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Review

Electrophysiological assessment of retinal ganglion cell function

Vittorio Porciatti

Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, McKnight Vision Research Center, 1638 NW 10th Ave., Miami, FL 33136, United States

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ABSTRACT

The function of retinal ganglion cells (RGCs) can be non-invasively assessed in experimental and genetic models of glaucoma by means of variants of the ERG technique that emphasize the activity of inner retina neurons. The best understood technique is the Pattern Electroretinogram (PERG) in response to contrast-reversing gratings or checkerboards, which selectively depends on the presence of functional RGCs. In glaucoma models, the PERG can be altered before histological loss of RGCs; PERG alterations may be either reversed with moderate IOP lowering or exacerbated with moderate IOP elevation. Under particular luminance-stimulus conditions, the Flash-ERG displays components that may reflect electrical activity originating in the proximal retina and be altered in some experimental glaucoma models (positive Scotopic Threshold response, pSTR; negative Scotopic Threshold Response, nSTR; Photopic Negative Response, PhNR; Oscillatory Potentials, OPs; multifocal ERG, mfERG). It is not yet known which of these components is most sensitive to glaucomatous damage. Electrophysiological assessment of RGC function appears to be a necessary outcome measure in experimental glaucoma models, which complements structural assessment and may even predict it. Neuroprotective strategies could be tested based on enhancement of baseline electrophysiological function that results in improved RGC survival. The use of electrophysiology in glaucoma models may be facilitated by specifically designed instruments that allow high throughput, robust assessment of electrophysiological function.

1. Introduction

For a very long time, a well-established notion has been that the ERG did not reflect electrical activity of retinal ganglion cells (RGCs) (Riggs, 1986). In 1981, however, a study in the cat (Maffei and Fiorentini, 1981) showed that the ERG in response to contrast-reversing patterns at constant mean luminance (Pattern-ERG, PERG) was abolished after section of the optic nerve that retrogradely killed RGCs leaving outer retina neurons and the standard Flash-ERG intact. This crucial experiment has been repeated many times in different mammals including non-human primates and rodents (rats and mice), with similar results. These studies sparked a considerable wave of interest resulting in a large number of clinical and experimental reports that the PERG is altered in glaucoma, even at early stages.

More recently, different laboratories discovered that under particular luminance-stimulus conditions, the Flash-ERG displays components (positive Scotopic Threshold response, pSTR; negative Scotopic Threshold Response, nSTR; Photopic Negative Response, PhNR; Oscillatory Potentials, OPs; multifocal ERG, mfERG) that may reflect electrical activity originating in the proximal retina. These inner-retina-sensitive ERG components have also been shown to be altered in clinical and experimental studies of glaucoma. Table 1 summarizes studies that used PERG and other inner-retina-sensitive ERG components in experimental models of glaucoma.

1.1. Response generators

Generators of PERG and inner-retina-sensitive ERG components have been investigated in a substantial number of studies. In summary, 1) Optic nerve transection/crush resulting in selective RGC loss invariably cause dramatic loss of PERG signal in cats (Maffei and Fiorentini, 1981; Weber et al., 2008) monkeys (Maffei et al., 1985) rats (Berardi et al., 1990) and mice (Miura et al., 2009; Porciatti et al., 1996; Xia et al., 2014); pSTR and nSTR appear to be reduced in rats (Bui and Fortune, 2004) and mice (Liu et al., 2014; Smith et al., 2014; Yukita et al., 2015), but relatively less than the PERG (Liu et al., 2014); PhNR, OPs do not seem to be reduced in rats and mice (Li et al., 2005; Liu et al., 2014; Smith et al., 2014); in

E-mail address: vporciatti@med.miami.edu.

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Table 1
Electrophysiological measurements used in glaucoma models.

Species	Model	Altered electrophysiological measure	Reference
Monkey	TM laser	PhNR in mfERG	(Luo et al., 2011)
Monkey	TM laser	OPs of mfERG	(Rangaswamy et al., 2006)
Monkey	TM laser	mfERG	(Fortune et al., 2012)
Monkey	TM laser	PhNR	(Viswanathan et al., 1999)
Monkey	TM laser	PERG	(Johnson et al., 1989)
Monkey	TM laser	PERG	(Marx et al., 1986)
Monkey	TM laser	PERG	(Marx et al., 1988)
Monkey	TM laser	nSTR	(Frishman et al., 1996)
Monkey	TM laser	mfERG Ops, STR	(Rangaswamy et al., 2006)
Monkey	TM laser	nSTR	(Frishman et al., 1996)
Monkey	TM laser	PhNR, PERG	(Viswanathan et al., 2000)
Monkey	TM laser	mfERG	(Frishman et al., 2000)
Monkey	TM laser	mfERG	(Raz et al., 2002)
Monkey	TM laser	mfERG	(He et al., 2014)
Monkey	TM laser	mfERG	(Nork et al., 2010)
Monkey	TM laser	mfERG	(Raz et al., 2003)
Monkey	TM laser	nfERG	(Nork et al., 2014)
Mouse	DBA/2J	PERG	(Saleh et al., 2007)
Mouse	DBA/2J	PERG	(Porciatti et al., 2007)
Mouse	DBA/2J	PERG	(Nagaraju et al., 2007)
Mouse	DBA/2J	PERG	(Porciatti and Nagaraju, 2010)
Mouse	DBA/2J	PERG	(Howell et al., 2007)
Mouse	DBA/2NNia	PERG	(Bayer et al., 2001a)
Mouse	DBA/2J	PERG	(Howell et al., 2012)
Mouse	DBA/2J	ERG	(Heiduschka et al., 2010)
Mouse	DBA/2J	ERG	(Harazny et al., 2009)
Mouse	DBA/2J	pSTR	(Perez de Lara et al., 2014)
Mouse	MYOC	PERG	(Chou et al., 2014b)
Mouse	MYOC	PERG	(Zode et al., 2011, 2012)
Mouse	Dexamethasone	PERG	(Zode et al., 2014)
Mouse	C57BL/6J, Indocyanine green + laser anterior chamber	ERG	(Grozdanic et al., 2003a)
Rat	Morrison	pSTR	(Fortune et al., 2004)
Rat	Episcleral vein cauthery	ERG, OPs	(Bayer et al., 2001b)
Rat	Episcleral vein cauthery	PERG, ERG	(Sandalon et al., 2013)
Rat	Morrison	ERG	(Georgiou et al., 2014)
Rat	Morrison	PERG	(Husain et al., 2012)
Rat	Morrison	PERG	(Abdul et al., 2013)
Rat	Morrison	pSTR	(Fortune et al., 2004)
Rat	Vortex and episcleral vein cauthery	ERG	(Grozdanic et al., 2003b)
Dog	Hereditary angle-closure glaucoma	PERG	(Grozdanic et al., 2010)

Pattern Electroretinogram, PERG; positive Scotopic Threshold response, pSTR; negative Scotopic Threshold Response, nSTR; Photopic Negative Response, PhNR; Oscillatory Potentials, OPs; multifocal ERG, mfERG; Trabecular Meshwork, TM; Morrison, hypertonic saline injection of episcleral veins (Morrison et al., 1997).

monkeys, retrograde RGC degeneration modestly alters the mfERG, and mfERG alterations are species-dependent (Nork et al., 2010), 2) Several pharmacological studies have demonstrated that interfering in various ways with activity of inner retina neurons reduces PERG as well as inner-retina-sensitive ERG components in cats, rodents and primates (Bui and Fortune, 2004; Hare and Ton, 2002; Hood et al., 1999; Viswanathan et al., 2000). Interestingly, both spiking and non-spiking electrical activity contributes to the PERG and inner-retina-sensitive ERG components (Luo and Frishman, 2011; Miura et al., 2009; Trimarchi et al., 1990; Harrison et al., 2006; Viswanathan et al., 2000), 3) Intraretinal recordings have demonstrated an inner retina origin for the PERG distinct from ERG b-wave (Baker et al., 1988; Sieving and Steinberg, 1987), 4) In the mouse, the bioelectrical field generated by the PERG is different from that of the Flash-ERG, and it is consistent with generators localized in the optic nerve head (Chou and Porciatti, 2012), 5) Functional retrograde transport of target-derived factors is necessary for PERG generation, as blocking axon transport in the optic nerve Chou (Chou et al., 2013) or lesioning the superior colliculus (Yang et al., 2013) impairs the PERG in the mouse.

Despite extensive investigation, the precise cellular origin of the PERG and inner-retina-sensitive ERG components is not yet known. While the PERG appears to be more specifically related to the presence of functional RGCs, different inner-retina-sensitive ERG components appear to arise from different classes of neurons and/or non-neuronal glial cells in the inner retina and be species-specific. IOP elevation often alters one or more of these components, and this may also occur when RGCs are retrogradely degenerated, suggesting a preganglionic component (Nork et al., 2010). Further investigation is needed to better understand species differences and which component is most sensitive to RGC damage (Liu et al., 2014) (Smith et al., 2014).

The standard scotopic and photopic ERG is generally considered insensitive to glaucoma, and is often used as a control that the procedure to elevate IOP in experimental models has not induced a generalized retinal damage (Bui et al., 2013). Some studies, however, have shown that the ERG can be altered in experimental models as well as in genetic models (Table 1).

Visually Evoked Potentials (VEP) have been sometimes used to assess whether RGC axons are capable to carrying retinal signals along the geniculo-cortical pathway (Chou et al., 2014b; Heiduschka et al., 2010). It should be considered that the numerical relationship between topographically matched RGCs and contralateral geniculate relay cells is approximately 3:1 in mice (Coleman et al., 2009). This retina-geniculate convergence, together with the compensatory mechanisms occurring in the visual cortex

in response to progressive reduction of the retinal output in disease (Keck et al., 2008) may offset peripheral losses and complicate the interpretation of VEP alterations.

1.2. The PERG

At present, the PERG is the most specific technique for electrophysiological assessment of RGC function in primate and rodent models of glaucoma. In the pattern-reversal stimulus, pattern elements alternate at constant mean luminance. Inner retina neurons with receptive field organized in antagonistic regions respond at each contrast transition, whereas photoreceptor activity generated by adjacent pattern elements is in opposition of phase and cancels out at the electrode (Porciatti, 2007). Thus, the PERG is dominated by inner retina activity whereas outer retina activity is minimized. The pattern stimulus, compared to luminance stimuli, has the unique advantage that its characteristics (spatial frequency, contrast, temporal frequency, chromaticity) can be independently modulated at constant mean luminance. Hence the activity of RGC subpopulations can be maximized by using appropriate pattern stimuli at which RGCs best respond (Hess et al., 1986; Morrone et al., 1994). In addition, important measures of visual performance such as spatial acuity and contrast threshold can be obtained by determining the smallest pattern size and contrast, respectively, at which a PERG signal larger than noise is recordable (Fig. 1) (Porciatti, 2007).

In experimental models, the PERG is typically recorded from the cornea using a variety of electrodes that do not interfere with the eye optics (Porciatti et al., 2007; Viswanathan et al., 2001). In primates and cats, optical correction for the viewing distance is needed to keep the stimulus focused in the retina. In mice, pupil dilation is not necessary as the small pupil size maximizes the depth-of-field (Remtulla and Hallett, 1985; Schmucker and Schaeffel, 2004). Recently, the PERG technique in mouse models has been greatly simplified by the introduction of a new recording paradigm that simultaneously derives responses from both eyes using one subcutaneous needle electrode in the snout and one channel recording (Chou et al., 2014a). The paradigm is now incorporated in a commercially available instrument (Miami-PERG, Jörvec Corp., Miami, FL).

Examples of mouse PERG waveforms and how PERG amplitude changes as function of spatial frequency and contrast are shown in Fig. 1. In C57B/6J mice, the PERG waveform (Fig. 1A) consists of a small negative wave peaking at about 50 ms (N1), a positive wave peaking at about 80 ms (P1) and a prominent, broad negativity peaking at about 300 ms (N2). In different mouse strains such DBA/2J the P1 peak latency can be longer by 20 ms compared to C57BL/6J (Porciatti et al., 2010) The general morphology of the mouse PERG waveform qualitatively resembles that of human and non-human primate PERG that consists of an early negativity (N35) followed by a larger positivity (P50) and a later negativity (N95) (Viswanathan et al., 2000) (Bach et al., 2013). However, it is not yet known whether the mouse N1–P1–N2 complex and the primate N35–P50–N95 complex reflect same neural substrates. One striking difference is that the mouse PERG latency dramatically increases (up to 60 ms) by reducing the stimulus contrast or increasing the spatial frequency (Porciatti et al., 2010) whereas in the primate contrast-dependent latency changes PERG are relatively minor. This has been interpreted as longer integration time over the large receptive field of mouse RGCs. Also, there are significant differences in the PERG amplitude/latency functions as a function of contrast in different mouse genotypes. This may reflect genotype-dependent contrast gain relationship in the circuitry involving RGC receptive field (Porciatti et al., 2010).

2. Contribution of electrophysiology to better understanding of structure–function relationships in glaucoma models

2.1. RGC dysfunction precedes RGC death

Several laboratories using different experimental models of ocular hypertension and different electrophysiological measurements of RGC function have shown that RGC dysfunction occurs early, is progressive, and precedes loss of optic nerve tissue and RGC density. Marx et al., (Marx et al., 1986, 1988) induced sustained IOP elevation in monkeys by means of laser photocoagulation of the trabecular meshwork. While the flash ERG was normal, the PERG was much reduced despite the absence of cupping of the optic nerve head, which occurred subsequently. In a similar monkey model, Luo et al. (Luo et al., 2014) recently recorded multifocal ERGs and analyzed several components of the mfERG including the PhNR. All mfERG measures captured functional losses that were more spatially extensive and profound than the structural losses as measured by spectral domain OCT, consistent with neuronal (and/or glial) dysfunction before structural loss. In rats made hypertensive with hypertonic saline injection into an episcleral vein, Fortune et al., (Fortune et al., 2004) demonstrated loss of pSTR before the onset of loss of optic nerve tissue assessed histologically. Comparable electrophysiological changes are reported to occur in genetic mouse glaucoma models. Howell et al., (Howell et al., 2007) showed in DBA/2J mice that the PERG is impaired early in the disease, as IOP becomes progressively elevated but before detectable axon loss. Saleh et al., (Saleh et al., 2007) showed in DBA/2J mice that PERG losses are progressive and precede loss of RNFL

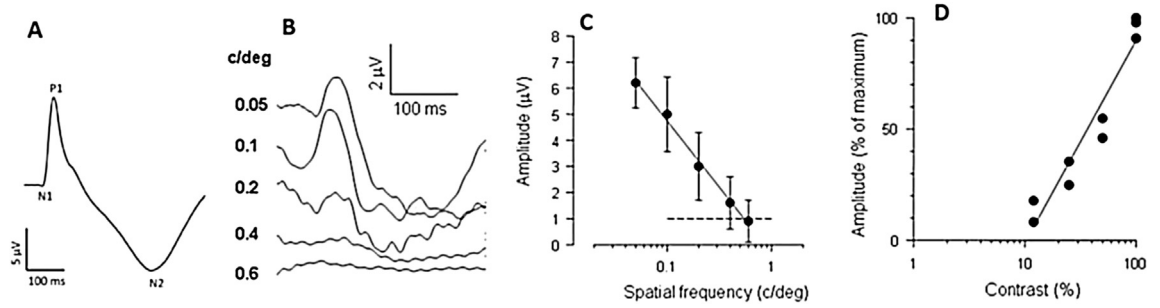

Fig. 1. Transient PERGs recorded in C57BL/6J mice in response to high-contrast gratings reversing 2 times/s. A: grand-average of 120 waveforms from different eyes (Chou et al., 2014a). Note the N1–P1–N2 complex. B: The PERG amplitude decreases with increasing spatial frequency (Porciatti, 2007). C: The mean (±SEM) PERG amplitude of 6 different mice decreases with increasing spatial frequency and reaches the noise level (dashed line) at 0.6 cy/deg (retinal acuity) (Porciatti, 2007), which is similar to the behavioral acuity (Gianfranceschi et al., 1999). C: For gratings of 0.05 cy/deg, the PERG amplitude decreases with decreasing contrast. The contrast threshold is about 10%, (Porciatti et al., 1996) which is similar to that measured with the optomotor system (Prusky et al., 2004).

thickness (Fig. 2). In some genetic models, progressive RGC dysfunction may develop without IOP elevation. Chou et al., (Chou et al., 2014b) showed in transgenic mice expressing Tyr437His mutant of human myocilin protein that PERG amplitude progressively decreases while PERG latency increases between 2 and 18 months at constant normal IOP levels. This model is associated with moderate RGC loss but axonal swelling and astrocytic activation in the optic nerve head. In a related transgenic mouse carrying the Y437H MYOC mutation, Zode et al. (Zode et al., 2011) reported sustained IOP elevation resulting in progressive, parallel loss of PERG signal and RGC density. Altogether, these results demonstrate that RGC dysfunction precedes RGC death and may depend on the level of IOP elevation. The time lag between RGC dysfunction and death may depend both on the magnitude of IOP elevation and the genetic susceptibility to IOP stress (Libby et al., 2005b). Axonal and dendritic dysfunction preceding loss of RGC somas has been also demonstrated with structural studies (Buckingham et al., 2008; Williams et al., 2013).

2.2. RGC dysfunction may be reversible with IOP lowering

If RGC dysfunction precedes death and depends on IOP elevation, then it may be reversible upon IOP lowering. This question has been addressed in a number of studies. In DBA/2J mice aged 11 months, the PERG signal is close to the noise level, but RGC death is still moderate (Howell et al., 2007; Libby et al., 2005a; Saleh et al., 2007; Williams et al., 2013). In these mice, Nagaraju et al., (Nagaraju et al., 2007) administered intraperitoneally mannitol 25% (2.5 g/Kg), which reduced IOP by 38%; the PERG amplitude increased by 83%. In mice, IOP is posture-dependent. IOP increases upon head-down (Aihara et al., 2003; Nagaraju et al., 2007) and decreases upon head-up (Nagaraju and Porciatti, 2008). For a 60 deg change from horizontal – either head-down or head-up – the posture-dependent IOP change is of the order of ± 5 mm Hg and it is stable over time, which allows testing the effect of posture on RGC function. Nagaraju et al. (Nagaraju and Porciatti, 2008) showed that head-up posture reduced IOP by about 5 mm Hg in DBA/2J mice of different ages. The normal PERG signal of young DBA/2J mice was unaffected, but the abnormal PERG signal of older DBA/2J mice improved in an age-dependent manner: the worse the baseline PERG amplitude, the larger the magnitude of PERG improvement (Fig. 3).

2.3. RGC dysfunction may be inducible with moderate IOP elevation in susceptible eyes

If RGC dysfunction precedes death and depends on IOP elevation, then it may be inducible upon transient IOP elevation (Bui et al., 2005) in susceptible eyes. As mentioned above, IOP increases during head-down posture. As IOP elevation is a gravity-induced response to elevation of the episcleral venous pressure, it is rather independent of mouse strain, age, and baseline IOP. Nagaraju et al., (Nagaraju et al., 2007) showed that 60° head-down posture resulting in IOP elevation of about 5 mm Hg did not have any effect on the normal PERG signal of DBA/2J mice 2 months old. However, it reduced the PERG signal of DBA/2J mice 6 months old and even more the PERG of mice 10 months old (Fig. 4). Some mouse strains, such as C57BL/6J appear to be less susceptible to IOP

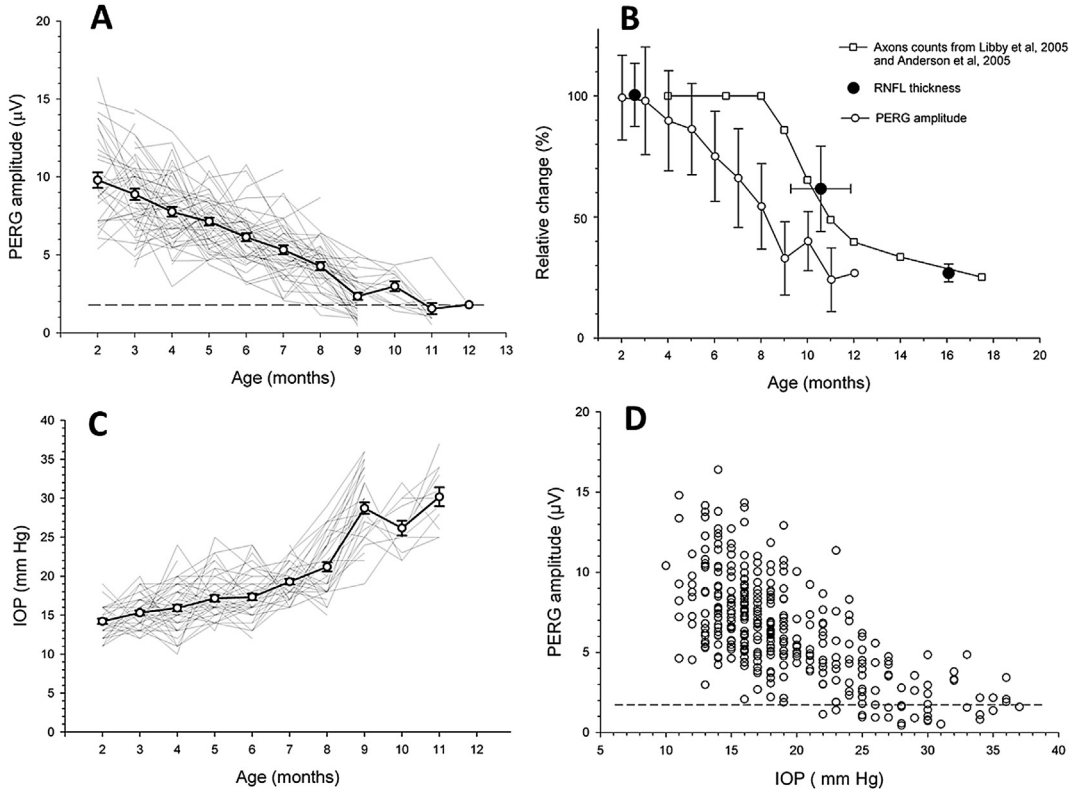

Fig. 2. Progressive loss of PERG amplitude in DBA/2J mice. A: serial PERG recordings in a population of DBA/2J mice (individual mice, grey lines). The PERG amplitude reaches the noise level (dashed line) at different ages between 8 and 12 months. Mice with PERG amplitude at noise level were eliminated from the pool for histological analysis. The open symbols connected by a thick line represent the group mean ± SEM amplitude. C: corresponding IOP measurements showing a progressive IOP increase with age. D: The PERG amplitude is inversely correlated to IOP. B: Relative changes of PERG amplitude (open circles), axon counts (open squares) and histological RNFL thickness (filled circles) as a function of age. Error bars represent the SD. Progressive loss of RGC axons and RNFL thickness lag behind progressive loss of PERG amplitude. Redrawn from ref. (Saleh et al., 2007). Axon counts estimates are from refs. (Anderson et al., 2005; Libby et al., 2005a).

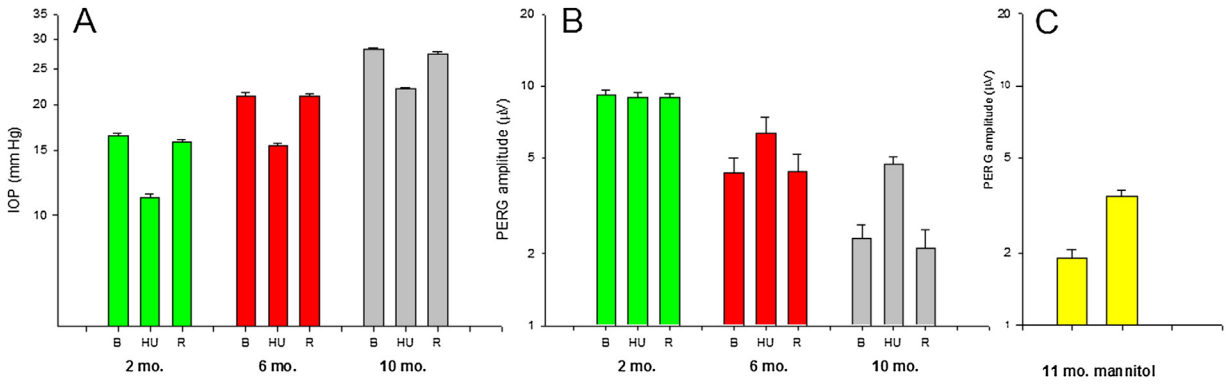

Fig. 3. Head-up posture reduces IOP and improves abnormal PERG in susceptible ages in DBA/2J mice. A: IOP decreases during 60° head-up posture (HU) by about 5 mm Hg compared to horizontal baseline (B) and recovery (R) in mice of different ages with different baseline IOP. B: PERG amplitude increases during HU in mice 6 and 10 months old, when baseline PERG is reduced. C: Improvement of PERG amplitude is also obtained in mice 11 months old with abnormal baseline PERG after mannitol 20% treatment, which reduced IOP by about 38%. Redrawn from ref. (Porciatti and Nagaraju, 2010).

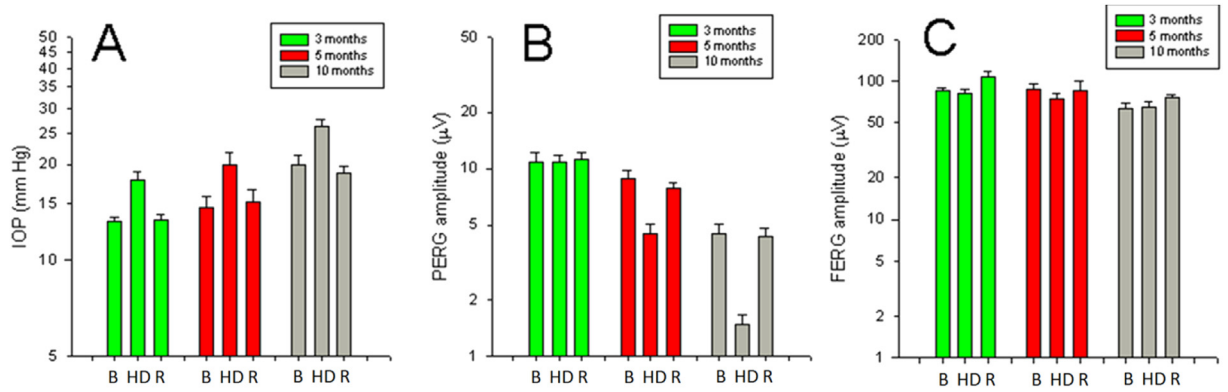

Fig. 4. Head-down posture increases IOP and reduces PERG in susceptible ages in DBA/2J mice. A: IOP increases during 60° head-down posture (HD) by about 5 mm Hg compared to horizontal baseline (B) and recovery (R) in mice of different ages with different baseline IOP. B: PERG amplitude decreases during HD in an age-dependent manner. C: The light-adapted, peak-to-trough flash ERG amplitude does not change during HD. Vertical bars represent the mean, whiskers represent the SEM. Redrawn from ref. (Nagaraju et al., 2007).

elevation than DBA/2J. Anderson et al., (Anderson et al., 2006) generated C57BL/6J-Tyrp1b.GpnmbR150X mice that develop the same iris disease as DBA/2J mice, but are resistant to high IOP and glaucoma. In these mice the PERG is normal (Howell et al., 2007). Experimental IOP elevation causes different mfERG alterations in different monkey species (Nork et al., 2010).

2.4. Neuroprotection and RGC function

A number of neuroprotective agents are known to spare at least part of RGCs from death in glaucoma models (Danesh-Meyer, 2011). Less is known about protection of RGC function. Surviving RGCs may not be functional. Also, it is not known whether neuroprotective agents alter RGC function in control eyes (McGill et al., 2007). So far, a few studies have linked RGC electrical activity to the number of surviving RGCs in genetic mouse glaucoma models. Zode et al., (Zode et al., 2012, 2014) showed that topical administration of ocular sodium 4-phenylbutyrate rescues glaucoma and preserves the PERG in transgenic MYOC (Y437H) mice with elevated IOP as well as in mice with dexamethasone-induced IOP elevation. Howell et al., (Howell et al., 2012) showed in DBA/2J mice that radiation treatment prevents neuronal damage and spares the PERG. Howell et al., (Howell et al., 2007) showed in DBA/2J mice that the *Wlds* allele, which is known to protect against insults to axons, strongly protects against DBA/2J glaucoma and preserves the PERG.

If RGC dysfunction precedes death, then the magnitude of electrophysiological change (worsening/improvement) upon transient IOP elevation/lowering may help to assess susceptibility/reversibility of RGC to IOP stress and predict the outcome of the disease without or with treatment. This hypothesis can be satisfactorily modeled (Porciatti and Ventura, 2012) and is supported by the studies on PERG modifiability to IOP challenge quoted above and others studies showing that IOP lowering rescues RGCs from death in glaucoma models (Schuettauf et al., 2002; Zode et al., 2011, 2014). A similar rationale could be used for neuroprotective strategies other than IOP lowering. This seems an important field of investigation, as it would allow testing neuroprotective strategies and formulating predictions based on baseline assessment of electrophysiological modifiability instead of waiting several months to assess the histological outcome.

2.5. Strengths and weaknesses of electrophysiological testing in glaucoma

As glaucoma impacts primarily RGCs but also inner and perhaps outer retina neurons, any technique that probes electrical activity of inner retina is an excellent candidate to monitor glaucomatous functional changes. Thus, both the PERG and a number of flash-ERG derived techniques may be effectively used to this purpose, and the choice of one method over the other is a matter of pros/cons considerations on particular experimental models and procedures at

the level of individual laboratories (Table 1). While the PERG appears to be the response most specific and sensitive for RGC dysfunction, and is also recordable in minutes under light-adapted conditions, it depends on intact eye optics. Large eyes of cats and monkeys need to be refracted for the viewing distance, and the presence of optical opacities precludes PERG recording. As mice are prone to developing reversible cataracts under stress, care is needed with the level of anesthesia and eye manipulation to prevent the formation of cataracts. Similar considerations apply to the mfERG. The presence of cataract is less of a problem with flash-ERG derived techniques. On the other hand, recording threshold responses such as pSTR requires long dark adaptation periods and a series of responses to different flash intensities to identify the response threshold.

It should be also considered that both the PERG and inner-retina sensitive ERG components may be secondarily altered for pathological conditions affecting the outer retina. In experimental models of glaucoma, when induced IOP elevation is high enough to cause outer retina injury, it is advisable to record a standard ERG to control for generalized effects.

2.6. Concluding remarks

Electrophysiological assessment of RGC function appears to be a sensitive and necessary outcome measure in experimental glaucoma models, which complements structural assessment and may even predict it. In addition to the PERG, several components of the luminance ERG appear to be inner-retina sensitive and have a promising role. The use of electrophysiology in mouse models may be facilitated by new, user-friendly protocols and instruments that allow high throughput, robust assessment of RGC function.

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