MATTHEW NICHOLS

BSc (Biochemistry/Biotechnology), Wilfrid Laurier University 2010
MSc (Chemistry), Wilfrid Laurier University 2012

DEPARTMENT OF PHARMACOLOGY

TITLE OF THESIS: MITOCHONDRIAL SIGNALLING AND BIOENERGETIC MECHANISMS THAT REGULATE NEURONAL CELL DEATH AND SURVIVAL IN MODELS OF ISCHEMIC BRAIN INJURY

TIME/DATE: 10:00 am, Friday, August 4, 2017

PLACE: Room 3107, The Mona Campbell Building, 1459 LeMarchant Street, Halifax NS

EXAMINING COMMITTEE:

Dr. Peter Stys, Department of Clinical Neurosciences, University of Calgary (External Examiner)

Dr. Ian Weaver, Department of Psychology and Neuroscience, Dalhousie University (Reader)

Dr. Keith Brunt, Department of Pharmacology, Dalhousie University (Reader)

Dr. George Robertson, Departments of Psychiatry and Pharmac ology, Dalhousie University (Supervisor)

DEPARTMENTAL REPRESENTATIVE: Dr. Christopher McMaster, Department of Pharmacology, Dalhousie University

CHAIR: Dr. Ian Folkins, PhD Defence Panel, Faculty of Graduate Studies

ABSTRACT

Mitochondrial collapse is considered a pivotal event in ischemic brain damage. Compounds that preserve mitochondrial function following an ischemic insult may thus protect the brain from stroke injury. Flavonoids are a diverse group of polyphenolic compounds reported to be neuroprotective in a wide-variety of ischemic stroke models. These compounds appear to increase resistance to ischemic injury by targeting multiple signal transduction and metabolic networks. In view of evidence that increased consumption of the flavonoids epicatechin (E) and quercetin (Q) may reduce stroke-risk, I have measured the effects of combining E and Q on oxygen-glucose deprivation (OGD)-induced damage, mitochondrial function and pro-survival signaling for cortical neuron cultures. Relative to E or Q alone, E+Q synergistically protected cortical neurons from OGD-induced damage in tandem with a corresponding preservation of mitochondrial bioenergetics. E+Q also produced supra-additive inductions of pro-survival pathways involving calcium, Akt, nitric oxide and CREB that converge on the mitochondrion. The therapeutic relevance of these findings was supported by the ability of oral administration of E+Q to protect mice from hypoxic/ischemic (HI) brain damage. Consistent with evidence that Q improves bioenergetics by stimulating the mitochondrial calcium uniporter (MCU), Q increased neuronal cytosolic calcium spikes and the mitochondrial membrane potential. However, excessive MCU-mediated calcium uptake promotes cell death. I therefore employed global MCU (G-MCU) nulls and central neuron-specific MCU (CNS-MCU) deficient mice to compare the effects of constitutive and inducible MCU ablation, respectively, on neuronal mitochondrial bioenergetics and resistance to ischemic damage. Despite reduced mitochondrial calcium uptake by forebrain mitochondria isolated from G-MCU nulls, cortical neuron cultures derived from these mice were not resistant to OGD. My findings suggest that increased neuronal glycolysis resulting in the suppression of Complex I activity may have compromised the resistance of G-MCU nulls to HI brain injury. By contrast, CNS-MCU deficiency, induced at adulthood, protected mice from HI brain injury. MCU suppression by siRNA-mediated silencing also protected cortical neuron cultures from OGD-induced viability loss. Unlike G-MCU ablation, siRNA-mediated MCU silencing did not enhance glycolysis in cortical neurons exposed to OGD. These findings suggest that acute MCU inhibition may be a viable therapeutic approach for stroke.