Acute mitochondrial impairment underlies prolonged cellular dysfunction after repeated mild traumatic brain injuries

Brad Hubbard, PhD [1] • Binoy Joseph, PhD [1] • Malinda Spry, MS [1] • Hemendra Vekaria, PhD [1] • Patrick Sullivan, PhD [2] • Kathryn Saatman, PhD [3]

[1]Spinal Cord and Brain Injury Research Center, SCoBIRC, University of Kentucky • [2]Spinal Cord and Brain Injury Research Center; Department of Neuroscience; Lexington VAMC, SCoBIRC, University of Kentucky • [3]Spinal Cord and Brain Injury Research Center; Department of Physiology, SCoBIRC, University of Kentucky

Abstracts will be considered for both poster and platform presentations

Neurotrauma (TBI, spinal cord injury, etc.)

Mild TBIs (mTBIs), accounting for over 80% of the 1.7 million TBIs reported yearly in the U.S., can cause cognitive and behavioral impairments, the severity and duration of which increase in individuals that sustain additional mTBIs. While it is known that mTBI does not cause widespread neuronal death, the mechanisms underlying neurological impairment and increased cellular susceptibility to subsequent head impacts are unknown. To investigate the hypothesis that altered mitochondrial bioenergetics following mTBI underlie cellular vulnerability to repeated insults, we employed a mouse model of bilateral diffuse closed head injury (CHI) to examine mitochondrial function after mTBI. Previous data outlines the time course of mitochondrial respiration, utilizing the Seahorse XFe24 Flux Analyzer, from bilateral ventral cortex (including entorhinal cortex) and bilateral hippocampus homogenates collected at 6, 24, 48, and 96h post-injury. These results show that mitochondria exhibit a decrease in State III (ADP-mediated) oxygen consumption rate (OCR) in both regions compared to sham at 48h post-injury with recovery by 96h post-injury. To investigate if this impairment determines cellular vulnerability after mTBI, repeated CHIs (rCHI) were given at intervals of 48h and 96h to examine whether mitochondrial dysfunction is worsened and/or prolonged after rCHI. rCHI at 48h or 96h intervals did not notably worsen the depression in State III respiration compared to a single CHI, but rCHI repeated at a 48h interval resulted in more prolonged cortical mitochondrial dysfunction. Markers of oxidative stress, 4-hydroxynonenal (4-HNE), 3-nitrotyrosine (3-NT), and protein carbonyls (PC), were measured from mitochondrial homogenates. All markers in the hippocampus and PC in the cortex were significantly elevated at 48h after rCHI delivered 48h apart, but not after single CHI or two CHI delivered 96h apart. On-going studies show that synaptic and non-synaptic mitochondrial populations, derived from novel magnetic labeling, likely have differing regional and temporal respiration profiles after rCHI. This study establishes that mTBI results in early mitochondrial dysfunction that has region-specific temporal characteristics and this dysfunction may be a determinant for cellular vulnerability to repeated head impacts.

Funding Sources: NSF EPSCoR Seed Grant 4978/111315, VA Merit Award 1I01BX003405-01A1 and Kentucky Spinal Cord and Head Injury Research Trust (KSCHIRT) Grant 14-13A.