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Measuring mitochondrial respiration in vivo: From mouse to human

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Abstract

Toward translation of a measure of neuronal mitochondrial respiration *in vivo*: From mouse to human

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Introduction: The mitochondrial energy ecosystem can be non-invasively interrogated in photoreceptors by combing a clinical tool, optical coherence tomography (OCT), with a mitochondrial protonophore (2,4 dinitrophenol, DNP). It remains unclear if only supra-clinical doses of DNP will be useful for mouse studies or if lower but clinically relevant doses of DNP would facilitate translation from mice to humans.

Methods: The experiment was a paired longitudinal design that took place over 2 days. On day 1, C57BL/6J mice were overnight dark adapted, then light-adapted for 5 h before OCT examination before regaining consciousness; a similar procedure was followed on day 2 but mice were injected IP with either saline or an acceptable human dose of DNP (0.5 mg/kg) 1 hour before OCT examination. Pre- and post-injection retinal laminae thickness were compared for evidence of toxicity. In particular, we measured the external limiting membrane – retinal pigment epithelium to look for thinning between day 1 and 2, which has a confirmed basis in DNP modulation of rod photoreceptor mitochondrial respiration upstream based on pH-triggering of RPE co-transporter-based water efflux.

Results: Compared to uninjected controls, saline evoked no changes in retina layer thickness between days 1 and 2. On the other hand, a clinical dose of DNP caused a reduction in ELM-RPE thickness in the absence of any other changes in retinal layer thickness, a finding consistent with increased mitochondrial respiration.

Conclusions: The promising results herein raise the possibility that combining a low dose of DNP with a standard clinical imaging tool will facilitate first-in-kind measurements of neuronal mitochondria in patients suffering from a range of diseases and morbidities.