SENSORY PROCESSING

Scratching an itch with VGLUT2

'Don't scratch it, you'll make it worse!' But our automatic response to an itch is to scratch it, and scratching does — at least temporarily — relieve the sensation of itching. Two new papers shed some light on the circuits that mediate the interaction between pain and itch, albeit while raising further questions.

Both studies used conditional knockout mice to show that neurons containing vesicular glutamate transporter 2 (VGLUT2), which carries glutamate into vesicles for release at excitatory synapses, are important components of the pain and itch circuitry and in particular are involved in the regulation of itching by painful stimuli. Liu *et al.* generated mice that lacked VGLUT2 in most of the Nav1.8-expressing population of nociceptors. As most of these neurons do not express other vesicular glutamate transporters, this manipulation impaired excitatory transmission from these nociceptors. The mice showed impaired sensitivity to various painful stimuli and sensitization of itch pathways, which manifested as skin lesions resulting from increased spontaneous scratching and as increased responses to both histamine-dependent and histamine-independent pruritogenic stimuli.

In these mice, capsaicin, which normally causes pain and can suppress itching, instead caused an itch response. These findings suggest that VGLUT2 activity is required in the pathways that mediate capsaicin-induced pain and suppression of itch, and that its absence unmasks a hidden, capsaicin-activated itch pathway.

In the second study, Lagerström *et al.* generated mice that lacked VGLUT2 in peripheral neurons that expressed tyrosine hydroxylase. The mice also lacked VGLUT2 in a subset of other peripheral neurons, presumably because they expressed tyrosine hydroxylase transiently during development. Like those studied by Liu *et al.*, these mice showed increased spontaneous scratching, suggesting that they too lacked the ability to regulate itch-responsive pathways. In addition, they showed a decreased sensitivity to thermal and inflammatory pain but, interestingly, did not observe a decreased sensitivity to mechanical pain.

Lagerström *et al.* generated other conditional knockout mice to refine their understanding of the neurons that were involved in these effects. The excessive scratching seen in mice that lacked VGLUT2 in peripheral tyrosine hydroxylase-positive neurons was not found in mice that also lacked the spinal receptor gastrin-releasing peptide receptor (GRPR), supporting previous evidence that GRPR signalling in the spine mediates the transmission of itch signals from the periphery.

Tyrosine hydroxylase expression in the periphery shows substantial overlap with the expression of TRPV1 receptors, which are activated by capsaicin. Mice in which VGLUT2 was knocked out in TRPV1-expressing neurons also showed increased itch responses and reduced sensitivity to thermal pain, and again, the sensitivity to mechanical pain was unaffected. Moreover, in contrast to the findings of Liu *et al.*, when Lagerström *et al.* generated mice in which Nav1.8-expressing neurons lacked VGLUT2, they did not find increased spontaneous scratching or decreased sensitivity to thermal pain, although the mice did show a temporary increase in sensitivity to the pruritogen 48/80. Thus, the Lagerström study suggests a link between itch and thermal — rather than mechanical — pain. The discrepancy between the findings from the two papers could be due to a difference in specificity of two distinct Nav1.8-Cre mice used in these studies.

These studies show that VGLUT2 is a key component of the circuits that mediate the regulation of itching and the suppression of itch by pain. However, more work is needed to clarify which subsets of peripheral neurons are involved, and how their circuits mediate the sensations of pain and itch, and the interactions between the two.

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ORIGINAL RESEARCH PAPERS Lagerström, M. C. *et al.* VGLUT2-dependent sensory neurons in the TRPV1 population regulate pain and itch. *Neuron* **68**, 529–542 (2010) | Liu, Y. *et al.* VGLUT2-dependent glutamate release from nociceptors is required to sense pain and suppress itch. *Neuron* **68**, 543–556 (2010)