Autoregulation of retinal ganglion cell function to metabolic challenge in glaucoma

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Background

Retinal ganglion cell (RGC) dysfunction occurs early in glaucoma and precedes RGC death and loss of optic nerve tissue. There is a critical time window between RGC dysfunction and death in which disease progress could be delayed or even reversed with a therapeutic intervention. A better understanding of the mechanisms of RGC dysfunction, of factors that influence it, of adequate tools to quantitatively assess it in vivo, represents a critical barrier to progress on prevention and treatment in glaucoma.

Failure of autoregulatory mechanisms is thought to trigger cell death in glaucoma.

We propose to investigate the autoregulatory response of RGC under flickering light to increase metabolic demand and cause vasodilation, using a mouse model of glaucoma (DBA/2J) and an healthy control group (C57BL/6J). RGC response dynamics, with and without flicker added, will be assessed with pattern electroretinogram (PERG), a sensitive measure of RGC function.

Methods

As the PERG is the fundamental tool of this proposal, PERG methods was optimized to record robust responses simultaneously from both eyes using a common non-corneal electrode. Comparing to standard, this approach eliminates the need of corneal manipulation that may spuriously alter IOP and induce cataract. Finally, the use of a common non-corneal electrode minimizes interocular variability and test-retest variability.

Results

Figure 1 (A and B) shows an example of flicker-induced neurovascular changes in a young C57Bl/6J mouse. As a 101 Hz flicker is superimposed to the PERG stimulus, a normal PERG signal is generated. The corresponding fluorescein angiograms (Figure 1C and D) show the inner retina vasculature. During 11 Hz flicker, the PERG signal substantially decreases, while fluorescein angiography reveals a corresponding vasodilation. These results indicate a clear autoregulatory PERG response to flickering light in healthy retina.

Results in the figure 2 indicate that there are genotypic differences in the autoregulatory RGC response to increased metabolic demand, with the DBA/2J mouse prone to glaucoma showing an altered PERG dynamics already at young age. When a 101 Hz flicker is superimposed to the PERG stimulus, a normal PERG signal is generated. During 11 Hz flicker, the PERG signal substantially decreases.

Conclusions

Preliminary results indicate that in control mice the flicker-PERG amplitude declines and the latency increases, while the opposite effect is seen in DBA/2J mice. This indicates that while in control mice the flicker-induced metabolic unbalance results in an autoregulatory RGC response, this process is altered in DBA/2J mice. Results are significant as the flicker-PERG can disclose early RGC dysfunction and predict severity of glaucoma and indicates a clear autoregulatory PERG response to flickering light in healthy retina. We will investigate the onset and magnitude of altered PERG dynamics in individual DBA/2J mice over time compared to controls, and we will correlate these changes with the magnitude of RGC degeneration to determine the predictive value of flicker-PERG for severity of disease progression.

Our research will contribute to establish if RGC metabolic homeostasis can be assessed in vivo as a modifiable PERG signal in response to physiological stressors, if it can predict severity of disease and serve as marker for early diagnosis in order to start treatment in a pre-symptomatic phase.

Figure 1: A) and B) show flicker-induced neurovascular changes in a young C57Bl/6J mouse; C) and D) show the corresponding fluorescein angiograms. P1 = Positive wave; N2 = Negative wave.