

Photoreceptor Mitochondrial Reserve Capacity: Is It the Etiology for Differential Compartmental Vulnerability?

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The study of mitochondrial function/dysfunction and its relation to neurodegeneration requires standardized and sensitive techniques that enable the identification of molecular targets for cell type-specific neuroprotection. Using small central retinal punches from light-adapted wild-type and transgenic (Tg) C57BL/6J mice, Kooragayala et al.¹ examined changes in the retinal oxygen consumption rate (OCR) from the Seahorse XF24 Bioanalyzer normalized to mitochondrial cytochrome c content. Maximal and high uncoupled OCRs in wild-type mice were achieved with Ames media or glucose plus lactate, but not with mitochondrial-specific fuels. Using mitochondrial uncouplers with wild-type and *Nrl*^{-/-} mice, they concluded that rod and cone photoreceptor (PR) mitochondria have a similar and limited mitochondrial reserve capacity (MRC) of 20% to 25%, albeit uncoupler-induced MRC in isolated rat retinal mitochondria is 82%.² In contrast, Tg mice with dysfunctional or no PRs have lower OCRs, but higher MRCs: results attributed to the inner retina.¹ They suggest the limited MRC in PR mitochondria serves as an early indicator of high metabolic stress, which increases vulnerability of PRs to energy challenges, oxidative stress, and degeneration. However, glucose use, lactate production [\sim P], and/or oxygen consumption are not uniform in different retinal layers or among the four distinct PR mitochondrial compartments.^{3,4} For example, PR synaptic terminals have a higher [\sim P], lower oxygen consumption, and increased vulnerability to toxicant-induced stress relative to inner segments.^{3,4} The current study¹ advances the understanding of PR mitochondrial vulnerability and thereby emphasizes the importance of determining the MRC of different retinal cells and their compartments in other models of retinal disease. To further enhance the usefulness of this *ex vivo* technique, future studies might also determine the Pasteur and Crabtree effects; MRC of the different PR mitochondrial populations during pathophysiological conditions and development; and alternative strategies that PRs use to accommodate their cellular requirements for [\sim P].

References

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