

Objective: Lateral hemisection spinal cord injury (SCI) at T10 produces nociceptive hyperreflexia in the cutaneous trunci muscle (CTM) reflex and the sprouting of nociceptive afferents in dorsal cutaneous nerves (DCNs), the afferent limbs of the reflex, 6 weeks after SCI, both above (T7) and below (T13) the level of injury, on both sides of the spinal cord. The numbers of Iba1+ microglia/macrophages, but not GFAP+ astrocytes, are also increased at T7 and T13 at this chronic time point following T10 SCI. Because a persistent inflammatory environment following SCI is thought to be related to the development of chronic neuropathic pain, we hypothesized that a selective soluble Tumor Necrosis Factor (TNF) blocker, XPro1595, could modulate chronic inflammation in these spinal segments away from the injury and alter the neural plasticity seen there. XPro1595 has been shown to impact inflammatory cell biology and could impact neural transmission by blocking microglial-derived TNF effects on glutamate and GABA receptors.

Design/Methods: Long Evans female rats were subjected to a T10 lateral hemisection SCI and injected with either 3 mg/kg or 10 mg/kg of XPro1595 subcutaneously every third day starting the day of surgery. Tissue samples were collected for electrochemiluminescence (Meso Scale Discovery) analysis to detect XPro1595 and for gene expression analysis using qRT-PCR 2 weeks and 6 weeks after SCI. Additional animals with SCI were then treated with XPro1595 at 10 mg/kg for 6 weeks following SCI. Three days before the terminal electrophysiological experiments, animals were injected with axon tracers, IB4 for C fibers and CTB for A fibers, at their T7 and T13 peripheral DCNs. CTM neurograms evoked by segmental DCN stimulations were recorded to measure reflex sizes 6 weeks after SCI. Animals were perfused to harvest spinal cord tissue for immunohistochemistry to quantify IB4+ C fibers and CTB+ A fibers as well as Iba1+ microglia/macrophages and GFAP+ astrocytes.

Results: Therapeutic levels of XPro1595 were detected in plasma, cerebrospinal fluid (CSF), brain, and spinal cord segments (T7, T10, T13) 2 weeks after SCI in a dose-dependent manner. After the chronic treatment for 6 weeks following T10 SCI, XPro1595 reduced the number of Iba1+ microglia/macrophages at T7 to uninjured levels and at T13 to lower than uninjured levels. XPro1595 treatment also reversed injury induced nociceptive hyperreflexia, returning T7 DCN evoked CTM reflex sizes to uninjured values and causing hyporeflexia relative to the uninjured state in T13 DCN evoked reflexes. The effect of 6 weeks of XPro1595 on nociceptive afferent sprouting in T7 and T13 DCNs is being evaluated. Gene expression levels were also investigated at T7 and T13 in uninjured, T10 SCI, and T10 SCI with XPro1595 treatment animals using qRT-PCR arrays. Groups of genes related to inflammation, neurotrophism, neural transmission, synaptic plasticity, and myelination are being evaluated in particular.

Conclusion: This study is the first we know of to examine the relationships between inflammation, reflex physiology, afferent anatomy and genetic changes associated with neural plasticity in the spinal cord away from the site of injury.

Support: DoD SC090469, Neilsen Foundation #284874, #297076

Learning Objectives:

Discuss the anatomical and physiological plasticity of pain afferents after SCI and how that can be influenced by controlling inflammation

Bibliography:

Effects of methylprednisolone and 4-chloro-3-hydroxyanthranilic acid in experimental spinal cord injury in the guinea pig appear to be mediated by different and potentially complementary mechanisms. Yates JR, Gay EA, Heyes MP, Blight AR. Spinal Cord. 2014 Sep;52(9):662-6. doi: 10.1038/sc.2014.118. Epub 2014 Jul 22.

Organization of sensory input to the nociceptive-specific cutaneous trunk muscle reflex in rat, an effective experimental system for examining nociception and plasticity. Petruska JC, Barker DF, Garraway SM, Trainer R, Franssen JW, Seidman PA, Soto RG, Mendell LM, Johnson

RD.
J Comp Neurol. 2014 Apr 1;522(5):1048-71. doi: 10.1002/cne.23461.

Simultaneous application of two neurotrophic factors after spinal cord injury.
Bohnert DM, Purvines S, Shapiro S, Borgens RB.
J Neurotrauma. 2007 May;24(5):846-63.