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Researchers identify itch-specific neurons in mice, hope for better treatments

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Historically, many scientists have regarded itching as just a less intense version of pain. They have spent decades searching for itch-specific nerve cells to explain how the brain perceives itch differently from pain, but none have been found.

Now researchers at Washington University School of Medicine in St. Louis have discovered that those itch-specific neurons do exist in mice, and their studies suggest that itch and pain signals are transmitted along different pathways in the spinal cord. Reporting in the Aug. 6 issue of Science Express, the advance online publication of the journal Science, the researchers say they can knock out an animal's itch response without affecting its ability to sense and attempt to avoid pain.

"This finding has very important therapeutic implications," says Zhou-Feng Chen, Ph.D., the study's principal investigator. "We've shown that particular neurons are critical for the itching sensation but not for pain, which means those cells may contain several itch-specific receptors or signaling molecules that can be explored or identified as targets for future treatment or management of chronic itching."

The new finding follows research by Chen and his team in 2007 that identified the first itch gene — gastrin-releasing peptide receptor (GRPR) — in the spinal cord. They also showed that when mice were exposed to things that make them itchy, those without a GRPR gene scratched less than their normal littermates. Chen's team also found GRPR in a group of spinal-cord cells called lamina 1 neurons that relay

both itch and pain sensations to the brain.

"But the identification of an itch receptor in spinal-cord neurons didn't mean those neurons were itch-specific because it was possible that they also could have pain-related genes," says Chen, associate professor of anesthesiology, of psychiatry and of developmental biology. "A key question was whether those GRPR neurons also were transmitting pain signals. We approached that question by injecting a toxic substance that binds to GRPR and then exposing mice to both itchy and painful stimuli."

Chen's team injected the spinal cords of mice with a neurotoxin called bombesin-saporin. It bound to GRPR and killed the neurons where the gene was expressed. When these mice then were exposed to things that caused itching, they didn't scratch. With an appropriate dose of the neurotoxin, their scratching could be reduced by more than 80 percent or completely eliminated in some instances. That finding proved that the neurons with GRPR were required for normal itch sensation.

There are two major types of itching that are classified according to the presence or absence of the chemical histamine. Histamine-dependent itching can be caused by bug bites or allergic reactions. It is treated with antihistamine drugs, such as Benadryl®. Most chronic, severe itching, however, is resistant to antihistamine treatment. But in this study, it made no difference whether mice were exposed to histamines or to other itch-inducing substances. Those mice whose GRPR-expressing neurons had been destroyed by the neurotoxin didn't scratch, regardless of what type of itchy agent they encountered.

"However, the same mice continued to respond normally to pain," Chen says. "This is a very striking and unexpected result because it suggests there is an itch-specific neuronal pathway in the spinal cord."

Further tests showed that other neurologic functions, such as motor control were not affected by the destruction of the GRPR-expressing neurons.

Whereas Chen's earlier work found that pain and itch are regulated through different molecular pathways, this study suggests they also are regulated through different cellular pathways. That, he says, could have important implications for treating itch because the neurons with GRPR may contain more itch-specific genes.

"We've shown that these GRPR neurons are important for itching sensation and not for pain, but we really don't know much more about them," Chen says. "We still have a lot of questions, and we are very interested to find more answers."

More information: Sun YG, Zhao ZQ, MengXL, Yin J, Liu XY, Chen ZF. Cellular basis of itch sensation. *Science Express*, Aug. 6, 2009.

Related paper: Sun YG, Chen ZF. A gastrin-releasing peptide receptor mediates the itch sensation in the spinal cord. *Nature* (448), pp. 700-703. Aug. 9, 2007 (published online July 25, 2007). doi:10.1038/nature06029

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