Electroretinography in dogs: a review

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ABSTRACT: Electroretinography (ERG) in the form of full-field, flash ERG is the most commonly used technique in veterinary ophthalmology for diagnosing the functioning of the outer retina. Under light stimulation spatially distributed different cell types within the retina produce time-varying electric responses. These are recorded in the form of ERG traces consisting of a series of positive and negative wavelets. The possibility of selective stimulation of individual types of retinal cells and the analysis of constituent components of ERGs are the basis for determining the source of abnormalities and diagnosis of various types of dysfunction. In many cases, the ERG allows diagnosis of hereditary retinal disorders in dogs before the appearance of behavioural and ophthalmoscopic symptoms. This review is an introduction to the electrophysiology of vision, intended for small animal practitioners, and aimed at presenting the benefits of ERG for early ophthalmic diagnostics in dogs.

Keywords: ERG; ophthalmology; PRA; retina

Abbreviations

crd1,2,3 = cone rod dystrophy 1,2,3; **CSNB** = Congenital Stationary Night Blindness; **ECVO** = European College of Veterinary Ophthalmologists; **erd** = elary retinal degeneration; **ERG** = electroretinography, electroretinogram; **FERG** = flash electroretinography; **ISCEV** = International Society for Clinical Electrophysiology of Vision; **PRA** = Progressive Retinal Atrophy; **PRA type-A** (**pd/PRA-A**) = photoreceptor dysplasia; **prcd** = progressive rod cone degeneration; **rcd1,2,3** = rod cone dysplasia type 1,2,3; **rcd4** = rod cone dystrophy 4 (late onset PRA); **rd** = rod dysplasia; **RPE** = Retinal Pigment Epithelium; **SARD** = Sudden Acquired Retinal Degeneration; **XLPR**A = X-Linked PRA

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1. Introduction

Electrophysiological examinations of vision allow evaluation of visual pathways from the retinal photoreceptor cells to the cerebral visual cortex. Electroretinography represents one of these test modalities and is a widely used technique for assessing outer retinal function (Gouras 1970; Ekesten 2013; Ekesten et al. 2013). This examination is objective, non-invasive and provides information on the function of the individual retinal cell types (Gouras 1970; Aguirre 1973). An analysis of ERGs can be used to characterise vision disorders

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(Acland 1988; Narfstrom et al. 1995; Yanase et al. 1995). Flash ERG is currently used in the early diagnostics of retinal diseases (Narfstrom et al. 2002; Ofri 2002; Ekesten et al. 2013) and may also be useful in making decisions on cataract surgery (Ofri 2002; Ekesten et al. 2013; Wilkie and Colitz 2013).

2. History

The beginnings of visual electrophysiology date back to the 19th century when DuBois-Reymond (1849) discovered the resting potential between the anterior and posterior pole of the unstimulated eye. Holmgren (1870) demonstrated differences in the eye electrical potential generated by light stimulation. This was independently discovered by Dewar and McKendrick (1873) and a few years later also by Kuhne and Steiner (1880). These discoveries provided the basis for experimental and clinical electrophysiology in humans and animals. In 1908, Einthoven and Jolly recorded detailed records of the frog's eye with a string galvanometer and were the first to describe ERG components with letters: the first negative deflection as a-wave, the next positive peak as b-wave, and the subsequent positive peak as c-wave (Einthoven and Jolly 1908). Kahn and Lowenstein (1924) presented ERG wavelets recorded in humans with a string galvanometer. Although they tried to incorporate ERG examination into standard ophthalmologic diagnostics, some practical problems with their method made it unsuitable for clinical conditions. In 1933, Granit performed a component analysis of ERG. Using ether-anaesthetised cats he discovered three processes, which he classified according to their order of disappearance: PI, PII, and PIII. This analysis formed the basis for understanding electroretinography. Granit defined the c-wave as PI because after a long period of implicit time, its values slowly increase and it is easily removed with anaesthesia. B-wave was defined as PII and the a-wave as a leading part of the PIII process. Granit noted that PII and PIII components are strongly correlated with the light stimulus. Due to the short implicit time, Granit believed that the PIII component was associated with photoreceptor activity (Granit 1933). In the mid-20th century, Karpe (1945) reported that electroretinography was an examination used to determine retinal function. He emphasised that the examination result was not influenced by the optic nerve or visual tract and it was minimally affected by the transparency of the optic system. Studies by Goodman and Gunkel (1958), as well as Ruedemann and Noell (1959) demonstrated low-amplitude responses in ERGs in patients with retinitis pigmentosa, a disease similar to PRA in animals (Acland et al. 1998). In 1970, Gouras claimed that an isolation of the responses, at least those of the rods from the cones, should form the basis of other retinal potential analyses (Gouras 1970). Taking clinically useful ERGs, which consist of clearly marked components originating from different retinal cells, requires rigorous adherence to strictly defined measuring conditions (Brigell et al. 2003). Therefore, in 1989 ISCEV published a guide to the practice and interpretation of ERGs (Marmor et al. 1989). It includes guidelines for technical procedures that ensure the reproducibility of ERGs. These guidelines are updated every few years (Marmor et al. 2009).

In veterinary medicine, Parry et al. (1953, 1955) were the first to perform ERG in healthy and diseased dogs, respectively. Rubin (1963) examined blind cats and was the first to justify the usefulness of ERG in evaluation before cataract surgery (Rubin 1967). Gum et al. (1984) noted that the retina in pups produces a detectable ERG from approximately two weeks of age. In subsequent years, many factors influencing ERG results have been investigated. For example, the impact of the electrodes used in an examination was determined (Steiss et al. 1992; Bayer et al. 1999; Mentzer et al. 2005). The usefulness of ERG in the diagnostics of retinal diseases has been confirmed in numerous publications (see, for example, the excellent reviews by Ofri (2002) and Ekesten (2013)). In order to provide guidelines for ERG examinations in dogs, the ECVO proposed a protocol for clinical canine ERGs (Narfstrom et al. 2002) that was similar to the ISCEV protocol (Marmor et al. 2009). They still required the implementation of procedures that significantly diverge from those used in humans, e.g. general anaesthesia (Narfstrom et al. 2002). These guidelines have recently been updated (Ekesten et al. 2013). Providing clear and concise recommendations enhances repeatability and enables comparison of results from different veterinary clinics and centres.

3. Essence of ERG

During an ERG, light of varied intensity, wavelength and duration is used to illuminate the retina (Ekesten 2013). Electrical charges induced by light, produced by individual types of nerve cells in the retina are recorded (Birch 1989). Because of the various arrangement of retinal cells in space (Steinberg et al. 1973; Blanks 1994), their electrical response is generated in varied time. This response is enhanced, filtered, averaged and graphically presented as a waveform (Gouras 1970; Rosolen et al. 2002; Ekesten et al. 2013).

In veterinary ophthalmology, full-field flash ERG is most commonly used. The most often measured components of FERG are a- and b-waves (Creel 2007; Ropstad and Narfstrom 2007).

The a-wave is the first negative deflection of the wavelet (Figures 1 and 2). It reflects a cumulative response of the retinal photoreceptor cells (Schaeppi and Liverani 1977; Yanase et al. 1995; Komaromy et al. 1998). The b-wave is the next positive peak (Figures 1, 2, 3 and 4). Initial studies suggested that this wave was generated by the Muller glial cells and bipolar ON cells stimulated by the flow of potassium ions (Newman 1980; Newman and Odette 1984; Xu and Karwoski 1994). According to Kofuji et al. (2000) the b-wave is not associated with Muller cell activity. These studies were performed on Kir4.1 transgenic mice without K⁺ channels in the Muller cells and on healthy mice. It was shown that the b-wave amplitude values did not differ between both types of mice, suggesting that the b-wave is not generated by the flow of K⁺ ions through these cells (Frishman 2006; Ekesten 2013). Amacrine cells are also involved in b-wave creation. Their responses, so called oscillatory potentials (OPs) are superimposed on the ascending part of the b-wave (Heynen et al. 1985; Asi and Perlman 1992; Wachtmeister 1998) (Figure 1).

The c-wave, d-wave and i-wave are the next components of the ERG. The c-wave, reflecting a change in the standing potential of the eye in response to light, is seen on the tracing as the second positive peak. It results from electrical activity of the retinal pigment epithelium and Muller cell hyperpolarisation (Frishman 2006; Ekesten 2013). The d-wave is the next positive peak, being a late OFF-type response (Xu and Karwoski 1995). The i-wave is the following positive peak. The origin of

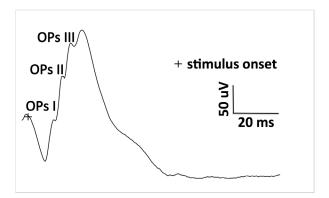


Figure 1. Electroretinogram from a normal five-year-old male dog. Dark-adapted, high-intensity (3 cd·s/m^2) flash stimulated ERG – a mixed rod-cone response. Oscillatory potentials are superimposed on ascending arm of the b-wave as OPs I-III. Calibration bars are denoted in the middle of the right side. Marker (+) indicates the onset of the light stimulus

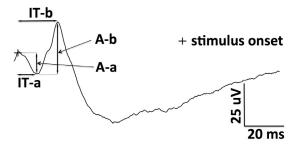


Figure 2. Electroretinogram from a normal five-year-old male dog demonstrates transient, cone-mediated and light-adapted response (stimulus intensity 3 cd·s/m², background illumination 30 cd/m²). Calibration bars are denoted in the bottom right. Marker (+) indicates the onset of the light stimulus. IT-a = implicit time of a-wave; IT-b = implicit time of b-wave; A-a = amplitude of a-wave; A-b = amplitude of b-wave

this wave is not completely elucidated. Kondo et al. (2000) classify it as a subunit of the d-wave (Nagata 1963; Peachey et al. 1989; Murayama and Sieving 1992), whereas Rosolen et al. (2004) believe that it may originate from a response of the ganglion and the optic nerve cells (Rousseau et al. 1996). In veterinary medicine, the above-mentioned ERG components are observed only under special measuring conditions and in a fraction of healthy adult dogs (Dawson and Kommonen 1995; Ekesten 2013).

Interpretation of generated ERGs requires determination of the amplitude and implicit time (time-to-peak) (Figure 2). The amplitude of the awave is measured from the baseline to the negative trough of the a-wave and the b-wave amplitude is measured from the trough of the a-wave to the following b-wave peak. The implicit times of the a-wave and the b-wave are measured from the flash onset to the trough of the a-wave and to the peak of the b-wave, respectively (Narfstrom et al. 2002; Ekesten et al. 2013).

Various types of stimulation allow the acquisition of selective retinal cell responses. The roddriven response is generated during an ERG under scotopic conditions when the dark-adapted retina is exposed to light stimulus with an intensity of 0.01 or 0.02 cd·s/m² (Figure 3). Under these conditions the cones are not activated. An increase in the intensity of the stimulus to 3 cd·s/m² activates the cones and provides a mixed rod-cone-type response (Figure 1). The cone-driven response is generated under photopic conditions, when the retina is exposed to a light intensity of 30 cd/m². These

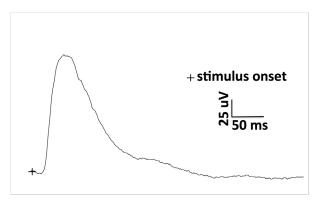


Figure 3. Electroretinogram from a normal five-year-old male dog demonstrates rod-driven response after 20 min of dark adaptation following low-intensity $(0.03~{\rm cd\cdot s/m^2})$ flash stimulation. Calibration bars are denoted in the middle of the right side. Marker (+) indicates the onset of the light stimulus

light conditions cause rod saturation and ensure a cone-driven response (Figure 2). In addition, flickering light stimulation with frequencies of 31 Hz or higher produces a pure cone response (Gouras 1970; Ekesten et al. 2013) (Figure 4).

4. Factors affecting ERG recordings

There are many factors, which can affect ERG recordings and thus impact on received wavelets. These factors can be divided into physiological and instrument-related (Mentzer et al. 2005).

Physiological factors include the individual features of an examined animal, such as the species and the breed (Ofri 2002). It is believed that breed-

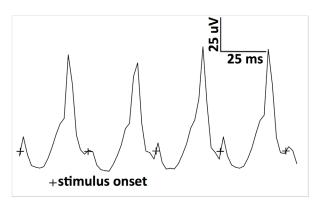


Figure 4. ERG from a normal five-year-old male dog demonstrates steady-state, light-adapted 31-Hz cone flicker response (stimulus intensity $3 \, \text{cd} \cdot \text{s/m}^2$, background illumination $30 \, \text{cd/m}^2$). Calibration bars are denoted in the upper right. Marker (+) indicates the onset of the light stimulus

related differences affect the results of an ERG examination (Aguirre and Acland 1997). Another important factor is the patient's age (Parry et al. 1955; Spiess 1994). Although Gum et al. (1984) and Hamasaki and Maguire (1985) demonstrated that an ERG examination might be performed after Week 1 or 2 of life, it should be noted that morphologically-correct ERG traces that resemble those recorded in adult animals, are obtained at the age of eight weeks (Gum et al. 1984). A reduction in the amplitude may result from age-dependent decreases in the numbers of photoreceptors and retinal pigment epithelium cells (Dorey et al. 1989). In dogs, the reduction in photoreceptors and RPE cells from about 60 days until six years of age may even reach 75% (Acland and Aguirre 1987). Therefore, normal ERGs values must be established for different age groups and breeds (Spiess 1994; Ekesten et al. 2013).

The group of physiological factors also includes body temperature (Mizota and Adachi-Usami 2002; Kong and Gouras 2003), the degree of tissue perfusion and serum glucose and oxygen levels (Macaluso et al. 1992; Reynaud et al. 1995; Varela Lopez et al. 2010). Endogenous sources of disturbance also result from changes in the electrical potential of muscles and peripheral nerves (EMG), brain neural cell activity (EEG), heart (ECG) and visual evoked potentials (VEP).

Animals undergoing an electrophysiological examination must be put into general anaesthesia (Ekesten et al. 2013). Each eye blink, movement of the globe or muscle tremor disturbs the flow of current, which unfavourably influences the recordings (Acland 1988). This explains the necessity of incorporating general anaesthesia into the ERG protocol. It should be remembered that each anaesthetic exerts a specific impact on ERG recordings (Kommonem 1988; Yanase and Ogawa 1997; Kommonen et al. 2007; Norman et al. 2008; Jeong et al. 2009; Lin et al. 2009). An understanding of the correlation between anaesthetics and ERG traces provides a basis for their correct analysis. Studies by Kommonen et al. (1988) and Jeong et al. (2009) showed that anaesthesia with a combination of xylazine and ketamine has the lowest impact on implicit times and amplitudes. In addition, the combination of these anaesthetics does not induce ventral rotation of the eyeball and miosis.

The status of retinal light adaptation is another factor that affects ERG recordings. This is determined by the transparency of the ocular tissues

(Aguirre 1973; Maehara et al. 2007), the pupil diameter and the pupillary light reflex (Fishman 2001; Ekesten 2013). These factors have an important impact on the level of fundus illumination during flash stimulation. Even illumination of the retina is a basis for obtaining reliable results (Kooijman 1986; Ekesten et al. 2013). In generalised photoreceptor disorders when retinal function may vary between different areas of the fundus, uneven illumination during an FERG examination may stimulate its normal parts and produce false-normal results. For instance, in the course of early retinal degeneration, the reduction in the number and size of photoreceptors varies in different regions of the fundus (Acland and Aguirre 1987). Another example is dominant PRA, where retinal thinning occurs in the central fundus and is distinctly separated from the surrounding parts of the retina until the 6th month of life (Kijas et al. 2002). A similar situation is seen in rcd2 when lesions are first noted in the central tapetal fundus and subsequently spread into the peripheral parts (Santos-Anderson et al. 1980). Therefore, before an ERG examination it is recommended to produce mydriasis in order to achieve maximum fundus illumination (Narfstrom et al. 2002; Ekesten 2013). Rotation of the globe requires a correction of its position as it impedes correct stimulation of the retina (Ekesten et al. 2013). In such cases, it is helpful to put a blepharostat and conjunctival stay sutures (Ropstad and Narfstrom 2007).

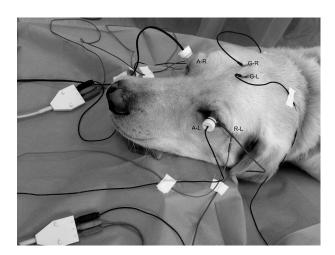


Figure 5. Electrode placement for simultaneous 2-channel FERG recording, with the use of Kooijman-Damhof corneal electrodes with a built-in light source and a light diffusing contact lens (active electrodes: A-L and A-R for right and left side separately). Subdermal ground (G-L, G-R) and reference (R-L) electrodes are indicated for right and left side separately

Instrument-related factors in the form of technical parameters of the ERG measurement device, as well as electrostatic and electromagnetic disturbances, are sources of noise. Methods which reduce background noise and maximise the signal originating from the retinal cells improve signalto-noise ratio. Such methods include band-pass filtering and selective signal amplifiers (Komaromy et al. 2002). This group of factors also comprises various types of electrodes. Their type, placement and conductivity exert an important impact on the measurement result (Steiss et al. 1992; Bayer et al. 1999; Mentzer et al. 2005). Many types of active electrodes are used: from mono- or bipolar contact lens electrodes, such as the Burian-Allen, Kooijman (Figure 5) and Jet (Figure 6) to gold-foil electrodes and Dawson-Trick-Litzkov fibre electrodes (Burian and Allen 1954; Lawwill and Burian 1966; Arden et al. 1979; Dawson et al. 1979; Kooijman and Damhof 1980; Kooijman and Damhof 1981; Grounauer 1982; Hebert et al. 1996; Komaromy et al. 2002; Mentzer et al. 2005). Reference and ground electrodes may take the form of a subdermal needle or surface cup electrodes (Komaromy et al. 2002; Ropstad and Narfstrom 2007). Electrode placement also has an impact on the shape and magnitude of ERG traces (Mentzer et al. 2005). Since the eyeball is like an electrical dipole, the positioning of electrodes near its poles results in the best response (Mentzer et al. 2005; Ekesten et al. 2013). The active



Figure 6. Electrode placement for simultaneous 2-channel FERG recording, with the use of Jet mono-polar corneal electrodes (active electrodes: A-L and A-R for right and left side separately). The eyelids were fixed with the use of eye speculum. Subdermal ground (G-L and G-R) and reference (R-L and R-R) electrodes are indicated for right and left side separately

electrode is positioned on the corneal surface, while the reference electrode is placed 3-5 cm from the lateral canthus (Komaromy et al. 2002, Mentzer et al. 2005; Ekesten et al. 2013) (Figures 5 and 6). Mentzer et al. (2005) discovered that the distance of a reference electrode from the examined eye and the type of active electrode determined the magnitude of wave amplitudes. They also observed that the same electrodes used in various species, i.e. humans and dogs, generated different results. The ground electrode is usually placed on a Fpz point (Figures 5 and 6) or near the auricle (Mentzer et al. 2005; Marmor et al. 2009). In order to achieve the best noise reduction, the distance between electrodes should be as small as possible (Acland 1988; Komaromy et al. 1998; Narfstrom et al. 2002).

5. Clinical applications

The ERG examination may be complementary to an ophthalmic examination in cases when clinical and ophthalmological signs are present. However, in some retinal diseases when behavioural changes or fundus lesions are not seen, an ERG examination is a key diagnostic element (Ekesten 2013).

Retinal diseases are classified according to different criteria: developmental-like dysplasia (rcd1–3, rd, pd/PRA-A) and degenerative or dystrophic (crd1–3, prcd, rcd4, XLPRA, erd); the part of the retina chiefly involved in the early stage of the disease (generalised vs. central); type of affected cells (rods, cones or both); the time of onset (early vs. late); time course (rapid vs. slow) – rcd1–2, erd and rcd4, prcd, XLPRA, respectively.

There are over 20 canine breeds in which in the course of PRA, ERG alterations occur much earlier than ophthalmoscopic lesions (Narfstrom and Petersen-Jones 2013). In the case of prcd in the English Cocker Spaniel (Aguirre and Acland 1988) and Labrador retrievers (Kommonen and Karhunen 1990; Raitta et al. 1991; Kommonen et al. 1997) and in crd in Dachshund shorthaired dogs (Ropstad et al. 2008), changes in ERG recordings are observed nearly three years earlier than fundoscopic or behavioural abnormalities. ERG allows detection of prcd in Miniature and Toy Poodles (Aguirre and Rubin 1972; Sandberg et al. 1986), American Cocker Spaniels and in Portuguese water dogs (Aguirre and Acland 2006), XLPRA in Samoyed (Dice 1980) and the Siberian Husky (Aguirre and Acland 1994) and PRA type-A in miniature Schnauzers (Parshall et al. 1991), one to two years earlier than an ophthalmoscopic examination. In Irish setters, Collies, and Cardigan Welsh Corgis, the difference between the appearance of electroretinographic and fundoscopic lesions is shorter (approximately five weeks) but ERG still offers the possibility of earlier diagnosis (Aguirre and Rubin 1975a; Wolf et al. 1978; Petersen-Jones et al. 2006). It should be emphasised that ERG is not determinative in all types of PRA. In the case of PRA in Akita, Papillon (Narfstrom and Ekesten 1998; Narfstrom and Wrigstad 1999) or Tibetan terriers (Millichamp et al. 1988), behavioural and ophthalmoscopic changes, as well as ERG alterations, can occur at similar times. In contrast, in bullmastiffs and Old English mastiffs, abnormal ERGs appear even later than lesions in the fundus (Narfstrom and Petersen-Jones 2013). Other inherited diseases that may be detected with ERG earlier than with an ophthalmoscopic examination include CSNB (Narfstrom et al. 1989; Nilsson et al. 1992; Narfstrom et al. 1994) and hemeralopia (Rubin 1971a; Rubin 1971b; Aguirre and Rubin 1975b).

6. Interpretation of results

ERGs in dogs affected with PRA differ depending on the type and severity of the disorder. These differences concern individual features of ERG wavelets - implicit times and amplitudes. In the early stage of disease during which the rod system is first inactivated, such as rd, rcd and erd, roddriven responses are absent, while cone-driven responses may be intact or slightly reduced (Aguirre and Rubin 1971; Aguirre and Rubin 1975a; Aguirre 1978; Buyukmihci et al. 1980; Petersen-Jones et al. 2003; Tuntivanich et al. 2009). Conversely, in cases when the cone system is inactivated first (for instance, in the course of crd1 in Dachshunds), cone-specific responses are significantly reduced, although the response of the rods remains within the normal range until 40 weeks of age (Curtis and Barnett 1993; Turney et al. 2007; Ropstad et al. 2007; Busse et al. 2011).

In the course of CSNB in Briards, a dysfunction of the rods is manifested by a reduction in a-wave and b-wave amplitude under scotopic conditions, while cone function impairment is determined by a reduction in the light-adapted 30 Hz flicker response. This becomes noticeable at five weeks of age, which is much earlier than in an ophthalmoscopic exami-

nation (Narfstrom et al. 1989; Nilsson et al. 1992; Narfstrom et al. 1994; Aguirre et al. 1998).

In animals with hemeralopia, a loss of cone system function may be seen at six weeks of age and may by manifested as a loss of the light-adapted cone flicker response (Hurn et al. 2003). Fundoscopic changes are not observed throughout life (Rubin 1971a; Aguirre and Rubin 1974).

In addition, ERG allows for differentiation of vision defects caused by retinal damage or disturbances in optic nerve functioning, for instance, in differentiating between SARD and optic neuritis. While both conditions are characterised by similar clinical signs, ERG is decisive. In the case of SARD, the ERG traces are non-recordable, the so-called "silent retina" (Acland et al. 1984; O'Toole et al. 1992; Cullen and Grahn 2002), whereas in optic neuritis, the ERGs are essentially normal (Montgomery et al. 2008).

The ERG examination also permits an evaluation of the retinal electrophysiological condition when the optic system is not transparent due to, for instance, hyphaema, corneal oedema, vitreous haemorrhage (Gelatt and Wilkie 2011; Ekesten 2013) or cataract (Ofri 2002; Ekesten et al. 2013; Wilkie and Colitz 2013).

7. Conclusions

The objective of this review was to introduce clinical veterinary electroretinography in dogs. ERG enables accurate and selective diagnostics of inherited retinal diseases. It provides both qualitative and quantitative information on retina functioning. Further, if abnormal results are obtained, it is possible to identify the cellular elements involved and characterise the visual deficit, its source, evolution and prognosis.

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