PERSPECTIVE

Adaptable retinal ganglion cell function: assessing autoregulation of inner retina pathways

Retinal ganglion cell (RGC) function in health and disease: RGCs are extremely high-maintenance neurons connecting the eye to the brain trough the optic nerve. In order to produce and propagate action potentials along the unmyelinated RGC axons and support axonal transport of materials back and forth from the eye to the brain, RGC require large amounts of energy. Therefore, RGCs are under considerable metabolic stress when healthy and become particularly vulnerable in disease, resulting in blindness (Morgan, 2004).

RGC function can be assessed non-invasively: RGC function can be non-invasively assessed by means of the pattern electroretinogram (PERG) (Porciatti, 2015). The PERG (**Figure 1**) is a special kind of ERG in which the visual stimulus, instead of a light flash, consists of a display with black and white bars or checks that alternate while the mean luminance remains constant. This results in an isoluminant contrast reversal, which primarily activates inner retina neurons with receptive field organized in antagonistic regions such as RGCs. That the PERG originates from RGCs has been shown in crucial experiments of optic nerve lesions in different mammals that retrogradely kill RGCs while leaving outer retina neurons intact (Porciatti, 2015). In these preparations, the PERG is abolished while the standard Flash-ERG is unaltered. Also, blocking retrograde axon transport in the optic nerve or impairing the source of target-derived factors to RGCs, reversibly reduces the PERG. Thus, the generation of the PERG signal requires the presence of functional RGCs as well as the normal trophic support of target-derived factors. Altogether, the PERG appears to be sensitive means to probe RGC function and an important outcome measure for in-vivo studies of optic nerve degeneration/regeneration.

The PERG as tool to probe RGC function in neurodegeneration/regeneration research: A large body of clinical and experimental studies have shown that the PERG is early altered in human and experimental models of progressive optic nerve degenerations such as glaucoma. Notably, the time course of PERG loss typically anticipates corresponding loss of optic nerve tissue, indicating that RGC dysfunction precedes RGC death (Porciatti and Ventura, 2012). Also, RGC dysfunction preceding death in glaucoma has been shown to be reversible after reduction of the intraocular pressure. Thus, the PERG can be used to non-invasively test whether neuroprotective treatments restore RGC function or minimize progression of RGC dysfunction (Williams et al., 2017; Yu et al., 2018). In neurodegeneration research, the PERG can contribute to answer the key question of whether surviving/regenerating RGCs are functional.

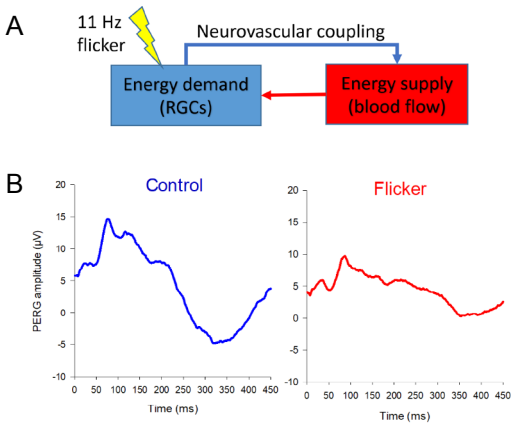

Figure 1 Simple RGC energy budget model.
(A) The normal dynamic equilibrium between RGC energy demand and energy supply from blood is unbalanced by the presence of 11 Hz flickering light, which requires substantial energy consumption. (B) Representative examples of PERGs in response to alternating black/white bars with superimposed flicker at either 101 Hz (control) and 11 Hz (test). Flicker at 101 Hz is beyond the temporal resolution of mouse cones and does not generate energy consumption. Upon 11 Hz flicker, a new dynamic equilibrium between energy demand and supply causes reduction of the PERG signal compared to control (flicker PERG adaptation). PERG: Pattern electroretinogram; RGC: retinal ganglion cell.

Adaptable RGC function: An important aspect of RGC function is response adaptation–the intrinsic ability of RGC to reduce their response gain upon a physiological challenge such as stimulus intensity (Chou et al., 2016) or the presence of a flickering light (Chou et al., 2019). This adaptive ability reflects integrative properties of RGC synaptic connectivity (Beaudoin et al. 2008) as well as autoregulatory neuro-vascular-metabolic coupling mechanisms driven by increased metabolic demand of active RGC (Newman, 2013). Adaptive RGC abilities may be early disrupted in disease, as RGC death in glaucoma and in other optic nerve degenerations is often preceded by alteration of synapse function and dendritic remodeling. These adaptive changes are reflected in the PERG response dynamics (Chou et al., 2016, 2019) and can be used to probe early degenerative alterations that are potentially reversible and may have predictive value on the progression of disease with or without neuroprotective treatment.

Adaptation due to contrast gain control: The response of RGC to increasing stimulus contrast is not linear. At high contrast, RGC typically reduce their response sensitivity and decrease their integration time (Beaudoin et al., 2008). These properties are reflected in the PERG response dynamics, that shows relatively reduced amplitude and shorter latency at high contrast compared to low contrast (Porciatti et al., 2010; Chou et al., 2016). Important, PERG contrast gain control characteristics may differ between mouse strains, suggesting strain-dependent connectivity in the inner retina (Porciatti et al., 2010; Chou et al., 2016). Also, PERG contrast gain control characteristics are modifiable in the same strain by manipulating neurotrophic support (Chou et al., 2016).

PERG contrast gain control characteristics are impaired after deficit of neurotrophic support and are partially restored after exogenous neurotrophic administration. As neurotrophic factors play a major role as synaptic modulators and as regulatory factors that mediate neuron survival (Poo, 2001), contrast-dependent changes of RGC electrical responsiveness conceivably reflect plastic changes in the inner retina pathways. Thus, assessing PERG contrast gain characteristics may offer an opportunity to identify and monitor early changes of RGC connectivity preceding cell death and probe the effect of neurotrophic treatments.

Adaptation due to flickering light: Flickering light around 10 Hz induces rapid dilation of retinal vessels in the inner retina (functional hyperemia). When flickering light is superimposed to slow-reversing PERG stimuli in the mouse, the resulting response progressively decreases in amplitude up to 50% over 4 minutes and slowly recovers baseline values over 20 minutes (Chou et al., 2019). The magnitude and time course of PERG adaptation to flicker may differ between mouse strains, suggesting phenotypic differences in neuro-vascular-metabolic autoregulatory mechanisms in response to increased metabolic demand. Flicker-induced PERG adaptation in the mouse has a counterpart in human for patterned visual stimuli flickering in counterphase at 8 Hz (contrast-reversing at 16 Hz at constant mean luminance). These stimuli generate a strong hemodynamical response at the optic nerve head, which is associated with a slow decline of PERG amplitude up to 30–40% over 2 minutes (Porciatti et al., 2005). The magnitude of PERG adaptation to counterphase flickering patterns is reduced in early glaucoma and optic neuritis. Thus, assessing PERG adaptation to counterphase flickering patterns may offer an opportunity to identify and monitor early changes of neuro-vascular-metabolic autoregulatory mechanisms in the inner retina and probe the effect of treatments targeting metabolic pathways.

Relevance for neuroregeneration research: A major challenge in neuroregeneration research is the establishment of novel neural-neural and neuro-vascular connections. Assessing neurovascular/neurometabolic autoregulation of inner retina pathways upon visual stimulation may represent an important non-invasive tool to probe and monitor RGC response dynamics under altered conditions, as well as their ability to adapt their function in response to a metabolic or molecular challenge. This might also help predicting the fate of surviving/regenerating RGCs.

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Tsung-Han Chou, Vittorio Porciatti*
Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, FL, USA
***Correspondence to:** Vittorio Porciatti, DSc, vporciatti@med.miami.edu.*
***orcid:** 0000-0002-1592-3532 (Vittorio Porciatti)*
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