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NEUROPEPTIDES

Novel targets for itch treatment

Current treatments for chronic itch are ineffective and new therapies are needed. Writing in *Science Translational Medicine*, Solinski et al. report the identification of small-molecule inhibitors that target neurotransmission pathways involved in itch sensation and reduce itch in mouse models.

The neuropeptide natriuretic polypeptide B (NPPB) and its receptor NPR1, a transmembrane guanylate cyclase (GC) that produces intracellular cyclic GMP (cGMP) when activated, are crucial for neurotransmission of itch stimuli. Indeed, the authors of this study previously showed that deletion of *Nppb* or ablation of NPR1-expressing spinal cord interneurons reduced the itch response in mice.

Using an assay for cGMP activity, the investigators performed quantitative high-throughput screening for novel compounds that block human NPR1 activity. 86,437 compounds from the Genesis library were assayed and 1,408 hits were obtained (a hit rate of 3.9%). Counter-screens whittled this number down to 15 candidate compounds, which were then examined for potency, efficacy and structural relationships. Three compounds (JS-5, JS-8 and JS-11) were structurally similar, suggesting that they have a common mode of action and share a binding site on NPR1.

To determine the specificity of these compounds for GCs, the authors measured the impact of JS-11 (used as an example compound) on cAMP production by the structurally related adenylyl cyclases and confirmed that these enzymes were not inhibited. Indeed, JS-11 is fairly selective as, amongst a panel of 44 common off-targets, including G protein-coupled receptors and ion channels, JS-11 only inhibited two receptors, neither of which have a reported role in itch sensation.

> “human NPR1 antagonists might be effective in treating chronic itch”

In an in vitro assay, 12 antagonists (those that could be obtained with sufficient purity and yield) inhibited cGMP production to a similar extent as in the cell-based assay. Furthermore, both basal and agonist-induced cGMP production were inhibited by these 12 compounds. Further experiments suggest that these compounds inhibit human NPR1 in a non-competitive manner.

For these compounds to be useful in treating itch, they must block itch sensation in vivo. Intraperitoneal administration of JS-11 in mice attenuated the scratching response to intradermal injection of histamine, without any untoward effects on their behaviour. Furthermore, JS-11 reduced itch stimulus signalling in spinal cord neurons, and intrathecal injection of JS-11 reduced histamine-induced scratch responses. Although similar tests cannot be performed in humans, NPPB is co-expressed with itch receptors in sensory neurons in human dorsal root ganglia sections, suggesting that these antagonists could have translatable potential in humans.

Furthermore, in a mouse model of contact hypersensitivity, JS-11 reduced scratching but not skin inflammation. Thus, NPPB–NPR1 signalling contributes to itch in both mice and humans; human NPR1 antagonists might be effective in treating chronic itch.

Of note, natriuretic peptides and their receptors have important functions in the kidneys and vasculature. Thus, although the NPR1 antagonists did not acutely affect blood pressure or heart rate in mice, the clinical development of these antagonists will need to confirm their specificity for the NPPB-mediated itch sensation signalling in spinal interneurons. However, the NPPB–NPR1 axis could be a useful target for anti-itch therapies, and these antagonists could be good starting points.

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ORIGINAL ARTICLE Solinski, H. J. et al. Inhibition of natriuretic peptide receptor 1 reduces itch in mice. *Sci. Transl Med.* **11**, eaav5464 (2019)