Skin has the nerve to tell you to scratch

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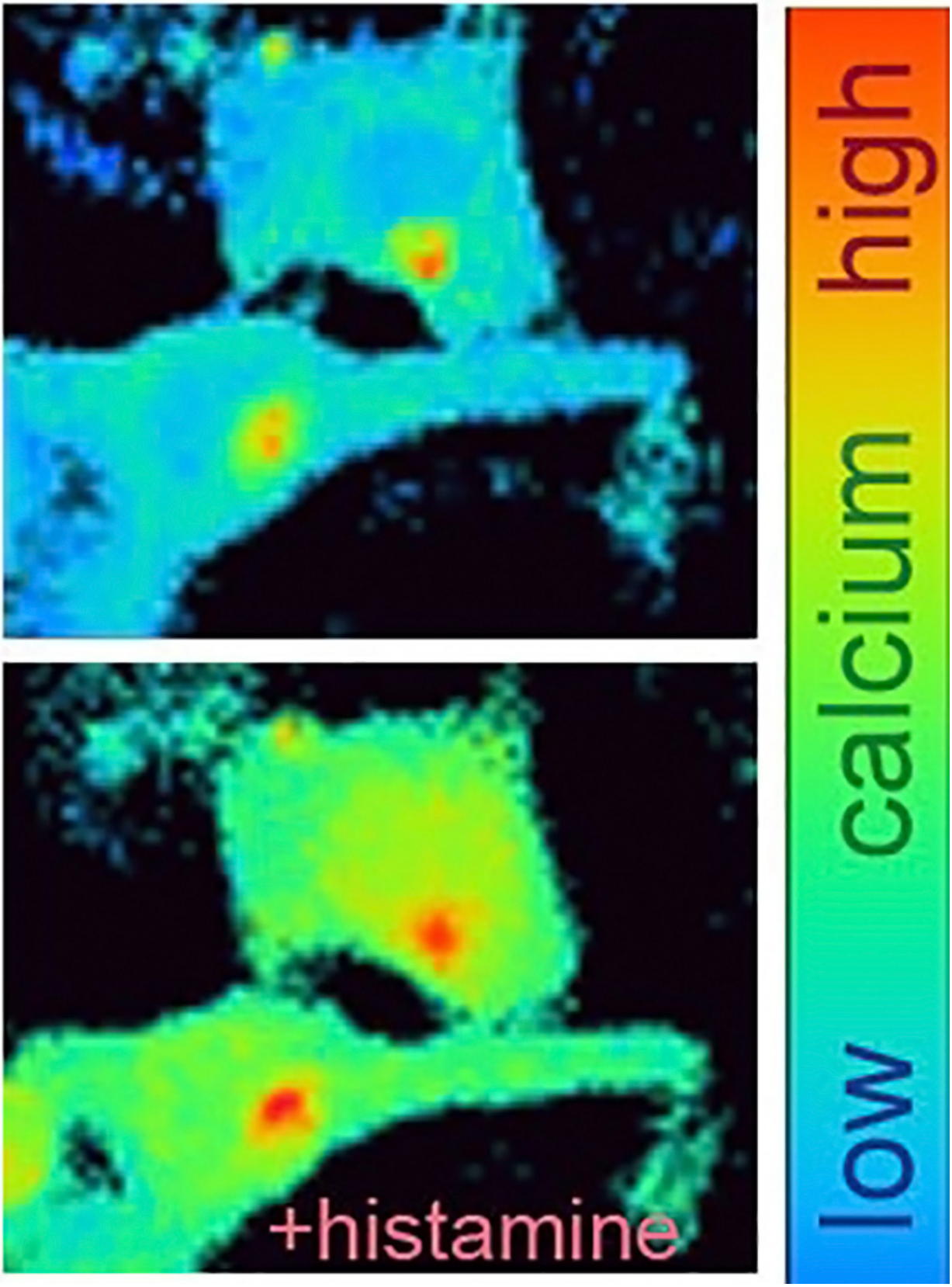
+histamine
low calcium high

Two skin cells of a mouse show the flow of calcium into the cell in response to a dose of histamine (lower panel). Duke researchers have shown that an ion channel called TRPV4 is the beginning of a chain of messages that ends up signaling "itch" to the brain. Credit: Yong Chen, Duke University

No matter the trigger—bug bites, a medication side-effect or an itchy wound—the urge to scratch can be a real pain. Researchers at the Duke University Medical Center have identified a potential drug target in the skin for that itchy feeling.

Published early online in the *Journal of Biological Chemistry*, their study also shows that skin can go beyond its known role as a protective barrier. When cells from outer layers of skin are exposed to certain itch-producing chemicals, they function to powerfully regulate sensory nerve cells, telling them to pass the feeling of itch along to the brain.

"This study is exciting for basic science but also from the translational-medical side. It means that [short-term] itch is something we can rationally treat," said the study's senior investigator Wolfgang Liedtke, M.D., Ph.D., a professor of neurology, anesthesiology and neurobiology at Duke University School of Medicine, who as a physician treats patients with head and face pain and also associated itch. "We can now envision developing topical treatments for the skin that target specific molecular pathways to suppress itch and inflammation."

In a 2013 study published in the *Proceedings of the National Academy of Sciences*, Liedtke and his collaborators showed that an ion channel protein abundant in skin cells called TRPV4 was crucial for conveying feelings of pain caused by over-exposure to ultraviolet-B radiation, such as in sunburn.

In that study, the team found that ultraviolet-B switched on TRPV4, which then caused skin cells to release a molecule called endothelin-1. Endothelin-1 has been implicated in both pain and itch sensations. But the scientists wondered whether TRPV4 was also involved in itch.

In the new study, Liedtke's team used genetically engineered mice in which they dialed down TRPV4 selectively in the animals' skin cells and then exposed them to a handful of itch-causing chemicals.

Remarkably, the mice scratched much less in response to the triggers known to convey 'histaminergic itch', which has a range of causes, including bug bites and certain medications, that can set off the allergic response.

That result suggests TRPV4 in the top layer of skin is a main hub for detecting itch and is a promising drug target for treating the condition, said co-author Yong Chen, a senior research associate in Liedtke's lab.

The scientists drilled down further into mechanisms inside skin cells, finding that TRPV4 triggers a rush of calcium into the cell and the flipping "on" of a molecular switch called ERK, (extracellular-signal-regulated kinase) into its activated form, pERK.

Drugs that block TRPV4 or pERK, when applied as topical ointments, quelled scratching in mice. Experiments in isolated mouse and human skin cells—the result of an ongoing collaboration with Jennifer Zhang, Amanda MacLeod and Russell Hall from Duke's Department of Dermatology—further corroborated the group's findings.

"For many decades, skin was believed to be a mere barrier, not endowed with sensory capability," Chen said. "Now it turns out skin has features reminiscent of sensory-neural cells that are instrumental in facilitating the sensation of itch."

TRPV4 is present on the surface of cells, which makes it an excellent target to reach with topically-applied drugs, Liedtke said. Before TRPV4 blockers could be used to treat people, however, they will need to be further formulated and then assessed in animals and human clinical trials.

In contrast, pERK is present not on the surface of skin cells but within them, and targeting it for the treatment of other conditions led to unwanted sideeffects. Liedtke is more skeptical of this approach.

Liedtke's neuro-dermatology team is interested in understanding the cell-to-cell communication within skin, and what sustains itch over longer time periods. Moreover, individuals naturally have varying susceptibility to itch, and it will be important to understand whether underlying TRPV4 molecular pathways are involved in such differences.

"Such studies, combined with DNA sequencing, can perhaps accelerate the dawning of personalized medicine and its extension into the dermato-neurology arena," Liedtke said.

More information: Yong Chen et al. Transient receptor potential vanilloid 4 ion channel functions as a pruriceptor in epidermal keratinocytes to evoke histaminergic itch, *Journal of Biological Chemistry* (2016). DOI: 10.1074/jbc.M116.716464

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