Phenelzine Administration following Traumatic Brain Injury Improves Mitochondrial Function and Reduces Lipid Peroxidation and Cytoskeletal Degradation

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Background: Traumatic brain injury (TBI) results in the production of peroxynitrite (PN), leading to oxidative damage of lipids and protein. PN-mediated lipid peroxidation (LP) results in production of reactive aldehydes such as 4-hydroxy-2-transnonenal (4-HNE) and acrolein. Additionally, previous studies have demonstrated that TBI results in not only mitochondrial respiratory dysfunction, but impaired calcium (Ca2+) buffering capacity.

Hypothesis: The goal of these studies was to explore the hypothesis that interrupting secondary oxidative damage following a TBI via acute pharmacological inhibition of LP by phenelzine (PZ), an aldehyde scavenger, would protect against LP-mediated mitochondrial and neuronal damage.

Methods: Male Sprague-Dawley rats (10-12 wks; 300-325 g) received a severe (2.2 mm) controlled cortical impact (CCI)-TBI. PZ was administered subcutaneously (s.c.) at 15 min (10 mg/kg) and 12 hrs (5 mg/kg) post-injury. Cortical mitochondria were isolated at 24 and 72 hrs post-injury. Mitochondrial respiration was measured using a Clarke-type electrode and Ca2+ buffering was monitored using a spectrofluorometer. Protein samples were assessed for α-spectrin breakdown as an indicator of axonal cytoskeletal degradation and 4-HNE and acrolein as markers of LP by Western immunoblot.

Results & Conclusions: Administration of PZ significantly improved mitochondrial respiration at 24 hrs compared to vehicle-treated animals and PZ-treated animals were never significantly lower than Sham. At 72 hours, injured animals had significantly lower respiration compared to Sham and PZ administration significantly improved mitochondrial respiration compared with vehicle-treated animals. These results demonstrate that PZ administration preserves mitochondrial bioenergetics at 24 hrs and that this protection is maintained out to 72 hrs post-injury. PZ administration also improved mitochondrial Ca2+ buffering capacity and mitochondrial membrane potential parameters compared to vehicle-treated animals at 24 hrs. The amount of α -spectrin breakdown in cortical tissue was also significantly reduced at both 24 hrs post-injury compared to vehicle-treated animals following administration of PZ. These results indicate that acute PZ treatment successfully attenuates LP-mediated oxidative damage eliciting multiple neuroprotective effects following TBI.

Effects of Controlled Cortical Impact Brain Injury on Cell Loss and Neurogenesis in the Mouse Dentate Gyrus

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Brain injury can result in neural impairments and the development of post-traumatic epilepsy but cellular targets to treat these types of pathology are not well identified. Selective cell loss is one prominent consequence of brain injury. The subgranular zone of the dentate gyrus (DG) is a site of continued proliferation and incorporation of new neurons, i.e., neurogenesis, throughout life. Brain insults may disrupt adult neurogenesis and lead to the formation of aberrant neuronal circuits. This study examined how cell loss and neurogenesis within the DG are affected by unilateral focal brain injury using controlled cortical impact (CCI). Ongoing work is using CCI to examine whether brain injury affects the physiology of adult born dentate granule cells or the signalling to their downstream synaptic targets.