Modulating Nav1.8-expressing neurons offers promising direction to address symptoms of atopic dermatitis

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**Introduction/Background:** Atopic dermatitis (AD) is an inflammatory skin condition characterized by eczematous lesions, itch and pain. The inflammation and itch associated with AD are caused in part by dysregulation of neuroimmune circuits. Understanding these circuits is crucial for comprehending the pathophysiology of AD. Nav1.8 is a sodium channel expressed on C afferent fibers in the dorsal root ganglia (DRG). Knockdown of signaling pathways in Nav1.8+ nerves has been previously shown to reduce severity of AD in mice.

**Objectives:** We hypothesized that ablating Nav1.8 receptor-expressing neurons would lead to reduced severity of AD symptoms including itch and pain, and decreased expression of AD-related genes in a mouse model for AD.

**Methods:** Mice expressing iDTR (diphtheria toxin receptor) under the control of Nav1.8-Cre were used. Diphtheria toxin (DTX) was injected to ablate Nav1.8+ nerves and phosphate-buffered saline (PBS) was injected as a control. We achieved AD-like symptoms in both Nav1.8-ablated mice and control mice using topically-applied MC903 to mouse shaved nape skin.

**Results:** We noted no obvious clinical differences between Nav1.8-ablated mice and control mice skin. We found that Nav1.8+ ablation resulted in a ~70% (p<0.05) reduction in scratching behavior and ~40% (p=0.05) reduction in pain-related behaviors compared to control mice with intact Nav1.8. Nav1.8-nerve ablation similarly resulted in reduced expression of Tac1 (substance P – a neuropeptide known to mediate itch signaling) (p<0.05) and Il31ra (an itch-related cytokine receptor) (p<0.05) in Nav1.8-ablated mouse DRG tissue. However, we see no changes in
expression of AD-related cytokines in Nav1.8-ablated nape skin tissue compared to control skin, including Il4, Il13, Il31, and Tslp.

**Conclusions:** These results suggest that Nav1.8-expressing neurons play a key role in the itch and pain associated with AD, but may have no effect on AD-induced cutaneous inflammation. These findings could offer a promising new direction for further research into treatments targeting the itch and pain caused by AD.

**Keywords:** Atopic dermatitis, itch, pain, treatment

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