



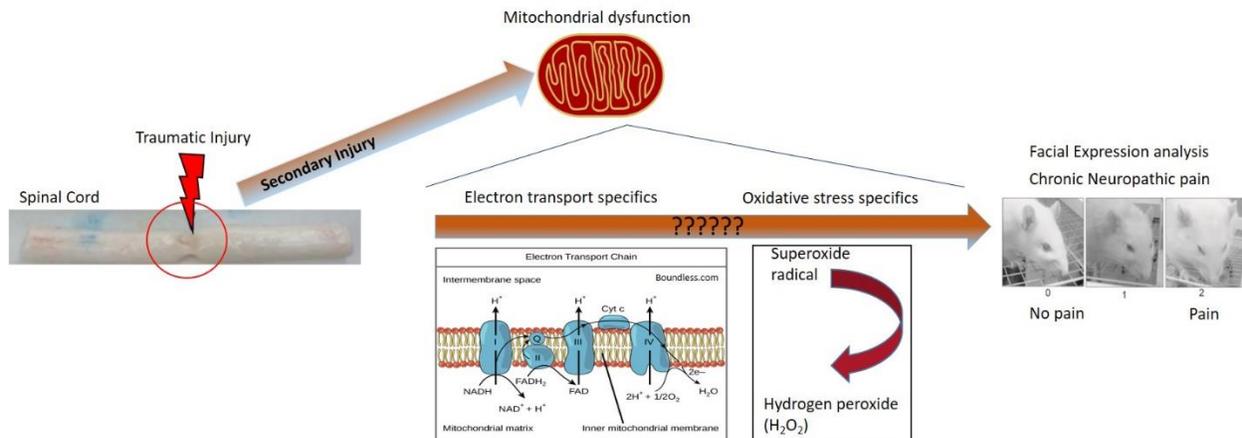
## EVALUATION OF NEUROPATHIC PAIN AND MITOCHONDRIAL FUNCTION AFTER SPINAL CORD INJURY

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### ABSTRACT

The overall goal of this project is to elucidate novel mitochondrial bioenergetic and oxidative stress mechanisms that underlie the formation of neuropathic pain after traumatic spinal cord injury.



Of the people who suffer from a spinal cord injury (SCI) 70% develop neuropathic pain (NP). It is well known that mitochondria play a role in SCI pathophysiology. However, it is unknown the specific role of mitochondria in the formation of neuropathic pain, in particular, the mechanisms, and timing of mitochondrial dysfunction and how it relates to NP. As such, a highly effective and viable mitochondrial based treatment for this mechanism of SCI-NP does not yet exist. The overall aim of this investigation was to understand the role of mitochondrial bioenergetics in the spinal cord and the role it plays in the formation and maintenance of neuropathic pain after SCI. Utilizing a previously established and highly relevant supraspinal-pain outcome measure, these experiments will establish a model in which to evaluate specific molecular mechanisms of SCI-NP. We hypothesized that the evaluation of supra-spinal pain using the Grimace Scale can detect

changes in mitochondrial function and oxidative stress related to SCI-NP. For the experiment, age and weight matched adult male and female Sprague Dawley rats were randomly assigned to one of the following groups: laminectomy (LAM) uninjured controls or spinal cord injured (SCI vehicle). Antioxidant treatment groups were high dose weekly (SCI-HDW), spinal cord injured given high dose daily (SCIHDD), and spinal cord injured given low dose daily (SCI-LDD). The animals received a C5 hemi-contusion SCI, induced on the right cervical spinal cord with a force of 300kDy followed by a 5-second dwell to induce ischemia. The LAM animals received all surgical procedures except the impact and ischemic dwell. The mitochondrial bioenergetics were evaluated from isolated spinal cord mitochondria using Oroboros High Resolution Respirometry. Oxidative stress was evaluated using Amplex Red for hydrogen peroxide production. We found that NP begins in week 3 post-SCI and continues at least until week six indicating that chronic NP can result from this model of spinal cord injury. Interestingly, administration of the MnSOD mimetic MnTnHex-2-PyP 5+ ameliorates NP starting at week three, suggesting that there is a mitochondrial based oxidative stress mechanism the underlies chronic pain. Next we evaluated mitochondrial function and found that abnormalities in electron transport chain persist at 6-weeks post-SCI and this dysfunction is associated with increased hydrogen peroxide ( $H_2O_2$ ) production. We identified mitochondrial complex I as decreased post-SCI, however the contribution to overall bioenergetics was variable. Overall, we concluded that the Grimace Scale can determine the onset of SCI-NP and evaluate the analgesic effects of antioxidant drugs. The changes in oxidative stress and bioenergetics are coincident with NP at 6-weeks post-SCI and may be differentially contributing to SCI-NP.  $H_2O_2$  production from complex I may be a key variable for SCI-NP in which there is global mitochondrial dysfunction. Future studies will evaluate the specific effects of MnTnHex-2-PyP 5+ on mitochondrial function in chronic SCI and identify the role of  $H_2O_2$  using the Grimace scale for supra-spinal neuropathic pain.