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NEURODEVELOPMENTAL DISORDERS

A painful role for SHANK3

> the proline-rich domain of SHANK3 is responsible for mediating these interactions and regulating TRPV1 function

Autism spectrum disorder (ASD) is often associated with marked sensory abnormalities, including altered sensitivity to pain; however, the mechanisms that lead to this dysfunctional sensory processing are unclear. Han *et al.* now demonstrate a role for the ASD-linked synaptic scaffolding protein SHANK3 (SH3 and multiple ankyrin repeat domains protein 3) in pain transduction and show that loss of this function alters responses to pain.

Mutations in *SHANK3* are one of the most common genetic causes of ASD, and many patients carrying these mutations exhibit altered pain sensitivity. To replicate the loss of SHANK3 function observed in these individuals, the authors generated mice lacking exons 18–22 of *Shank3* (*Shank3*$^{-/-}$ mice), resulting in a complete absence of SHANK3 protein expression. Although baseline sensitivity to thermal and mechanical stimuli was unaltered in these mice, they showed impairments in heat hyperalgesia, which was induced through injection of an inflammatory agent into the paw or a chronic constriction injury. Similar effects were observed in mice in which *Shank3* deletion was restricted to nociceptive neurons, suggesting that peripheral SHANK3 has an important role in the transduction of pain.

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The loss of heat hyperalgesia in *Shank3*$^{-/-}$ mice indicates that the transmission of information by thermally sensitive nociceptors — which are characterized by their expression of the capsaicin- and heat-sensitive ion channel TRPV1 (transient receptor potential cation channel subfamily V member 1) — may be disrupted. Indeed, the authors observed SHANK3 expression in primary sensory neurons in the dorsal root ganglion (DRG) and demonstrated a loss of sensitivity to capsaicin-induced pain in *Shank3*$^{-/-}$ mice. They also reported a reduction in capsaicin-induced currents and Ca^{2+} influx in dissociated DRG neurons from the mutant mice. Small interfering RNA-mediated knockdown of *SHANK3* also suppressed capsaicin-induced currents in cultured human DRG neurons, confirming that loss of SHANK3 impairs TRPV1 signalling in human neurons.

The contribution of SHANK3 to postsynaptic signalling is well known. However, the authors found that SHANK3 is expressed in the cell body and axon terminals of primary sensory neurons, suggesting that it has a presynaptic function. TRPV1 modulates glutamate release from nociceptor afferents in the spinal cord, and the authors found that loss of SHANK3 impaired this function. In spinal cord slices taken from control mice, capsaicin increased mini excitatory postsynaptic current frequency in dorsal horn neurons receiving input from TRPV1-expressing peripheral afferents. This response was reduced in slices from *Shank3*$^{-/-}$ mice and restored only on overexpression of *Shank3*.

These findings suggest a functional, and perhaps physical, interaction of SHANK3 and TRPV1. Indeed, the authors demonstrated co-expression of the two proteins in primary sensory neurons. Biochemical experiments showed that SHANK3 and TRPV1 can physically interact and that SHANK3 regulates the surface expression and trafficking of TRPV1 in cell culture. Further analysis showed that the proline-rich domain of SHANK3 is responsible for mediating these interactions and regulating TRPV1 function.

This study demonstrates an important role for SHANK3 in the modulation of TRPV1 function and pain transduction, the loss of which might contribute to pain processing abnormalities in individuals carrying *SHANK3* mutations (and could point to a general mechanism underlying sensory deficits in ASD). The insights provided by this study into the mechanisms of pain processing and the generation of hyperalgesia might also enhance our understanding of and suggest future treatment strategies for chronic pain conditions.

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ORIGINAL ARTICLE Han, Q. *et al.* SHANK3 deficiency impairs heat hyperalgesia and TRPV1 signaling in primary sensory neurons. Neuron http://dx.doi.org/10.1016/j.neuron.2016.11.007 (2016)