Pioglitazone Maintains Mitochondrial Bioenergetics via Binding to mitoNEET Following Spinal Cord Injury

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Abstracts will be considered for both poster and platform presentations

Neurotrauma (TBI, spinal cord injury, etc.)

mitoNEET is a homodimer protein present within the outer membrane of mitochondria comprising a redox active [2fe-2S] cluster that has an essential role in regulating energy metabolism, iron homeostasis, and production of reactive oxygen species in mitochondria. mitoNEET is also a primary target of type II diabetes drug, pioglitazone (Pio), which we have recently shown to be neuroprotective after contusion spinal cord injury (SCI) and traumatic brain injury in mice. Accordingly, the current study was designed to test the novel hypothesis that Pio maintains mitochondrial respiration following SCI via its specific interaction with mitoNEET protein. Adult male C57BL/6 (n=80) or mitoNEET knockout (n=32) mice received either T9 laminectomy (sham; n=16) or contusion SCI (75 kdyn, IH Impactor; n=96), and 3 hr later they were treated i.p. with either Vehicle (1:1 DMSO + polyethylene glycol 400), Pio (1, 10, 20 or 40 mg/kg) or NL1, a specific mitoNEET ligand (10, 20 or 40 mg/kg), followed by boluses at 24 and 48 hr post-injury. At 49 hr post-injury, mitochondria were isolated from 5 mm of spinal cord centered on injury site and assessed for their respiration in terms of oxygen consumption rate (OCR) using Seahorse XF(e) 24 Extracellular Flux Analyzer. The OCR for naïve mitoNEET KO mice mitochondria was found to be ~25% lower than for naïve WT mitochondria, and SCI significantly reduced OCR in both WT and mitoNEET KO mice; the latter ~25% lower than WT. However, while treatments with Pio or NL1 in WT injured mice significantly maintained mitochondrial OCR to near normal levels in a dose-dependent manner, neither Pio nor NL1 were effective in preserving OCR in mitoNEET KO mice. These results indicate that the protection afforded by Pio is related to its interactions with the mitochondrial protein, mitoNEET, and not entirely dependent upon activation of Peroxisome Proliferator Activated Receptor (PPAR) as customarily reported. Ongoing experiments are extending the effective therapeutic time windows after SCI for both Pio and NL1 before assessing their long-term effects on functional neuroprotection. Supported by The Craig H. Neilsen Foundation # 476719.