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Comparison of focal macular cone ERGs in complete-type congenital stationary night blindness and APB-treated monkeys ☆

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Abstract

Focal macular cone electroretinograms (ERGs) and multifocal ERGs were recorded to study the macular function in patients with the complete-type of congenital stationary night blindness (cCSNB). The waveforms of the focal macular cone ERGs and the on- and off-responses of the multifocal ERGs in the cCSNB patients were similar to those recorded from monkey retinas treated with L-2 amino-4-phosphonobutyric acid (APB), suggesting that patients with cCSNB have a complete defect of the on-pathway even in the central retina. The results also demonstrated that there was a paradoxical positive response in the central retina of cCSNB patients, as compared to the negative full-field ERGs in the same subjects.

Keywords: Electroretinogram (ERG); Focal macular cone ERG; Congenital stationary night blindness (CSNB); Complete-type; APB (L-2 amino-4-phosphonobutyric acid)

1. Introduction

The complete-type of congenital stationary night blindness (cCSNB) is a non-progressive retinal disease characterized by congenital night blindness with a moderate decrease of the visual acuity and myopia (Miyake, Horiguchi, Suzuki, Kondo, & Tanikawa, 1997; Miyake, Yagasaki, Horiguchi, Kawase, & Kanda, 1986). The inheritance pattern of cCSNB is usually X-linked or autosomal recessive. It was recently reported that most X-linked cCSNB resulted from mutations in the *NYX* gene (Bech-Hansen et al., 2000; Pusch et al., 2000), and some cases of autosomal recessive cCSNB resulted from mutations in the *MGR6* gene (Dryja et al., 2005).

cCSNB patients have very characteristic electroretinograms (ERGs). When elicited by a bright stimulus after dark-adaptation, the ERGs are the negative-type with an a-wave of normal amplitude and a b-wave that is smaller than the a-wave. When a long-duration photopic stimulus is used, the b-waves of the ERGs of cCSNB patients are severely reduced while the off-response d-wave is well-preserved (Houchin, Purple, & Wirtschafter, 1991; Miyake, Yagasaki, Horiguchi, & Kawase, 1987; Young, 1991). These ERG waveforms are very similar to those in the monkey photopic ERGs after an intravitreal injection of 2-amino-4-phosphonobutyric acid (APB), which blocks neurotransmission from photoreceptors to the on-bipolar cells (Evers & Gouras, 1986; Knapp & Schiller, 1984; Sieving, Murayama, & Naarendorp, 1994). These results demonstrated that the defect in the neural pathway of cCSNB patients lies in the signal transmission from the photoreceptors to the depolarizing on-bipolar cells (DBCs) in both the rod and cone pathways. Recent ERG analysis using sinusoidal and ramping on/off flicker stimuli also indicated that the deficit in eyes with cCSNB is localized to the DBC pathway with no apparent involvement of the hyperpolarizing off-bipolar cells (HBCs) (Khan et al., 2005).

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Although there are many electrophysiological studies on the full-field ERG in patients with cCSNB, there are very few studies on the macular function of eyes with cCSNB using either the multifocal or focal macular cone ERG techniques (Kondo et al., 2001; Leifert, Todorova, Prunte, & Palmowski-Wolfe, 2005). During our extensive studies of the complete and incomplete type of CSNB, we have been gaining the impression that the cone on-pathway may be functioning relatively well only in the central retina in cCSNB because these patients have relatively good visual function in the central field (Miyake et al., 1997; Terasaki et al., 1999).

The purpose of this study was to investigate the macular function of patients with cCSNB in more detail using focal macular cone ERGs and multifocal ERGs. To accomplish this, we separated the on- and off-responses of the photopic ERGs using long-duration photopic stimuli in the macular area of patients with cCSNB, and then compared the obtained waveforms with those recorded from monkey retinas in which the on-pathway was completely blocked pharmacologically by an intravitreal injection of L-2 amino-4-phosphonobutyric acid (APB).

2. Materials and methods

2.1. Patients with complete-type CSNB

From the patients with cCSNB examined in our clinic (Department of Ophthalmology, Nagoya University Hospital), we selected three patients who agreed to participate and were cooperative with the electrophysiological examinations (Table 1). All patients had poor night vision from birth and had no fundus abnormalities except for myopic changes. Their corrected visual acuities were 0.4, 0.4, and 0.6, and the rod branch of the dark-adaptation curve was missing as determined by psychophysical dark adaptometry. The full-field ERG rod responses were undetectable, and the rod and cone mixed maximal ERG had a negative-shape with no detectable oscillatory potentials.

An informed consent was obtained from the three patients after a full explanation of the procedures. All studies were conducted in accordance with the principles embodied in the Declaration of Helsinki.

2.2. Animals

Four rhesus (*Macaca mulata*) monkeys were studied under protocols approved by Nagoya University School of Medicine. All experiments were conducted in accordance with NIH guidelines on animal use and with the ARVO statement on the Use of Animals in Ophthalmic and Vision Research. The animals were anesthetized with intramuscular injection of ketamine hydrochloride (7 mg/kg, 5–10 mg/kg/h maintenance dose) and xylazine (0.6 mg/kg). The respiration and heart rate were monitored, and hydration was maintained by a slow, continuous infusion of lactated Ringer solution. The cornea was anesthetized by topical 1% tetracaine, and the pupil was dilated with topical 0.5% tropicamide, 0.5% phenylephrine HCL, and 1% atropine.

2.3. Drug application to animals

The drugs were injected into the vitreous with a 30-gauge needle inserted through the pars plana approximately 3 mm posterior to the limbus. The drugs (Sigma Chemical Co., St. Louis, MO) were dissolved in sterile saline and injected in amounts of 0.05–0.07 ml. The intravitreal concentration was 1–2 mM for L-2 amino-4-phosphonobutyric acid (APB) and 5 mM for *cis*-2, 3 piperidine dicarboxylic acid (PDA). Recordings were begun about 60–90 min after the drug injections, and studies were completed within 5 h. Although the drug effects are mostly reversible after a recovery period of several weeks, the results that are presented were recorded from the eyes not previously treated.

2.4. Focal macular cone ERG

Focal macular cone ERGs were elicited by stimulating the macula with small stimulus spots (Miyake, 1988b; Miyake, Shiroyama, Ota, & Horiguchi, 1988a). The position of the spot on the fundus was monitored during the recording with a modified infrared fundus camera. The Burian-Allen bipolar contact lens electrode (Hansen Ophthalmic Development Laboratories, Iowa City, IA) which was used to record the focal macular cone ERGs, allowed a clear view of the fundus on the television monitor. The luminances of the stimulus and the background were 30.0 cd/m^2 and 3.0 cd/m^2, respectively. A 5-Hz rectangular stimulus (100 ms-on and 100 ms-off) was used with a stimulus spot of 15 degrees in diameter. A total of 512 responses were averaged by a signal processor, and the time constant was 0.03 s with a 300-Hz high-cut filter. The ERG responses produced by this method are generated by the cone system, and the responses elicited by the spot stimuli are considered to be local responses (Miyake, 1988b; Miyake et al., 1988a).

2.5. Recording multifocal on- and off-responses

Our method for recording on- and off-responses of the multifocal ERGs has been described in detail (Kondo & Miyake, 2000; Kondo, Miyake, Horiguchi, Suzuki, & Tanikawa, 1998). In brief, multifocal ERGs were obtained with the VERIS system (EDI, San Mateo, CA). The stimulus array consisted of 61 hexagonal elements that were displayed on a CRT monitor (GDM, Sony, Tokyo, Japan) and driven at 75 frames/s. At a viewing distance of 27 cm, the subtense of the visual field was approximately 50°.

To obtain on- and off-responses with the VERIS system, we used consecutive white TV frames. Each hexagon was modulated between two stimulus patterns according to a binary m-sequence: eight consecutive white frames followed by eight consecutive dark frames (pattern A) or 16 consecutive dark frames (pattern B). In this stimulus setting, a stimulus is not continuously bright during its bright phase because the focal flash decays within a few milliseconds. However, there is evidence that a high-frequency train of flashes can roughly simulate the effects produced by a long-duration stimulus and thus can produce a corneal positive off-response (Saeki & Gouras, 1996; Young, 1991).

Based on our preliminary study, the following stimulus parameters were found to be suitable for eliciting maximal on- and off-responses from each local retinal area: stimulus intensity of 120 cd/m^2 with a duration of 8 frames (106 ms) on a 20 cd/m^2 background illumination. The m-sequence stimulation rate was, therefore, 4.7/s and the base interval was 213.3 ms (Kondo & Miyake, 2000; Kondo et al., 1998).

Table 1
Clinical characteristics of three patients with complete type CSNB

Case	Age	Sex	Inheritance pattern	Refractive error (*D*)	Visual acuity
Case 1	54	M	Autosomal recessive	−4.0	0.4
Case 2	20	M	X-linked	−9.5	0.4
Case 3	15	F	Autosomal recessive	−6.0	0.6

The signals were amplified by 100 K and filtered between 3 and 300 Hz (Grass, Quincy, MA). The data sampling rate was 1200 Hz. To reduce the artifacts due to eye movements, an "artifact rejection" algorithm (VERIS software, EDI) was used once (Marmor et al., 2003). The length of the m-sequence used was 2^{11}–1. Thus, the total recording took 7.3 min, and it was divided into 16 segments.

For recording multifocal ERGs from monkeys, a modified ophthalmoloscopic technique was used to locate the projection of the fovea on the center of the stimulus pattern (Rangaswamy, Hood, & Frishman, 2003). This modified ophthalmoscope was kindly provided by Dr. L. Frishman (University of Houston). The position of the fovea was checked frequently before and after the multifocal ERG recordings.

2.6. Recording full-field ERGs

Full-field ERGs were recorded with long-duration stimuli (166 ms or 100 ms) using a densely-packed array of 102 green LEDs (525 nm peak wavelength; 50 nm at half-amplitude). The array was positioned at the top of the Ganzfeld dome and covered by a diffuser (Ueno et al., 2006). The LEDs were controlled by a digital function generator (WF1945, NF Corporation, Tokyo, Japan). The stimulus intensity and background illumination measured in the dome was 120 cd/m^2 and 40 cd/m^2, respectively. In the last experiment, the stimulus intensity and background illumination was set at 30 cd/m^2 and 3 cd/m^2, respectively, in order to compare the waveforms of full-field ERG and focal macular cone ERG at the same stimulus and background condition.

After 10 min of light adaptation, ERGs were recorded with a Burian-Allen bipolar contact lens electrode (Hansen Ophthalmic Development Labs, Iowa City, IA). A ground electrode was attached to the ipsilateral ear. Responses were amplified by 10 K and the bandpass was set to 0.3–1000 Hz. The data were digitized at 4.3 kHz. Twenty responses were averaged (Power Lab, AD Instruments, Castle Hill, Australia).

3. Results

3.1. Focal macular cone ERGs in cCSNB

Representative focal macular cone ERGs recorded from a myopic control (38-year-old man; refractive error, −5.50 D) and the three patients with cCSNB are shown in the left panel of Fig. 1. The waveforms from the three patients are clearly different from those of the myopic control: the amplitudes of the a-waves are normal, but the amplitudes of the following positive wave are smaller than the b-wave of the myopic control (see also Table 2). These changes resulted in a reduced b-wave to a-wave (b/a) ratio. In addition, the implicit times of the a- and b-waves in

Table 2
Amplitudes and implicit times of focal macular ERGs (FMERGs) from three patients with complete type CSNB and 15 patients with myopic controls

	Amplitude (μV)			Implicit times (ms)	
	a-wave	b-wave	b/a ratio	a-wave	b-wave
Case 1	2.4	2.4	1.0	21.4	47.2
Case 2	1.9	2.9	1.56	28.0	46.8
Case 3	2.4	3.1	1.29	28.0	59.5
Myopic controls ($n = 15$)	2.0 ± 0.5	5.1 ± 0.9	2.51 ± 0.44	19.6 ± 1.7	40.9 ± 3.0

Data in myopic controls are expressed as the mean ± SD.

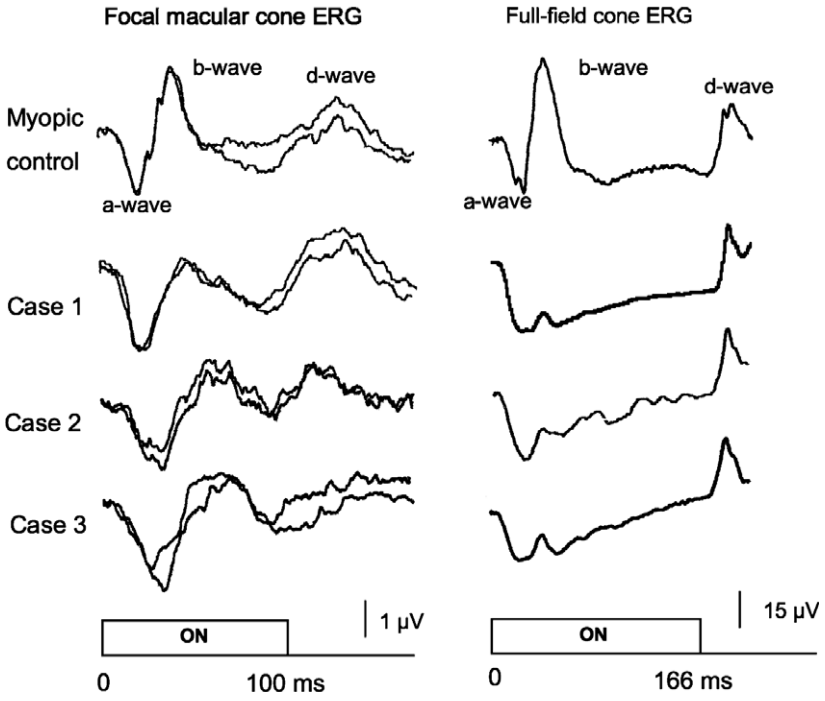

Fig. 1. Focal macular cone ERGs (left panel) and full-field ERGs (right panel) elicited by long duration stimuli recorded from a myopic control and three patients with complete-type congenital stational night blindness (cCSNB). Note that the amplitude ratios of the positive wave to the a-wave was <1.0 for the full-field ERG, but >1.0 for focal macular cone ERGs in the cCSNB patients.

cCSNB patients were prolonged (Table 2). The d-waves seen at the offset of the stimulus was not so prominent for both myopic controls and patients.

The full-field, photopic ERGs elicited by a long-duration stimulus (166 ms) from the same subjects are shown in the right panel of Fig. 1. In all three cCSNB patients, the b/a amplitude ratio was clearly <1.0 resulting in a "negative" ERG waveform.

3.2. Focal macular cone ERGs in monkey retina after APB

It is known that the on-response b-wave of the photopic long-flash ERG originates mainly from the neural activity of the cone depolarizing bipolar cells (DBCs) (Knapp & Schiller, 1984; Sieving et al., 1994). Based on the focal macular cone ERGs in the cCSNB patients, we thought that the function of cone on-pathway may be preserved to some degrees in the central retina of the cCSNB patients. To test this hypothesis, it was necessary to record the focal macular cone ERGs from the monkey retina after the cone on-pathway was completely blocked pharmacologically by APB, and to compare these waveforms with those from cCSNB patients.

The focal macular cone ERGs recorded from two rhesus monkeys before and after intravitreous injection of APB are shown in Fig. 2. After the APB injection, the a-wave amplitude became larger, and the peak time of the a- and the following positive wave became prolonged. The d-wave was slightly enhanced after APB. The ratio of the b-wave to the a-wave amplitudes became smaller than controls, but was still larger than 1.0 (monkey #1, 1.24; monkey #2, 1.33).

We initially interpreted this to indicate that remaining positive wave might be caused by an incomplete blockage of APB and thus injected more APB. However, the addition of APB did not change the waveforms of the focal macular cone ERGs, and the b/a amplitude ratio still remained greater than 1.0 even after increasing the APB concentration to twice the original concentration (2 mM).

The similarity in the waveforms between cCSNB patients and monkeys treated with APB indicated that the cone on-pathway seemed be completely blocked even in the central retina in cCSNB.

3.3. Multifocal on- and off-responses in cCSNB and APB-treated monkey

We also noted that the waveforms of photopic ERG with long duration stimuli were different between full-field cone ERGs and focal macular cone ERGs in cCSNB patients; the amplitude of remaining positive wave was still larger than that of the a-wave, whereas the amplitude ratio of the positive wave to the a-wave was always less than 1.0 for the full-field ERGs (Fig. 1). However, these differences in the waveform could be due to the different stimulus and recording conditions in the two methods. Therefore, we next compared these waveforms between the central and peripheral retinas directly in a patient with cCSNB. For

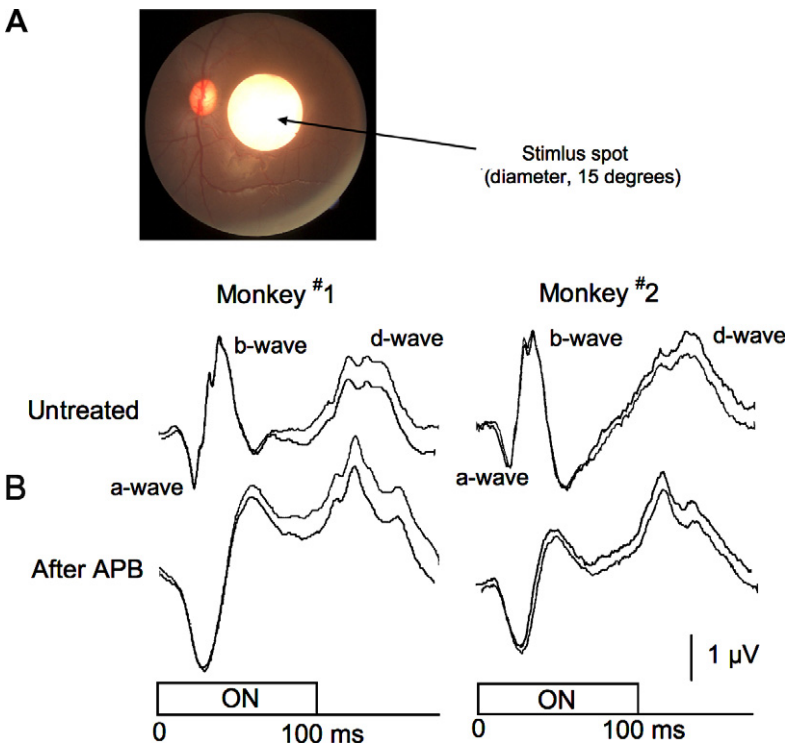

Fig. 2. Stimulus location and focal macular cone ERGs recorded from two monkeys. (A) Fundus photographs showing the stimulus spot. The 15° stimulus spot (diameter) was focused on the fovea. (B) Waveforms of focal macular cone ERGs before and after intravitreal injection of APB for two rhesus monkeys. Intravitreous concentration of APB was 1.0 mM.

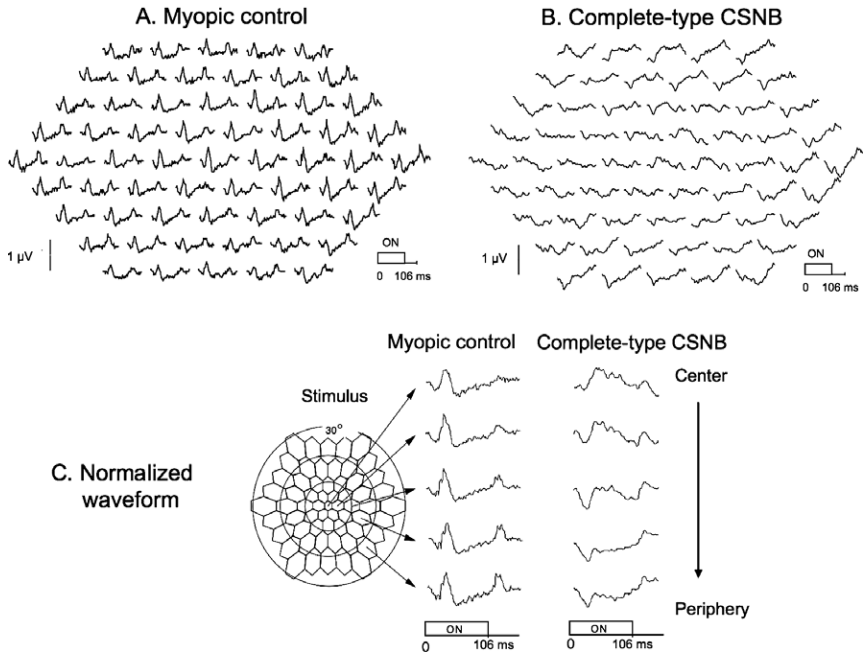

Fig. 3. Multifocal on- and off- responses using eight consequtive white frames. (A) Results from a myopic control. (B) Results from a patient with cCSNB (Case 1). (C) Normalized waveforms from five eccentric rings. Note that in cCSNB, the amplitude ratio of the positive wave to the a-wave is >1.0 in the central retina, but gradually become smaller towards to the periphery.

this purpose, we recorded the multifocal on- and off-responses (Kondo & Miyake, 2000; Kondo et al., 1998).

The multifocal on- and off-responses recorded from a representative myopic control (A), and a patient with cCSNB (B, Case 1 of Table 1) are shown in Fig. 3. It was clear that when compared to myopic control, the amplitudes of the positive wave are reduced at all locations in cCSNB. However, the amplitude of the positive wave is relatively preserved in the central retina, and the relative amplitude of the positive wave to the a-wave became small from the center to the periphery. The changes in the waveforms were clearly seen when the responses were grouped for each eccentric rings (Fig. 3C). The remaining positive wave is well preserved in the central retina, but gradually became smaller towards the peripheral retina. The amplitude ratio of the positive wave to the a-wave was >1.0 in the central retina, but <1.0 in the periphery. These findings are consistent with our combined findings of full-field ERG and focal macular cone ERGs in patients with cCSNB.

We also confirmed these results in a monkey retina after treatment with APB (Fig. 4). The remaining positive response was relatively large in the central retina, but the relative ratio of the positive wave to the a-wave gradually became smaller towards the periphery (Fig. 4C). These findings were quite similar to those in patients with cCSNB.

3.4. Origin of the remaining positive wave of photopic ERG at central retina

One question that still remained was the origin of the remaining positive component of the focal macular cone ERG seen even after blockage of cone on-pathway. To study the retinal origin of this component, we added PDA to block the neural activities of post-synaptic off-pathways and horizontal cells in monkeys. Fig. 5 shows the changes in the waveforms of photopic ERG with long duration stimulus before and after APB and PDA application for full-field and focal macular cone ERGs in a rhesus monkey. In this experiment, the same stimulus (30 cd/m^2) and background (3 cd/m^2) intensities were used for both full-field and focal macular cone ERGs, because the waveform of photopic ERG is dependent on the stimulus and background intensities (Kondo et al., 2000; Ueno, Kondo, Niwa, Terasaki, & Miyake, 2004). We found that after the PDA injection, the remaining positive wave of focal macular cone ERGs completely disappeared (lower traces of Fig. 5).

4. Discussion

We compared the waveform of focal macular cone ERGs recorded from cCSNB patients with those from APB-treated monkeys, and found that the waveforms were very similar: the amplitude of the a-wave was normal or slightly larger than control; a positive wave was still present after the a-wave, and the amplitude of this positive wave was larger than that of the a-wave; and the implicit time of the positive wave was delayed. These similarities in the waveform of focal macular ERG between the cCSNB patients and APB-treated monkeys suggested that the cone on-pathway is nearly completely blocked even in the central retina of the cCSNB patients.

Although the waveform of the a-wave and the following positive wave were very similar for cCSNB patients and

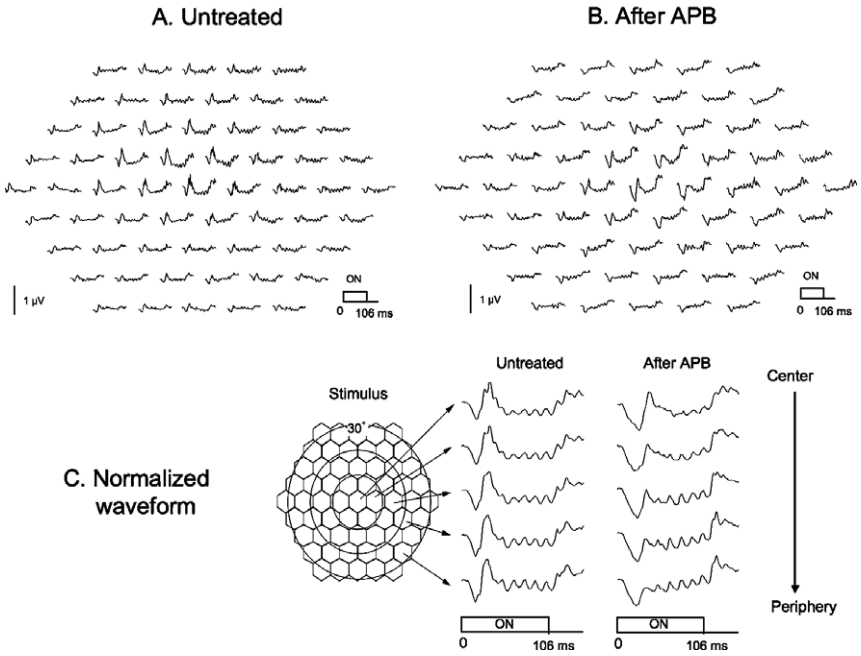

Fig. 4. Multifocal on- and off-responses before and after intravitreous injection of APB in a rhesus monkey. Intravitreous concentration of APB was 1.0 mM. Unstretched hexagonal elements (same size) are used for these monkey experiments. (A) Multifocal ERGs before APB. (B) Multifocal ERG after APB. (C) Normalized waveforms from five eccentric rings after APB application. The waveform after APB are very similar to those recorded from cCSNB patients.

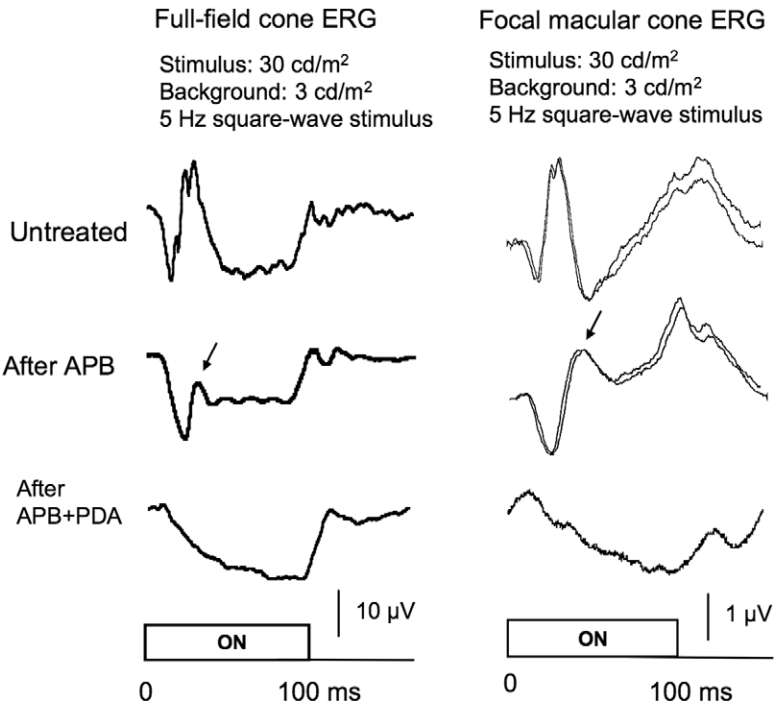

Fig. 5. Comparison in the waveforms of photopic ERG with long duration stimulus before and after APB and PDA application for full-field and focal macular cone ERGs in a rhesus monkey. Five hertz square-wave flickering stimulus of 30 cd/m^2 was presented on a background illumination of 3 cd/m^2 for both ERGs. After APB and PDA, the remaining positive wave at stimulus onset disappears completely for both ERGs (arrows).

APB-treated monkeys, the waveform of the d-wave at the offset of the stimulus was slightly different: the amplitude of the d-wave of the focal macular cone ERG was enhanced after the intravitreal injection of APB in monkeys, whereas the d-wave of focal macular cone ERG in cCSNB patients was not larger than that of myopic control. We do not know the reason for this difference in the waveform of the d-wave between the cCSNB patients and

APB-treated monkeys. However, it may be partly due to the differences between inherited human disease and the pharmacological animal model.

Although our electrophysiological study showed functional similarity between the retina of patients with cCSNB and APB-treated monkey retinas, there still remained the question of whether the retinal on-pathway is completely blocked in the retina of patients with cCSNB. Two psychophysical studies suggested that rod on-pathway may not be completely blocked in cCSNB patient (Allen et al., 2003; Young, Price, & Harrison, 1986).

We also found that even after a complete blockage of the cone on-pathway, there still remained a sizeable positive wave of the cone ERG in the central retina. The multifocal ERG results also demonstrated that the amplitude ratio of the positive wave to the a-wave was maximal in the central retina, and became gradually decreased towards the peripheral retina in a cCSNB patient and an APB-treated monkey supporting our combined findings of the full-field ERGs and focal macular cone ERGs. These results indicated that there is a unique spatial variation in the waveform of the cone ERGs. Other pharmacological studies in monkeys (Hare & Ton, 2002; Hood, Frishman, Saszik, & Viswanathan, 2002) also showed several spatial variations in the waveform of the cone ERGs using multifocal ERG technique, but they did not separate the on- and off-responses.

By adding PDA to APB, we found that the remaining positive wave of the cone ERG, which was seen even after blocking the cone on-pathway, originated from post-photoreceptor neurons which are sensitive to PDA, i.e., retinal neurons of the off-pathway or horizontal cells (Fig. 5). However, we could not identify exactly which retinal neurons/circuits contributed to this positive component. To identify the exact origin of this positive wave, further studies are needed using other pharmacological agents which affects specific retinal neurons.

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