Peripheral Hypersensitivity to Subthreshold Stimuli Persists after Resolution of Acute Experimental Disc-Herniation Neuropathy and is Mediated by Heightened TRPV1 Receptor Expression and Activity

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Introduction

Pathophysiology of sciatica

- Mechanical compression
- Biochemical irritation

(Olmarker, Winkelstein, Murata, Aoki, Onda (1996–2008))

Rat radiculopathy model

- Autologous NP on DRG leads to allodynia and abnormal gait, with immune cytokine expression

(Shamji Spine, 2009)

Rationale

- Surgical intervention in appropriate patients can reduce pain, expedite return to work, and improve HRQOL

(Weinstein Spine, 2006)

- A significant fraction of surgical patients exhibit failed back surgery syndrome (FBSS)
- Transition from acute inflammatory neuritis to chronic neuropathic pain

Objectives

- To explore the molecular and cellular mediators of painful neuropathy associated with intervertebral disc degeneration
- To investigate the transition from acute inflammatory radiculopathy to chronic neuropathic pain following spinal degenerative disease

Methods

- C57BL/6 mice underwent mid-thigh sciatic nerve dissection, with exposure only (sham) or nucleus pulposus placement (NP)
- Behavioral analyses: mechanical (von Frey), thermal (Hargreave's), cold (acetone), gait (RotaRod)
- Immunohistochemical: sciatic nerve (F4/80, TNFa)

Following resolution of radiculopathy

- Intraplantar subthreshold capsaicin stimulation (NP and sham)
- Repeat with macrophage depletion at index operation
- Ex vivo: subthreshold DRG capsaicin stimulation to assess cation influx

Results

- Acute inflammatory painful phenotype developed in NP-treated animals (Figure 1)
- Mechanical sensitivity, heat and cold allodynia, gait imbalance
- Associated intraneural macrophage migration (Figure 2)

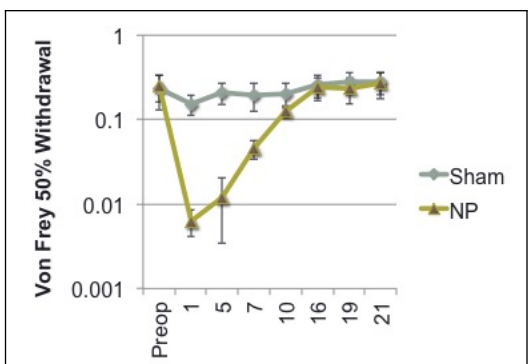

Figure 1: NP-treated animals (yellow) exhibit transient mechanical sensitization compared to sham animals (grey).

Results

- Upon resolution of acute inflammatory pain, mice at three and five weeks (but not one week) demonstrated mechanical allodynia to subthreshold capsaicin compared with sham-operated controls or NP-stimulation animals delivered vehicle (Figure 3, left)
- DRG explants derived from NP-treated animals exhibited greater cobalt staining upon capsaicin stimulation compared with controls (Figure 3, right)

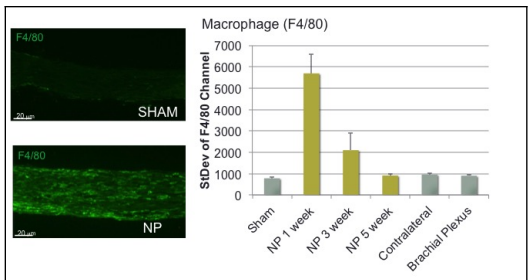

Figure 2: NP-treated animals (yellow) exhibit intraneural macrophage migration compared with sham animals (grey).

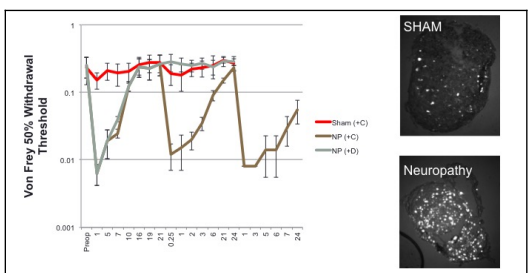

Figure 3: NP-treated animals (yellow) exhibit hypersensitivity to subthreshold intraplantar stimulus compared with sham (red). Ex vivo DRG stimulation shows heightened ganglion cell activation.

Results

- Pre-injury macrophage depletion prevents the development of long-term hypersensitivity in this animal model (Figure 4).

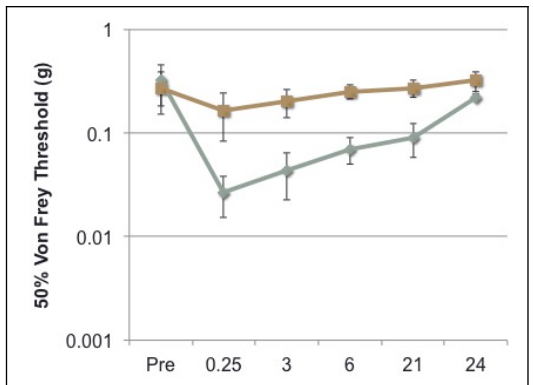

Figure 4: Strategies depleting macrophage function at the original injury (yellow) prevent this hypersenitivity from developing compared with NP-treated animals (grey).

Learning Objectives

- 1) Understand transition of acute inflammatory pain to chronic neuropathic pain.
- 2) Identify molecular targets to treat neuropathic pain after disc herniation radiculopathy.

Conclusions

- Acute lumbar disc radiculopathy requires intraneural macrophage migration
- Conversion to chronic neuropathic pain requires early macrophage activity and may be associated with altered structurally-encoded ganglion cell sensitivity