Editorial Commentary

NPR1 inhibitors: new drugs for itch treatment?

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In this issue of *Science Translational Medicine*, Solinski *et al.* (2019) (1) reported that pharmacological blockade of natriuretic peptide receptor 1 (NPR1), a receptor of neuropeptide natriuretic polypeptide b (NPPB), expressed by a subpopulation of mouse and human spinal cord neurons, may be the key to alleviate chronic itching. Further, the authors have identified small-molecule human NPR1 antagonists which could suppress chronic itch in mice without inducing significant adverse side effects.

Itch is a form of somatosensation that causes a desire to scratch (2). Current treatment for itch, especially chronic itch, is limited. Refractory scratching and skin lesion take a heavy toll on the life quality of patients suffering chronic itch (3). Therefore, it becomes more and more urgent to translate basic research into clinical practice for the treatment of chronic itch. In recent years, much progress has been made in understanding the molecular and cellular mechanisms of itch at the spinal level, which makes molecular targeting therapy possible for itch treatment (4). In 2007, Sun *et al.* identified the first itch-specific G-protein coupled receptor, the gastrin-releasing peptide receptor (GRPR). The GRPR-expressing neurons were distributed within the superficial layers of the spinal dorsal horn. Pharmacological inhibition or genetic deletion of GRPR reduced scratching behavior induced by multiple pruritogens in mice, without affecting mechanical and thermal pain behaviors (5). Further, toxin-based ablation of the spinal GRPR neurons produced profound scratching deficits in response to multiple exogenously administered pruritogens (6).

Interestingly, in 2013, Mishra *et al.* reported that NPPB is also an itch-specific transmitter, released by the primary afferent fibers. *Nppb* knockout mice exhibited no response to multiple pruritogens while intrathecal application of NPPB induced robust scratching behavior in mice. Moreover, NPPB was selectively expressed in TRPV1/MrgprA3-expressing DRG neurons. As the receptor of NPPB, NPR1 was also expressed in spinal dorsal horn neurons which did not express GRPR. *Nppb* knockout mice selectively lost almost all behavioral responses to itch-inducing agents and toxin-mediated ablation of NPR1-expressing cells blocked histamine-induced itch response in mice (7). These findings suggest that NPPB may be a potential neurotransmitter for itch sensation from the peripheral to the central nervous system (CNS) and spinal NPR1-expressing neurons may be the upstream of spinal GRPR neurons in itch signaling.

To further explore the translational potential of the NPPB/NPR1 signaling in the generation of itch, Solinski *et al.* investigated if specific NPR1 inhibitors could be used for the treatment of both acute and chronic itch. They firstly examined the expression of *Nppb* in both human and mouse DRGs in which they found that NPPB has similar distributional and functional characteristics, suggesting that both mouse and human itch transmission neurons likely share the same signaling molecule which could be used as a drug target for itch inhibition. Surprisingly, A-71915, a previously found hNPR1 antagonist did not show effect when applied in vivo. By measuring cGMP in human

embryonic kidney (HEK) 293 cells co-expressing mNpr1 and a cGMP sensor, they found that, A-71915 actually acted as a partial agonist instead of an antagonist of mNPR1, which also explains why intrathecal injection of A-71915 failed to alleviate acute itch in mice.

To identify effective NPR1 antagonists for the treatment of itch, Solinski *et al.* (2019) took a quantitative high-throughput screening (qHTS) approach and screened a large chemical library. By using the established HEK-cGMP sensor cells and HEK-hNPR1-cGMP sensor cells, they sorted out a series of compounds based on their efficacies and structures using an automated robotic system. They eliminated false positives and identified 15 candidate inhibitors after the counter screens. Among them, JS-5, JS-8 and JS-11 shared similar structures, indicative of similar functions and binding sites of these compounds. Thus, JS-11, which possesses relative high-water solubility and membrane permeability and a reasonable half-life, was chosen for mouse behavioral testing. Indeed, i.p. injections of JS-11 inhibited both histamine- and CYM5442 (a selective S1P1 receptor agonist)-induced acute itch as well as chronic itch associated with allergic contact dermatitis in mice.

Although NPR1 may be a potential target for the treatment of acute and chronic itch, the side effects of the NPR1 antagonists should not be overlooked. Thus, Solinski *et al.* (2019) also determined that the NPR1 antagonists they tested did not affect blood pressure and heart rate based on the known vasodilatory effects of these receptors. More importantly, Solinski *et al.* also identified a novel human NPR1 antagonist which effectively alleviated itch in a non-competitive antagonistic manner. Taken together, inhibition of NPR1 signaling presents an effective strategy for treating both acute and chronic itch, providing a critical step toward developing effective treatment of chronic itch in clinic. However, there are still remaining questions concerning the pharmacological approach used to target NPR1 for itch treatment. For instance, JS-11 could also inhibit CCKAR and HTR2A. Future studies should focus on identification of better NPR1 antagonists with a higher selectivity.

Of note, besides GRPR- and NPR1-positive spinal neurons, many other CNS neurons, either inhibitory or excitatory, have been shown to contribute to either mechanical or chemical itch signaling, including neurons expressing Bhlhb5 (8), NPY (9), SOM (10), Ucn3 (11), Tac1 (12), GABA and DA (13). These exciting findings have not only advanced our understanding of circuit mechanisms of the itch-scratch cycles and highlighted the complexity of itch signaling in the CNS, but also provided important insights on additional cellular targets for itch treatment.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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