FULL PAPER *Surgery*

Electroretinography Using Contact Lens Electrode with Built-In Light Source in Dogs

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ABSTRACT. Electroretinography (ERG) is an effective method for the diagnosis of retinal disease. In the dog, dependable ERG recording is difficult without the use of an expensive device like a Ganzfeld full-field stimulator. The International Society for Clinical Electrophysiology of Vision has defined the standard flash stimulus condition (SF) and evaluation of the retina using the b/a ratio in humans. In dogs, evaluation using the b/a ratio has not been reported, whereas the intensity of SF has been defined. In this study, we performed a convenient ERG recording method using a contact lens electrode with a built-in light source (LED-electrode), and confirmed SF as reported previously. ERG recordings were performed on 15 healthy beagle dogs under sedation. We performed bilateral ERG at 12 different intensities after 30 min dark adaptation. After 10 min light adaptation, we recorded single flash cone and flicker cone response using the SF determined in this study. In this study, SF of 3.0 cd/m^2/sec (6,000 cd/m^2, 0.5 msec) resulted in b/a=2. The intensity for rod response that recorded only the b-wave was 0.0096 cd/m^2/sec (80 cd/m^2, 0.12 msec). We could achieve ERG for each response easily and smoothly under sedation, and without general anesthesia. Using an LED-electrode, we could perform more quantitative and reproducible ERG examinations than with traditional methods. We propose that the b/a ratio is the most useful parameter in ERG reporting for evaluating retinal function.

KEY WORDS: canine, contact lens electrode, electroretinography, rod response, standard flash.

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Electroretinography (ERG) is a valuable non-invasive tool in the evaluation of retinal function, and it requires no subjective response from the patient [4, 14, 19, 24, 25]. ERG has been used to detect diseases, evaluate the efficacy of treatment and determine surgical indications, enabling doctors to detect subliminal change before it becomes apparent by direct observation [3, 6, 8, 13, 18, 19]. Especially in the primary case of progressive diseases like progressive retinal atrophy (PRA), periodic quantitative examination is required for diagnosis [8, 10, 12, 15, 19]. Evaluation by ERG of retinal function in the presence of a dense cataract when the fundus is not visible is a valuable clinical use [3, 13, 16]. Especially in veterinary medicine, ERG is more important than in human medicine, because the patients cannot express their subjective symptoms to the doctor.

ERG records changes in membrane potential and ion movement in retinal cells when exposed to light. It records the early receptor potential, a-wave, oscillatory potential, b-wave, c-wave and d-wave in order of appearance. The early receptor potential originates in photoreceptors, the c-wave originates in retinal pigment epithelium cells, and the d-wave in the shape of the off response has not been utilised in clinical diagnosis. In diagnosis, the a-wave originating in photoreceptors, the oscillatory potential originating in amacrine cells, and the b-wave originating in Muller cells and bipolar cells are usually utilised [4, 6, 18–20, 24, 25].

The standard technique for diagnosis and differentiation of retinal disease in small animals by ERG using Ganzfeld stimulus has been reported [12]. In humans, ERG examination is performed according to the standard protocol established by the International Society for Clinical Electrophysiology of Vision (ISCEV) [7]. The ISCEV defined the standard flash (SF), and the ERG a-wave amplitude recorded by the standard flash is half of the b-wave amplitude (b/a=2) [7]. Evaluation of retinal function using the b/a ratio is commonly used in human ophthalmology, because in cases with dense opacity observed in the anterior segment and vitreous body, the b/a ratio is an indicator of disorders of the retina. Despite proposed guidelines of a previous paper for standard flash of 2–3 cd/m^2/sec using Ganzfeld stimulus, evaluation of the retina using the b/a ratio has not been established in the dog [12]. In this study, we applied a different stimulator for veterinary use, and clarified the standard flash intensity using this new device. In the dog, the standard flash producing b/a=2, as defined ISCEV, has not been established, so we recorded ERG at various stimulus strengths in clinically healthy beagle dogs and ascertained the stimulus strength producing b/a=2.

The European College of Veterinary Ophthalmology (ECVO) recommended the following parameters for diagnosis of photoreceptor disorders: 1) rod response during dark adaptation, 2) mixed rod and cone response, 3) single flash light-adapted cone response, and 4) flicker cone response. This protocol is intended to test for inherited photoreceptor disorders [12]. PRA, a typical inherited photoreceptor disorder in dogs, is classified into three types: progressive retinal atrophy, central progressive retinal atrophy, and hemeralopia [13, 16]. Separate rod and cone recording is important for the diagnosis of these retinal dis-

orders [12, 13, 16]. Rod function is recorded 100 times weaker than the standard flash in the dark adapted eye. Cone function is recorded in two ways: single flash cone response using SF with background light, and flicker cone response using a rapidly repeated stimulus [7, 12]. We have also investigated the intensity rod ERG, and recorded the cone response in two ways using the standard flash determined in this study.

ERG was introduced clinically by Riggs and Karpe who invented the contact lens electrode [14, 24, 25]. In the 1960s, Rubin applied ERG to differentiate between retinal and other diseases in veterinary ophthalmology [16]. When ERG using an external light source is used, there is the possibility of variation in stimulus among laboratories. Goldmann and Weekers developed a stimulus device called the Ganzfeld dome, which is a semicircular machine with a diffuser built inside, allowing stimulation of the entire retina [11, 25]. Following the development of the Ganzfeld dome, separate recording of rod and cone responses became possible [11]. The Ganzfeld dome, however, has some defects in veterinary ophthalmological use: 1) it is a large and expensive system that is difficult to install in every animal hospital; 2) bilateral stimulating recording is difficult; 3) fixation of animals for recording is difficult; and 4) the head of the dog has to be kept within a sphere of 60 cm diameter [17, 24, 25]. So the Ganzfeld dome is not practical for use in private veterinary hospitals.

A contact lens electrode with a built-in high luminance diode (LED-electrode) has been recently developed, which may enable ERG to be performed more economically in terms of space and cost [21–23]. The LED-electrode has three or four built-in high luminance diodes, enabling creation of the same condition as a Ganzfeld dome when placed on the cornea in humans [21–23].

In this study, we performed ERG recording on healthy beagle dogs using an LED-electrode. We ascertained the standard stimulus strength in the dog using this device.

MATERIALS AND METHODS

Fifteen clinically healthy beagle dogs were used. The dogs underwent ophthalmic examinations (pupillary light reflex, menace reflex, Schirmer tear test, tonometry, slit lamp examination and funduscopy), complete blood count and biochemical blood examination (glucose, total cholesterol, BUN, total bilirubin, AST, ALT and creatinine) before this study. All dogs had normal results in all these examinations. The ranges of body weights and ages were 6.8 to 11.0 kg (median: 10.2 kg) and 1 to 3 years old (median: 2.0 years old), respectively. Fourteen were male and one was female.

An ERG measuring instrument, a portable ERG LE-3000 (TOMEY Corporation, Nagoya, Japan), was used. The LE-3000 combines a stimulus instrument, amplifier and recorder. The frequency band is from 0.3 to 300 kHz. We used an ERG contact lens electrode with built-in diode light sources (LED-electrode H2000, Kyoto Contact Lens, Kyoto, Japan) as active electrodes (Fig. 1). We used two

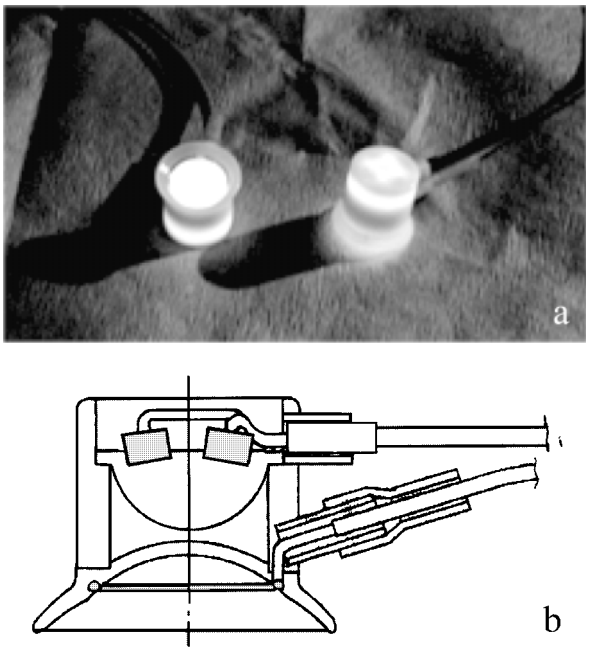

Fig. 1. Contact electrode with built-in diode light source. (a) Photograph of LED-electrode (flashing). (b) Schema of LED-electrode in section. Three or four light-emitting diodes are built into the contact electrode.

sizes of LED-electrode, outer diameter 20 or 16 mm and diameter of stimulus surface 12 or 10 mm. The larger one had four built-in diodes and the smaller one had three. We used a needle-type electrode as the reference electrode, and a plate-type electrode as the earth electrode.

Examinations were performed under dim red light in a dark room. The pupils were dilated with 0.5% tropicamide and 0.5% phenylephrine hydrochloride (Mydrin-P, Santen, Osaka, Japan). After producing mydriasis, animals were dark-adapted for more than 30 min in a dark room. ERG was performed under sedation with a combination of 0.01 mg/kg medetomidine (Domitor, Meiji, Tokyo, Japan), 0.15 mg/kg midazolam (Dormicam, Yamanouchi, Tokyo, Japan), and butorphanol 0.025 mg/kg (Stadol, Bristol-Myers, Tokyo, Japan), injected intravenously. The LED electrode was positioned on the cornea after topical anesthesia with 0.4% oxybuprocaine hydrochloride (Benoxil ophthalmic solution 0.4%, Santen, Osaka, Japan) and protection with 0.15% methylcellulose (SCOPISOL 15, Takeda, Osaka, Japan). A needle-type electrode was positioned subcutaneously in the front region as the reference electrode. The electrodes were positioned in the configuration of an equilateral triangle formed by LED electrodes on each eye and the reference electrode. A plate-type electrode was placed at the tip of the ear as the earth electrode (Fig. 2). We performed ERG at twelve gradations of stimulation in the order of weaker to stronger degree (Table 1). We performed measurements three times at each condition. The interval between flashes was more than 30 seconds, in order not to

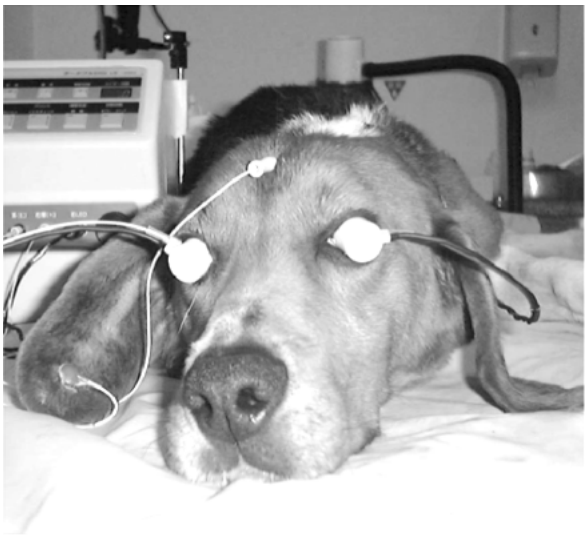

Fig. 2. Equipment of electrodes. An LED electrode was positioned on the cornea under topical anesthesia and protection with 0.15% methylcellulose. A needle-type electrode was positioned subcutaneously in the frontal region as a reference electrode. The electrodes were positioned in the configuration of an equilateral triangle with an LED electrode on each eye and the reference electrode. A plate-type electrode was placed at the tip of the ear as the earth electrode.

light adapt the rods.

After 10 minutes' light adaptation, we recorded a single flash cone ERG and 30 Hz cone flicker ERG using the SF determined in this study. These responses were recorded under background light of 25 cd/m^2.

Wilcoxon's signed-rank test was used for statistical analysis of the reproducibility of ERG data. The statistical significance of differences was determined with $p<0.05$ as the minimum level of acceptable significance.

RESULTS

In all animals, sedation was adequate to perform bilateral simultaneous ERG examinations easily.

The results are shown in Table 1, as the mean of 30 eyes for each intensity. There was no significant difference between the first and second measurements, between the first and third measurements, and between the second and third measurements in each condition.

Waveform change by increasing stimulus strength is shown in Fig. 3. The a-wave was not clear until intensity no. 3. In contrast, the b-wave was not observed at intensity no. 1, but was clear from intensity no. 2. With an increase in stimulus strength, both a- and b-wave amplitudes increased, but both a- and b-wave amplitudes unchanged at intensities no. 11 and no. 12 in spite of increasing stimulus strength. With an increase in stimulus strength, the b/a ratio decreased. Intensity no. 9 (3.0 cd/m^2/sec) was the standard flash as defined by the ISCEV and ECVO [7, 12]. In this study, the standard flashproducing b/a=2 was also intensity no. 9.

We recorded single flash cone ERG and flicker cone ERG, under 25 cd/m^2 background light, at an intensity of 3.0 cd/m^2/sec which was determined as the SF in this study after 10 minutes' light adaptation. We could also perform reproducible ERG examinations very smoothly for single flash cone response and flicker cone response. The amplitude of single flash cone ERG was 54.98 ± 13.55 μV (mean ± SD) and that of 30Hz flicker ERG was 76.06 ± 13.20 μV (mean ± SD). There was no significant difference between the first and second measurement, first and third, and second and third under each condition. Representative waveforms of the single flash cone ERG and 30Hz flicker ERG are shown in Fig. 4.

DISCUSSION

In this study, we performed ERG using an LED electrode and established the standard stimulation intensity. The LED electrode enabled quantitative and reliable measurements of

Table 1. Intensity, a- and b-wave amplitude and b/a ratio at each intensity

Intensity no.	Luminance (cd/m^2)	Stimulus time (msec)	Intensity (cd/m^2/sec)	Amplitude of a-wave (μV)	Amplitude of b-wave (μV)	b/a ratio
1	25	0.12	0.003	4.43 ± 4.83	12.44 ± 6.74	
2	25	0.3	0.0075	8.16 ± 6.50	63.35 ± 47.72	
3	80	0.12	0.0096	7.07 ± 4.99	88.46 ± 56.22	
4	120	0.12	0.0144	9.99 ± 6.39	90.12 ± 51.09	9.33 ± 7.43
5	240	0.12	0.0288	10.86 ± 6.30	133.91 ± 54.79	12.56 ± 8.11
6	600	0.12	0.072	16.01 ± 6.93	150.82 ± 29.62	9.47 ± 3.92
7	600	0.5	0.3	36.77 ± 14.99	154.74 ± 39.69	5.27 ± 4.35
8	3000	0.3	0.9	74.53 ± 28.54	191.06 ± 55.14	2.91 ± 1.55
9	6000	0.5	3.0	121.67 ± 29.83	233.00 ± 53.07	1.96 ± 0.34
10	9000	1	9.0	154.96 ± 43.33	252.09 ± 55.48	1.70 ± 0.38
11	12000	3	36.0	184.48 ± 43.82	280.48 ± 55.62	1.56 ± 0.30
12	20000	10	200.0	186.09 ± 47.60	279.65 ± 56.75	1.54 ± 0.24

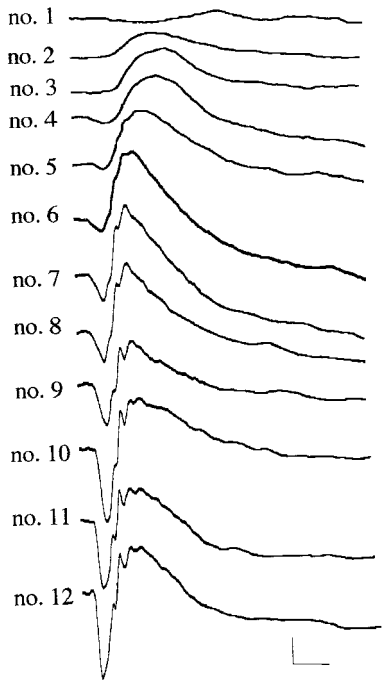

Fig. 3. Change in waveform. Calibration: horizontal 25 msec, vertical 25 μV. The waveforms are shown at intensities no. 1 to no. 12. The a-wave was not clear until intensity no. 3 (0.0096 cd/m^2/sec), and was clearly visible from condition no. 4 (0.0144 cd/m^2/sec). The b-wave was not visible only at intensity no. 1 (0.003 cd/m^2/sec), and was clearly visible from intensity no. 2 (0.0075 cd/m^2/sec). With increasing stimulus strength, both a- and b-wave amplitudes increased. Both a- and b-wave amplitudes were unchanged at intensities no. 11 (36.0 cd/m^2/sec) and no. 12 (200.0 cd/m^2/sec) in spite of increasing stimulus strength. With increasing stimulus strength, the b/a ratio decreased. We detected b/a=2 at intensity no. 9 (3.0 cd/m^2/sec).

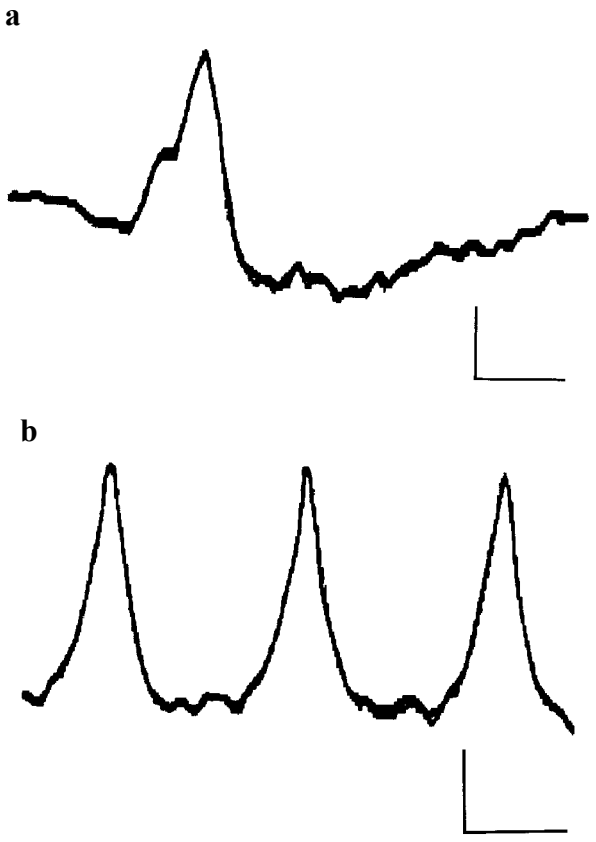

Fig. 4. Representative waveforms of cone function ERG (a) and cone flicker ERG (b). Calibration: horizontal 10 msec, vertical 10 μV. The amplitude of cone function was 54.98 ± 13.55 (mean ± SD) and that of cone flicker waas 76.06 ± 13.20 (mean ± SD).

ERG in dogs.

The most important result of this study was the establishment of the standard stimulus intensity using a new LED-electrode device for the field of veterinary ophthalmology. Full-field reproducible ERG is important in the diagnosis or evaluation of retinal diseases [7, 12]. Especially in progressive diseases like PRA, periodical examination is needed for their diagnosis [8, 10, 12, 15, 19]. Repeated recordings of the same dog throughout treatment are important for evaluating drug efficacy [25]. Comparison of the eye from a different dog presenting with similar symptoms is also important in the differential diagnosis of retinal disease.

In this study, the intensity producing a b/a ratio of 2 was 3.0 cd/m^2/sec in the dog using the LED-electrode. In humans, the ISCEV established standard flash is b/a=2 [7]. In dogs, the ECVO defined standard flash is 2.0–3.0 cd/m^2/sec when using a Ganzfeld stimulator [12]. In this study, we established the standard stimulus based on examinations in dogs using the LED-electrode. The a-wave was hardly recorded at intensities no. 1 to no. 3, while the b-wave was recorded from intensity no. 2. The a-wave amplitude began to respond from intensity no. 4, increased in accordance with the increase of amplitude, and both a- and b-wave amplitude reached a maximum at intensity no. 11. The threshold of the a-wave is reported to be 100-fold higher than that of the b-wave, under dark adaptation or low light adaptation [1, 2, 5]. Thus, at intensities no. 1 to no. 3, the a-wave with a high threshold was barely recordable recorded, and only the b-wave with a low threshold was recorded. Both a- and b-wave amplitudes reached maximums at intensities no. 11 and no. 12. It was considered that these intensities were limits of the a- and b-waves. With increasing stimulus strength, the b/a proportion decreased, and at condition no. 9, b/a was 1.96. The ISCEV established standard flash is b/a=2 in humans [7]. In this study, at intensity no. 9, in which luminance was 6000 cd/m^2 and stimulus time was 0.5 msec (3.0 cd/m^2/sec), induced a b/a ratio of 2. This condition was fortuitously similar to that in humans [7]. Thus, the equipment for human ERG might also be applicable to the field of veterinary ophthalmology. The intensity was also the same as that defined by the ECVO [12].

Rod response separated from cone response is important in the field of veterinary ophthalmology. In this study, the condition at which the a-wave was barely recordable was condition no. 3 (0.0096 cd/m^2/sec) $\log_{10}$=2.5 weaker than the standard flash (no. 9), at which only the b-wave was recorded clearly. As an intensity for recording rod ERG, the stimulation condition was similar to that established for human ophthalmological examination [7]. The condition for rod response defined by the ECVO was 100 times lower than that of the standard flash, 0.02–0.03 cd/m^2/sec [12]. The intensity for rod ERG determined in this study was lower than that defined by the ECVO. The reason for this difference may be the different stimulator. In a previous paper, a Ganzfeld dome was used, whereas in this study we used an LED-electrode. The globe moves down under anesthesia or sedation in dogs, so we think that the external stimulation intensity will not be sufficient using an external light source like a Ganzfeld dome, whereas using an LED-electrode, the light source can move in conformity with movement of the animal's eye. We considere that the LED-electrode enables more authentic full-field stimulation than the Ganzfeld dome in dogs under anesthesia or sedation. Thus, that using an LED-electrode enables recording of rod response with a weaker stimulus.

As a standard, we would like to propose that the b/a ratio is also an important parameter in ERG reporting. ERG is often performed in dogs with opacity of the ocular media, for example, due to cataract, but ERG is affected by such opacity [19, 24, 25]. A previous paper reported that ERG recording should include the following parameters: a- and b-wave amplitudes, implicit time, and a plot of the dark adaptation curve [12]. Considering the effects of opacity of the ocular media on ERG, we consider that ERG recording should include not only a- and b- wave amplitude, but also the b/a ratio.

We were able to perform reproducible ERG examinations very smoothly for single flash cone ERG and 30 Hz cone flicker ERG. The ECVO proposed a short protocol for evaluation of gross retinal function in animals that are about to undergo cataract surgery or, for instance in cases where the diagnosis of retinal versus central blindness needs to be evaluated [12]. They recommended the following parameters: 1) retinal function in ambient light using SF, 2) turn off the light and test retinal function within the first minute of dark adaptation using SF, and 3) test retinal function again after 5 min of dark adaptation using SF [12]. We propose adding flicker cone ERG to the aforementioned parameters recommended by the ECVO, because dark adaptation is not needed for flicker cone ERG, and this test is useful for screening of gross retinal function.

The LED-electrode system is very useful for veterinary clinics. The LED-electrode enabled us to perform simple and reliable recording of full-field ERG. Today, the Ganzfeld dome is widely used for full-field ERG in veterinary clinics as well as in human clinics [7, 11, 12, 14]. However, the Ganzfeld dome has some defects: 1) it is a large and expensive system that is difficult to install in every animal hospital; 2) bilateral stimulating recording is difficult; 3) fixation of the animals for recording is difficult; and 4) the dog's head need to be kept within a sphere of 60 cm diameter [17, 24, 25]. The LED-electrode has three or four built-in high luminance diodes, and enables creation of the same condition as the Ganzfeld dome when placed on the cornea in humans [21–23]. The LED-electrode enables a more economical ERG in terms of space and cost [21–23]. Having a fully opened eyelid is also important when an external light source is used. Keeping the dog's eyelid open is needed throughout recording using a Ganzfeld system. In contrast, using an LED-electrode does not require opening the eyelid during the examination, because the LED-electrode itself opens the eyelid and protects the cornea. In addition to these advantages over the usually used external light source systems, the LED-electrode is compact compared to the Ganzfeld dome system, which needs stimulus calibration before every ERG recording. The luminance meter of the Ganzfeld system needs to be calibrated [7]. In contrast, the LED-electrode system is calibrated automatically and easily with equipment attached to the LE-3000. Furthermore, this new device enables reproducible ERG examination under mild sedation, because the LED-electrode can move in conformity with movement of the animal's eyes. We found that mild sedation rather than general anesthesia was sufficient for ERG measurement using an LED-electrode in dogs. In animals, general anesthetization was thought to be important in order to prevent artifacts through involuntary muscle movement [4, 12, 19]. In this study, we obtained reliable ERG using an LED-electrode under sedation (with a combination of medetomidine, midazolam and butorphanol). Medetomidine produces sedation, analgesia and muscle relaxation, midazolam produces muscle relaxation and weak sedation, and butorphanol produces inhibition of vomiting due to medetomidine [9]. We achieved immobilization of animals with this combination and were able to perform ERG examination smoothly, and animals did not need to be restrained by hand.

In veterinary clinics, ERG is used to evaluate retinal function in animals with cataract, glaucoma, PRA, suddenly acquired retinal degeneration, and other conditions [3, 4, 8, 10, 12–14, 19]. The recording methods, stimulus strength, dark adaptation, methods of sedation or anesthesia etc. seem to differ between institutions. Using an LED-electrode it has become possible to perform more quantitative and reproducible ERG examinations. It should also be possible to evaluate the progression or change of a disease and the effects of therapy. In this study, we used white LED, but we could have changed it to red, green or blue LED. Without using a color filter, the use of a colored LED-electrode would easily allow evaluation of cone function in detail. We used only beagle dogs ranging in age from 1 to 3 years old, so it will be necessary to record ERG in other breeds and ages.

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