1521-0103/389/S3/supplement: ASPET 2024 Annual Meeting Abstract
The Journal of Pharmacology and Experimental Therapeutics

dx.doi.org/10.1124/jpet.521.942280
J Pharmacol Exp Ther 389: June 2024

Dorsal Root Ganglion NSUN2 Regulates Acute Sensory Hypersensitivity after Peripheral Injury

Zahra Farzin pour,[1] Randal A. Serafini,[2] Ilinca Giosan,[3] Schahram Akbarian,[4] Li Shen,[4] and Venetia Zachariou[1]

[1]Chobanian and Avedisian School of Medicine at Boston University; [2]Icahn School of Medicine at Mt Sinai; [3]Boston Univ Chobanian & Avedisian Sch of Med; and [4]Ichan School of Medicine at Mount Sinai

Abstract ID 94228 **Poster Board 521**

Chronic postsurgical pain, which develops in ∼10% of patients undergoing surgery, usually presents as complex acute pain but evolves into a persistent condition with neuropathic characteristics and a lack of responsiveness to several pain treatments. While opioids are currently the most effective option available, they also have drawbacks, such as tolerance, hyperalgesia and addiction risk.

NOL1/NOP2/SUN domain family member 2 (Nsun2) is an RNA methyltransferase modifying cytosine-5that targets tRNAs, mRNAs, and ncRNAs, thereby influencing the levels and/or function of these RNAs. However, Nsun2-induced cytosine methylation of RNA also epigenetically contributes to the regulation of gene expression – a process that has been understudied in several disease states, including acute/chronic pain. Here, we investigated whether acute postoperative pain altered levels of Nsun2 in the dorsal root ganglia (DRG) and whether exogenous changes in Nsun2 gene expression could affect pain-like behaviors.

Using qPCR analysis, we found that paw incision led to a significant Nsun2 gene upregulation in L3-6 DRGs on days 1 and 5 after surgery in male and female C57BL/6J mice. To determine whether Nsun2 upregulation is sufficient to cause pain-like behaviors, we administered AAV8-hSyn-Nsun2-Gfp or AAV8-hSyn2-Gfp vectors to the sciatic nerve of naïve mice. Nsun2 overexpression induced mechanical hypersensitivity (von Frey assay) but not thermal (Hargreaves and 42°C hot plate) or cold (0°C cold plate) hypersensitivity after three weeks of vector expression. Moreover, anxiety-like behaviours were observed inNsun2-overexpressing animals, as evidenced by decreased time in the open arms of the elevated plus maze, as well as increased marble burying activity. Locomotory activity in an open-field arena remained unchanged between vector groups, suggesting no movement deficits.

L3-6 DRGs from mice that received AAV8-hSyn-Nsun2-Gfp or AAV8-hSyn2-Gfp were then processed for RNA-sequencing analysis. This analysis aims to uncover unique gene expression signatures and the impact of Nsun2 on intracellular pathways associated with mechanical sensitivity and spontaneous pain states. Our findings so far point to a dynamic role of Nsun2 in mechanical sensitivity and suggest that increased Nsun2 activity in the DRG may promote sensory and emotional manifestations of chronic pain. Future directions include assessing the role of DRG Nsun2 expression in RNA stability and chromatin accessibility under injured states, as well as the molecular and behavioral effects of conditionally knocking down Nsun2 in the DRG of floxed Nsun2 mice after acute post-operative and chronic spared nerve injury treatment.