

Editorial

Electroretinography in veterinary medicine – easy or accurate?

In 1865 the Swedish electrophysiologist Fritiof Holmgren was the first person to measure the sum of retinal action potentials in response to light stimulation.¹ The work was carried out on excised frog eyes. Some years later he found, by removing the anterior segment and placing the corneal electrode directly on the retinal surface, that the retina itself was the origin of the response. At around the same time, Dewar showed that the electrical potentials could be recorded from an intact animal eye by applying the reference electrode on the skin. He also reported on the first human electroretinogram (ERG)² for which the recording and reference electrodes were connected to a galvanometer. He used an elaborate instrumental set-up, but never published the resulting curves. Granit did extensive studies with improved techniques that led to the component analysis of the ERG that is still in use.³ Karpe introduced electroretinography as a routine diagnostic test for use in clinical ophthalmology and he was one of the first to emphasize the importance of ERG as an objective record of retinal function.⁴

Since then, the development of clinical electrophysiology has moved forward tremendously, but many of the basic findings are still valid. The various ERG diagnostic techniques in use today enable doctors and researchers to clinically evaluate most parts of the retina and visual pathways in a variety of species. Different types of retinal disorders have been characterized, including developmental abnormalities, toxic influences, inflammatory and infectious etiologies and a wide variety of vascular and degenerative diseases.

Different types of electrophysiologic examination techniques and methods of analysis have been developed and prove useful in the work-up of various disease entities. Some of these include focal and multifocal ERGs, pattern ERGs, on-off ERGs, DC- and double flash recordings, analysis of early receptor potential, bright flash ERGs, analysis of the leading edge of the a-wave, analysis of retinal sensitivity, and the recording of scotopic threshold responses.

When examining human patients with hereditary retinal disorders some innovations have had major influences. Gouras noted the importance of isolating the separate rod and cone responses as a basis for analyzing retinal potentials.⁵ Berson studied the temporal aspects of the ERG and stressed the usefulness of assessing b-wave implicit times in progressive retinal hereditary disease.⁶ Goodman, Gunkel, Ruedeman and Noell reported that it was possible to measure low amplitude responses in patients with early retinitis pigmentosa (RP)^{7,8}, a disease comparable to canine and feline progressive retinal atrophy (PRA). For this group

of diseases the use of full-field stimulation (also called Ganzfeld stimulation), and computer averaging was advocated. Further, Berson described that by using an analog narrow band filter, combined with full-field stimulation and computer averaging, the lower amplitude limit could be extended down to 0.05 microvolts.⁹ Reproducible and stable recordings were obtained, a prerequisite for obtaining reliable ERG results.

Significant progress in visual electrodiagnostics was made when standardization of ERG procedures was initiated by the International Society for Visual Electrophysiology of Vision (ISCEV). In 1989, Marmor and collaborators published the first human standard for ERG recordings.¹⁰ Simple procedures were recommended, utilizing either custom-made or commercially available equipment, which included five specific responses from the rod and cone systems, separately, from both rods and cones together, and the recording of the oscillatory potentials. The published human standard (last revised in 1999)¹¹ facilitated reporting of specific responses and comparison of results between laboratories, on an international basis.

It has become obvious during the last decade that there is also a need for similar standardization of ERG procedures to take place in veterinary medicine.¹² A group was appointed by the European College of Veterinary Ophthalmology to finalize recommendations for ERG procedures in the dog. The committee's recommendations were first reported at an international meeting on veterinary visual electrophysiology in Vienna, May, 2000, and have since been published in *Documenta Ophthalmologica*,¹³ the official journal of ISCEV.

Clinical practice requires a rapid and simple ERG procedure to be readily available in a variety of situations. For example, this type of ERG is an integral part of the presurgical work-up for cataract surgery when funduscopy is prohibited by the presence of mature cataracts. Another such need arises when a pharmaceutical company needs to screen for or characterize toxic effects on the retina of a newly developed compound. Still another example is when a breeder wants to differentiate between normal Abyssinian cats and those that will develop PRA in future years (Fig. 1a,b). In the research field there is a need to critically evaluate various treatment regimes, such as the effect of gene transfer in the Briard dog (Fig. 2). These examples illustrate the need to establish at least two types of ERG protocols: one that is efficient and practical for use in a pure clinical situation; another that utilizes a more labor-intensive, meticulous procedure which can differentiate rod and cone function. The latter technique makes it possible to calculate various ERG parameters, such

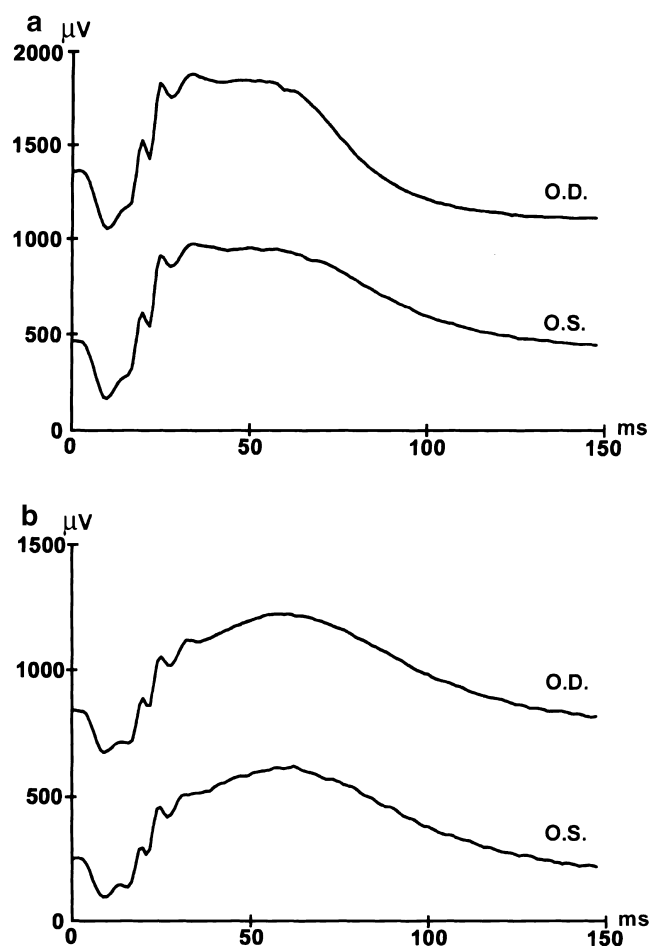


Figure 1. (a) Full-field bilateral ERGs of an 18-month-old normal Abyssinian cat after 2 h of dark adaptation. The recordings depict the response to 20 microseconds of 2 cds/m² white light stimulus. (b) Same recording conditions for an 18-month-old cat that is homozygous for hereditary retinal degeneration but still has a normal appearing fundus. Note the differences between the normal and affected cat in a- and b-wave amplitudes and b-wave timing, and also in waveforms.

as timing, amplitude and wave-form characteristics of the rod and cone ERG, respectively, in order to obtain a more precise evaluation of retinal function and diagnosis.

The published ERG recommendations for dogs (also useful for cats) in *Documenta Ophthalmologica* takes both of these needs into account. Basically, two types of procedures are described. One type is a rapid ERG examination procedure that determines whether a response is present or absent and is used mainly before cataract surgery or for the diagnosis of specific blinding disorders in the dog, such as Sudden Acquired Retinal Degeneration (SARD). The other type of ERG is the method used to diagnose generalized, often hereditary, retinal disease, or to characterize a retinopathy of unknown origin. The second method includes a minimum of four required procedures and does not preclude that more extensive investigations can be performed. To assure accurate result comparison among different laboratories, the four procedures recommended should also be standardized as to

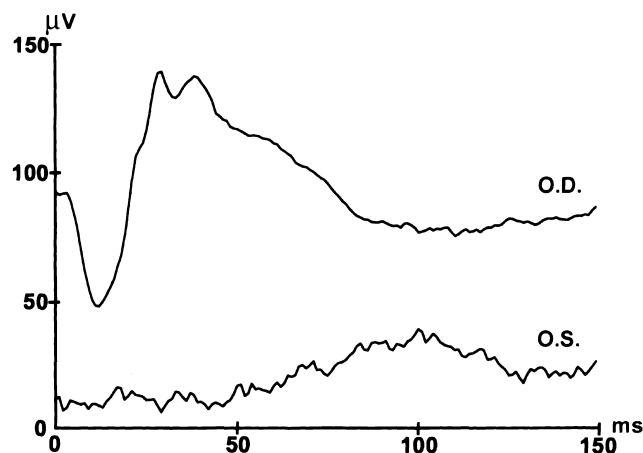


Figure 2. Full-field bilateral ERG from a mixed-breed dog affected with the RPE65 null mutation.¹⁴ The right eye (upper recording) was treated by gene transfer 3 months before the recording. Note the normal appearing ERG waveform in the right eye compared to the untreated left eye (lower recording).

lighting conditions prior to induction of general anesthesia and the type of anesthesia used for the ERG procedure. Equally important is that every laboratory which aims to perform the second, more involved ERG procedure establishes normal values for ERG timing, amplitude and wave-form parameters from age- and breed-matched controls of their test animal. This latter prerequisite may be difficult to obtain and illustrates that these procedures will probably be accomplished by specific retinal electrophysiologic units working in referral situations.

A quick summary of the two types of recommended ERG protocols are as follows:

Type I: Short ERG protocol

The dog is prepared in ambient light.

- 1 Test retinal function in ambient light using a white standard flash (SF = 2–3 cd · s · m⁻²).
- 2 Turn off the light and test retinal function within the first minute of dark adaptation using white SF.
- 3 Test retinal function again after 5 min of dark adaptation using white SF.

Type II: 'Diagnostic' ERG protocol

The dog is prepared in ambient light after which the light is turned off.

- 1 Dark adapt for 20 min while evaluating rod function and the dynamic process of dark adaptation, every 4 min using two log units below SF using white light.
- 2 Test the mixed rod and cone response using white SF.
- 3 Light adapt for 10 min using white background light, intensity 30–40 cd · m⁻², then test for cone function.
- 4 Perform the cone flicker test using 30 Hz of flickering white light.

If needed, the oscillatory potentials can be extracted from the mixed rod and cone response (see Type II protocol, #2 above).

Retinal electrophysiology is a fascinating discipline. Diagnostic ERGs provide the vision scientist and clinical ophthalmologist with a noninvasive and objective evaluation of retinal function. Let us not misuse this fantastic tool. I would submit to the veterinary ophthalmology community that it is both appropriate and timely for our members to decide which ERG protocol is most appropriate for their professional needs and goals. Type I will indicate, in most cases, if the patient's retina is functioning; type II requires breed and age-matched controls and the precise calibration of equipment and procedures, as well as an understanding of basic retinal physiologic processes. My personal opinion is that both types of protocols are needed in veterinary ophthalmology, and individuals or groups of ophthalmologists working together should decide whether to offer Type I or both Type I and II ERGs in their practice(s). For those committing to performing only Type I, then referral centers performing type II ERGs should be identified as sites where the more comprehensive procedures are routinely performed, enabling researchers to have a more focused approach to the elucidation of retinal disease.

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