A pharmacologic neuroprotective approach to experimental TBI: targeting mitochondria & lipid peroxidation-derived aldehydes

Jacqueline Kulbe [1] • Indrapal Singh, PhD [1] • Jacob Dunkerson [1] • Juan Wang, MD [1] • John Cebak, PhD [2] • Rachel Hill, PhD [1] • Rebecca Smith, PhD [1] • Peter Huettl [3] • Edward Hall, PhD [1]

[1]SCoBIRC, University of Kentucky • [2]DeBusk College of Osteopathic Medicine, Lincoln Memorial University • [3]CenMeT, University of Kentucky

Abstracts will be considered for both poster and platform presentations

Neurotrauma (TBI, spinal cord injury, etc.)

Traumatic brain injury (TBI) represents a significant health crisis in the United States. Currently there are no neuroprotective FDA-approved pharmacotherapies for TBI. Due to the complex pathophysiology which occurs following TBI, more robust pharmacological approaches must be developed. Mitochondrial dysfunction and the formation of lipid peroxidation-derived neurotoxic aldehydes contribute extensively to TBI pathology, making them promising therapeutic targets for prevention of cellular death and dysfunction following TBI. The following are evaluated. 1) The neuroprotective effect of cyclosporine A (CsA), on synaptic and non-synaptic mitochondria. Mitochondria are heterogeneous, consisting of both synaptic and non-synaptic populations, which have distinct properties. Our results indicate that compared to non-synaptic mitochondria, synaptic mitochondria sustain greater damage 24h following severe controlled cortical impact injury in young male rats, and are protected to a greater degree by CsA, an FDA-approved immunosuppressant, capable of inhibiting mitochondrial permeability transition. 2) The neuroprotective effects of a 72h subcutaneous continuous infusion of CsA combined with phenelzine (PZ), an FDA-approved monoamine oxidase inhibitor (MAOI) class anti-depressant capable of scavenging neurotoxic aldehydes. Our results indicate that individually CsA or PZ attenuate neurotoxic aldehyde formation, PZ maintains mitochondrial respiratory control ratio and cytoskeletal integrity, but together, PZ + CsA, do not maintain neuroprotective effects. 3) Although neurotoxic aldehyde scavenging, a PZ mechanism of action, has proven neuroprotective properties, the effect MAO inhibition has on pathology following TBI is currently unknown. Therefore, we compared the effects of PZ (aldehyde scavenger, MAOI), hydralazine (HZ, aldehyde scavenger, non-MAOI), and pargyline (PG, non-aldehyde scavenger, MAOI) on learning and memory following TBI using the Morris water maze. However, none of the drugs were able to improve injury-induced deficits in retention memory and the PZ animals lost more weight compared to other groups, potentially due to increases in norepinephrine or serotonin. In fact, when HPLC was utilized to evaluate monoamine and metabolite levels of our PZ, HZ, PG dosing paradigm in naïve rats, PZ showed a significant increase in norepinephrine and serotonin compared to other groups. Ongoing studies include histological analysis of PZ, HZ, and PG groups, as well as characterization of monoamine and metabolite levels acutely following TBI.