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Is Optogenetic Activation of Vglut1-Positive Aβ Low-Threshold Mechanoreceptors Sufficient to Induce Tactile Allodynia in Mice after Nerve Injury?

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Mechanical allodynia is a cardinal feature of pathological pain. Recent work has demonstrated the necessity of Aβ-low-threshold mechanoreceptors (Aβ-LTMRs) for mechanical allodynia-like behaviors in mice, but it remains unclear whether these neurons are sufficient to produce pain under pathological conditions. We generated a transgenic mouse in which channelrhodopsin-2 (ChR2) is conditionally expressed in vesicular glutamate transporter 1 (Vglut1) sensory neurons (Vglut1-ChR2), which is a heterogeneous population of large-sized sensory neurons with features consistent with Aβ-LTMRs. In naive male Vglut1-ChR2 mice, transdermal hindpaw photostimulation evoked withdrawal behaviors in an intensity- and frequency-dependent manner, which were abolished by local anesthetic and selective A-fiber blockade. Surprisingly, male Vglut1-ChR2 mice did not show significant differences in light-evoked behaviors or real-time aversion after nerve injury despite marked hypersensitivity to punctate mechanical stimuli. We conclude that optogenetic activation of cutaneous Vglut1-ChR2 neurons alone is not sufficient to produce pain-like behaviors in neuropathic mice.

Key words: allodynia; neuropathic; optogenetics; pain

Significance Statement

Mechanical allodynia, in which innocuous touch is perceived as pain, is a common feature of pathological pain. To test the contribution of low-threshold mechanoreceptors (LTMRs) to nerve-injury-induced mechanical allodynia, we generated and characterized a new transgenic mouse (Vglut1-ChR2) to optogenetically activate cutaneous vesicular glutamate transporter 1 (Vglut1)-positive LTMRs. Using this mouse, we found that light-evoked behaviors were unchanged by nerve injury, which suggests that activation of Vglut1-positive LTMRs alone is not sufficient to produce pain. The Vglut1-ChR2 mouse will be broadly useful for the study of touch, pain, and itch.

Introduction

Low-threshold mechanoreceptors (LTMRs) are a heterogeneous class of primary sensory neurons (PSNs) that subserve the sensation of innocuous touch (Zimmerman et al., 2014). Fast-conducting, myelinated LTMRs are known as Aβ-LTMRs, and these comprise the major tactile receptors in the skin (Abraira and Ginty, 2013). In addition to touch, previous studies in humans and rodents have suggested that under pathological conditions such as inflammation or neuropathy, Aβ-LTMRs can also mediate the sensation of pain induced by touch, a phenomenon referred to as mechanical allodynia (Torebjörk et al., 1992; Loligner et al., 2015). For chronic pain sufferers, mechanical allodynia can be highly disabling because the myriad tactile stimuli of daily living (e.g., clothing brushing against skin) evoke pain.

Despite much study, it is still unknown which type of PSN mediates mechanical allodynia. Mechanical allodynia could result from the sensitization of nociceptors such that innocuous tactile stimuli are able to activate them. Another possibility is that LTMRs, which are normally activated by innocuous tactile stimuli, could gain the ability to signal to central nociceptive circuits after an insult, giving rise to pain from touch (i.e., allodynia)

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