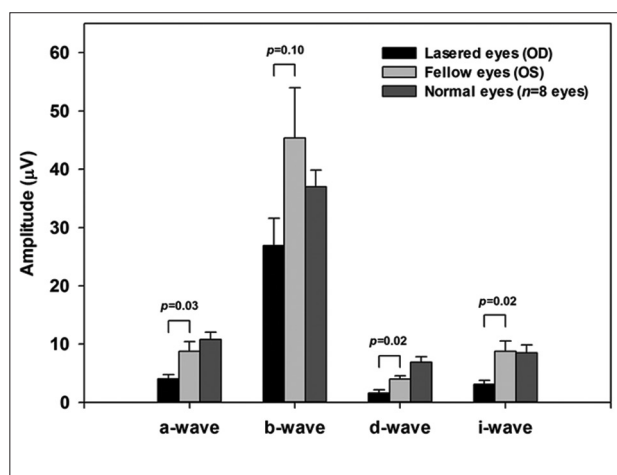

Figure 4: Mean amplitude of the photopic OFF-response components in lasered monkeys ($n = 5$ eyes) and normal monkeys ($n = 8$ eyes). OD: Right eye; OS: Left eye.

suggested that OFF-responses are affected in monkeys with long-term ocular hypertension when dysfunction of photoreceptor is involved.

Visual stimuli are transduced by photoreceptor cells that dominate the whole procedure of vision including the OFF-responses. The cones synapse directly with a number of ON- and OFF-bipolar cell types. The cones contact both depolarizing bipolar cells (DBCs) and hyperpolarizing bipolar cells (HBCs) through sign-inverting (−) synapses (ON synapse) and sign-preserving (+) synapses (OFF synapse), respectively. Ueno et al.'s[14] results demonstrated that the origin of the d-wave of primate photopic ERG is very complex, and they also found that not only the cone photoreceptors, but also postreceptoral components of the inner retinal neurons contributed to the d-wave. The HBCs appear to be the primary generators for the d-wave, but photoreceptors and DBCs also play a role in shaping the morphology of the waveform. Kawasaki et al.[15] suggested that the human ERG OFF-effect was related rather directly to cone activity. According to the current information, the ON- and OFF-responses originate not only from the postsynaptic bipolar cells, but also from cone photoreceptors.[14,16] Therefore, eyes with large a-waves should show a good OFF-effect whereas those with small a-waves had poor OFF-effects. Interestingly, high IOP does not cause dysfunction of the ON- and OFF-pathways in parallel in glaucoma patients. The possible reason might be that the retina had been subjecting to fluctuating IOP and undergoing ischemia and reperfusion injury alternatively in monkeys with ocular hypertension. Some experiments have reported that the d-wave and the PhNR to increment and decrement stimuli are somewhat reduced while b-wave amplitude is typically unaffected in patients with glaucoma.[17-19] Reduced OFF-responses and PhNR were also observed in the results while b-wave was not altered between the lasered eyes and fellow eyes in these monkeys with long-term high IOP. It has been proposed that the "push-pull" activity of the HBCs and DBCs is summated in the photopic ERGs recorded at the cornea. In addition, the b- and d-waves of the photopic ERGs elicited by long flashes are produced by an interaction of the HBCs and DBCs.[20]

The retinal circuitry whereby cone photoreceptor signals pass through the retina to RGCs is rather complex. Histological examination of retina can make cross-sectional observations and quantitative analysis of the retinal circuitry. With the rapid development of OCT technology, the components of retinal circuitry can be examined layer by layer in vivo. Evidences of recent OCT images show that central macular thickness is thicker in monkey glaucoma model[21] and in human glaucoma patients.[22] Loss in cone density along with expected inner retinal changes was demonstrated in well-characterized glaucoma patients with visual field loss.[5] These results suggest that swelling of photoreceptors might occur under high IOP, which had been confirmed by a histological study in monkey glaucoma model and human glaucoma patients.[23] In the DBA/2J mice (a hereditary glaucoma model), there is photoreceptor death, loss of bipolar and horizontal cell processes, and loss of synaptic contacts.[24] In adult albino Swiss mice, elevated IOP results in loss of ON-rod bipolar, horizontal cells, and their dendritic processes.[25] Morphological changes of cone photoreceptor under long-term high IOP are likely to reduce the signal pulse

to the second order of neurons including ON- and OFF-bipolar cells. Thus, reduced OFF-responses were recorded when dysfunction of cone photoreceptors was involved under long-term high IOP in this study. To evaluate the functional integrity of retinal circuitry, the ERG can not only inform us about the functional status of retinal cells and circuits, but also reflect the whole procedure of visual transmission. The laminated organization of the retina generates two streams of visual information, a main or vertical pathway, from the photoreceptors to bipolar cells and then to RGCs. The other is lateral interaction pathway, comprising local feedback circuits from horizontal cells back to photoreceptors and from amacrine cells back to bipolar cells. On the one hand, dysfunction of photoreceptors might result in the reduction of signal transduction in cone-dominated vertical pathway. On the other hand, the reduced OFF-responses in this study appeared that the integrity of the lateral feedback circuitry in cone pathway might be dysfunctional or disconnected as anatomical evidences had revealed loss of horizontal cells and abnormalities of synaptic contacts under long-term high IOP.

There are some limitations about the research. First, we only recorded the ERG responses in monkeys with long-term IOP after 6 years when we got the ERG facilities for monkey use. We missed the chance to record the ERG before laser and soon after laser coagulation. Therefore, only cross-sectional data are now available for analysis. Second, the present results are obtained from monkeys under long-term high IOP. Ocular hypertension was still maintained in the lasered eyes in these monkeys by the time ERGs were recorded. Although reduced OFF-responses were recorded in these monkeys, we have not tested glaucoma patients using the same ERG protocols. However, human glaucoma is different from that of monkey with high IOP to a great extent because human glaucoma is a multifactorial disease, while in this study, only one factor, that is, high IOP, might contribute to the results. Moreover, IOP was usually controlled below 20 mmHg when recording ERG in glaucoma patients. Third, we examined five monkeys with long-term high IOP. The sample size might be relatively small, although the experiment results had been tested and adjusted by statistical methods. We will continue to expand the sample size and propose histological examination on the premise of ethical approval to verify the present results later.

In summary, reduced OFF-responses were recorded in monkeys under long-term ocular hypertension when dysfunction of photoreceptor was involved. The reduced OFF-responses to long-flash stimulus showed evidence of anomalous retinal circuitry in glaucomatous retinopathy.

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Conflicts of interest

There are no conflicts of interest.

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