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Tricyclic Antidepressants Induce Anti-Inflammatory Signatures in Dorsal Root Ganglia after Prolonged Nerve Injury

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Monoamine-targeting antidepressants serve as frontline medications for chronic pain and associated comorbidities, including depression and anxiety. Widely used antidepressants for chronic pain include tricyclic antidepressants (such as amitriptyline and desipramine), selective serotonin reuptake inhibitors (such as fluoxetine and citalopram), and serotonin-norepinephrine reuptake inhibitors (such as duloxetine and venlafaxine). While a majority of existing evidence suggests that antidepressant efficacy in treating chronic pain is associated with effects on a dysregulated mesocorticolimbic system, few studies have assessed effects on the peripheral sensory nervous system.

In this study, we used the tibial spared nerve injury (SNI) model of neuropathic pain to assess the effects of desipramine (DMI) treatment on the transcriptional profile of L3-6 dorsal root ganglia (DRGs). Animals received SNI or Sham surgery four weeks prior to three weeks of treatment with DMI or Saline (15 mg/kg BID i.p.). Using whole-transcriptome RNA-sequencing and a cutoff of $\log_2 FC \geq |0.32|$ and p-nominal < 0.05, we identified 1,745 differentially expressed genes (DEGs; 572 p-adjusted < 0.1) in the SNI-Saline versus Sham-Saline comparison and 1,441 DEGs (105 p-adjusted < 0.1) in the SNI-DMI versus SNI-Saline comparison. Rank-rank hypergeometric overlap analysis showed that, from a threshold-free perspective, DMI had a concordant transcriptomic signature between SNI and Sham conditions. However, when comparing 1) SNI-DMI versus SNI-Saline and 2) SNI-Saline versus Sham-Saline comparisons, we observed the emergence of a non-concordant signature in which the two conditions had opposing regulation of several genes. To explore this further, we used Ingenuity Pathway Analysis (IPA), which predicted an increase in the activity of pro-inflammatory regulators in the SNI-Saline versus Sham-Saline comparison, such as IL1B, IL6, IL21, IL27, IFNG, and TNF. Conversely, in the SNI-DMI versus SNI-Saline comparison, IPA predicted a decrease in the Inflammasome Pathway, including neutrophils, leukocytes, and phagocytes, while also suggesting a reduction in CREB Signaling in Neurons. Accordingly, cell subtype deconvolution comparing SNI-DMI and SNI-Saline conditions demonstrated alterations primarily in neuronal transcriptional signatures.

Ongoing studies are focusing on the level of conservation of anti-inflammatory transcriptomic effects across tricyclic antidepressants and the lasting effects of antidepressants on sensory hypersensitivity in acute, subacute, and chronic mouse models of peripheral neuropathy and inflammation. For the former, we are repeating the paradigm above with Tianeptine (30 mg/kg BID i.p.), an atypical tricyclic antidepressant that our group has found more efficient at treating SNI-induced mechanical allodynia than DMI.