Pioglitazone Improves Functional Neuroprotection Following Spinal Cord Injury

Samir Patel, PhD[1] • David Cox, MS[2] • Jenna Gollihue[1] • William Bailey[2] • John Gensel, PhD[1] • Patrick Sullivan, PhD[3] • Alexander Rabchevsky, PhD[1]

[1]Spinal Cord & Brain Injury Research Center, Department of Physiology, University of Kentucky • [2]Spinal Cord & Brain Injury Research Center, University of Kentucky • [3]Spinal Cord & Brain Injury Research Center, Department of Anatomy & Neurobiology, University of Kentucky

Background: Emerging evidence suggests that pharmacological interventions which preserve mitochondrial integrity acutely following neurotrauma promote significant neuroprotection and functional recovery. Pioglitazone belongs to a class of drugs called thiazolidinediones (TZDs) and is primarily a PPAR-γ agonist that rapidly crosses the blood-brain barrier. Pioglitazone is an FDA-approved drug for treatment of type-2 diabetes that is also reported to be neuroprotective after CNS injuries. Novel findings indicate that these therapeutic effects of pioglitazone may also depend on PPAR-independent mechanisms that ameliorate mitochondrial dysfunction based on its interactions with the unique mitochondrial protein, mitoNEET, which when dimerized under stress conditions causes mitochondrial dysfunction.

Hypothesis: We hypothesized that pioglitazone would improve mitochondrial dysfunction acutely after spinal cord injury (SCI) through specific inhibition of mitoNEET dimerization that would result in improved functional neuroprotection at later stages. Accordingly, in these initial experiments we assessed the protective efficacy of pioglitazone on acute mitochondrial respiration and long-term functional neuroprotection following SCI in wildtype mice in order to subsequently compare outcome measures to transgenic mitoNEET knockout mice.

Methods: For acute mitochondrial assessments, adult male C57BL/6 mice (n=31) were divided into 4 groups: 1) Sham, 2) SCI+Vehicle 15min, 3) SCI+Pio 15min, and 4) SCI+Pio 3hr. Mice received either T9 laminectomy (n=7) or contusion SCI (75 kdyn, IH Impactor; n=7-9/group). Injured mice received (i.p.) vehicle (DMSO) or pioglitazone (10 mg/kg) either at 15min or 3hr post-injury, and a booster at 24hr. At 25hr, isolated mitochondria from sham and injured spinal cords were assessed for respiration. For long-term behavioral testing, injured mice (n=22) were divided in two groups: 1) SCI+Vehicle and 2) SCI+Pio (n=10-12/group) and received DMSO vehicle or pioglitazone (10mg/kg) at 15min post-injury and once daily for 5 days. Mice were assessed weekly for hindlimb function using the Basso Mouse Scale (BMS) for 4 weeks followed by terminal gridwalk analysis. The mice were then perfused with paraformaldehyde and coronal spinal cord sections were processed for histology.

Results and conclusions: Pioglitazone treatment following contusion SCI significantly maintained compromised mitochondrial respiration acutely and improved long-term hindlimb locomotor recovery. Such significant recovery was correlated with increased gray and white matter sparing, suggesting that maintaining mitochondrial bioenergetics limited secondary tissue damage resulting in greater functional recovery. Based on such therapeutic potential of pioglitazone to treat SCI, we are now using mitoNEET knockout mice and mitoNEET ligand (NL1) to establish the mechanism(s) by which pioglitazone exerts its neuroprotective effects.

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