Chili peppers help to unravel the mechanism of pain

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Capsaicin, the active ingredient in chili peppers, is most often experienced as an irritant, but it may also be used to reduce pain. A new work published by Drs. Feng Qin and Jing Yao in this week's *PLoS Biology* uses capsaicin to uncover novel insight into how pain-receptor systems can adapt to painful stimuli. Sensory systems are well known to adapt to prevailing stimuli. For example, adaptation happens when your eyes adjust from a dark movie theater during a matinee to the bright sunlight outside. Whether pain receptors truly adapt or rescale their responses (versus simply desensitizing) has been an open question.

Capsaicin acts by binding to a receptor in the cell wall of nerve endings and triggering an influx of calcium ions into the neuron. Eventually, the nervous system interprets this cascade of events as pain or heat, depending on which nerves are stimulated. Scientists had previously

linked the pain-relieving effects of capsaicin to a lipid called PIP2, found in cell membranes. When capsaicin is applied to the skin it induces a strong depletion of PIP2 in the cell membrane.

"The receptor acts like a gate to the neurons," said Qin. "When stimulated it opens, letting outside calcium enter the cells until the receptor shuts down, a process called desensitization. The analgesic action of capsaicin is believed to involve this desensitization process. However, how the entry of calcium leads to the loss of sensitivity of the neurons was not clear."

Capsaicin creams are commonly sold over the counter as effective treatment for a variety of pain syndromes, from minor muscle or joint aches to those that are very difficult to treat, such as arthritis and neuropathic pain.

By combining electrical and optical measurements, the authors now have been able to link directly the depletion of PIP2 and the desensitization of the receptor. The authors also showed that the receptor is fully functional after desensitization - i.e. although you stop feeling pain - are desensitized - if another event occurs that would normally trigger a 'pain' response - such as an increased concentration of capsaicin - the desensitization does not affect that feeling. "What changed was the responsiveness threshold," said Qin. "In other words, the receptor had not desensitized per se, but its responsiveness range was shifted. This property, called adaptation, would allow the receptor to continuously respond to varying stimuli over a large capsaicin concentration range."

The findings have implications for pain sensation mechanisms as well as clinical applications. With an adaptive response, the receptors are essentially autoregulated without a fixed threshold, thus the intensity of the pain you experience is dependent on the recent history of pain.

More information: Yao J, Qin F (2009) Interaction with phosphoinositides confers adaptation onto the TRPV1pain receptor. PLoS Biol 7(2): e1000046. doi:10.1371/journal.pbio.1000046, biology.plosjournals.org/perls … journal.pbio.1000046

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