Pharmacological inhibition of oxidative damage by the lazaroid U-74389G improves cortical mitochondrial function following TBI

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Introduction:
Traumatic brain injury (TBI) results in hemoprotein breakdown leading to cellular accumulation of free iron. Iron (Fe) can react with hydrogen peroxide (H2O2) and/or lipids resulting in post-traumatic Fe-mediated oxidative damage. The lazaroid U-74389G (desmethylated Tirilazad; TZ), an inhibitor of Fe-dependent lipid peroxidation (LP), was used to protect mitochondrial function following TBI in young adult male rats.

Methods:
Male SD rats received a severe (2.2 mm) controlled cortical impact-TBI. TZ was administered intravenous (iv) at 15 min and 2 hrs post injury (hpi) followed by an intraperitoneal (ip) dose at 8 hpi at the following doses (mg/kg): 0.3 (iv) + 1 (ip), 1 + 3, 3 + 10, 10 + 30. Total cortical mitochondria were isolated at 72 hpi and respiratory rates were measured using a Clarke-type electrode. Mitochondrial 4-HNE and acrolein were evaluated as indicators of LP-mediated oxidative damage by quantitative Western immunoblot.

Results:
At 72 hrs post-TBI injured animals had significantly lower mitochondrial respiration rates compared to Sham. Administration of TZ at the 1 mg/kg dosing paradigm significantly improved mitochondrial respiration rates for State II, State III, Complex II driven State V and RCR compared to vehicle-treated animals. At 72 hrs post-TBI injured animals had significantly higher levels of mitochondrial 4-HNE and acrolein compared to Sham and administration of TZ reduced reactive aldehydes levels compared to vehicle-treated animals.

Conclusions:
The aim of this study was to explore the hypothesis that interrupting secondary oxidative damage via acute pharmacological inhibition of Fe-mediated LP by TZ following a CCI-TBI would provide mitochondrial neuroprotective effects in a dose-dependent manner. We found that acute administration of TZ to injured rats resulted in improved mitochondrial function and lowered the levels of reactive aldehydes in the mitochondria. These results establish not only the most effective dose of TZ treatment to attenuate LP-mediated oxidative damage, but also set the foundation for further studies to explore additional neuroprotective effects following TBI.