Too hot to handle! Scientists identify heat sensing regulator

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Neuroscientists at Johns Hopkins are a step closer to understanding pain sensitivity - specifically why it's variable instead of constant - having identified a gene that regulates a heat-activated molecular sensor. Their description of the function of a membrane protein called Pirt appears in the May 2 issue of *Cell*.

"Pain sensitivity increases during inflammation or injury and we want to know what molecules are involved in pain sensation when sensitivity is elevated," says Xinzhong Dong, Ph.D., an assistant professor of neuroscience at Hopkins.

The ability to sense temperature heat and spice is controlled by the TRPV1 protein channel found on the surface of certain nerve cells. In an inactive state, TRPV1 channels remain closed-there is no pain sensation. However, when noxious heat-temperatures above 108 degrees Fahrenheit-or capsaicin-the main ingredient in "hot" peppers-activates a TRPV1 channel, ions flow through, depolarizing the nerve to create an electrical current that sends pain signals to the brain.

"The interesting thing about this channel is it's not always constant," says Dong, whose team set out to find proteins that modulate TRPV1's action. They found the Pirt protein,phosphoinositide interacting regulator of TRP, and named it for its ability to regulate the TRPV1 channel.

To better understand how Pirt works, the researchers made mice that lacked Pirt and tested their ability to respond to heat. The mice were

placed on a hot surface and monitored for how long it took them to scurry off. Mice lacking Pirt responded significantly slower than normal mice.

The team then exposed one hind paw to capsaicin and found that mice lacking Pirt did not lick their paws as long as normal mice, suggesting that without Pirt, they were compromised in their ability to sense the spice of capsaicin. The researchers also tried mustard oil on the hind paw and found mice lacking Pirt licked for about the same amount of time as normal mice. These observations suggest that Pirt's action is specific to capsaicin and not other chemicals.

To figure out whether Pirt directly affects TRPV1 channel action, the researchers measured electrical currents generated by TRPV1 in single nerve cells with or without Pirt. They exposed some nerves to noxious heat-108 degrees Fahrenheit-and some nerves to capsaicin and compared currents generated in each cell. Cells containing Pirt generated stronger currents in heat and spice than cells lacking Pirt, leading the researchers to conclude that Pirt is required for a full pain response to both heat and spice.

Further research revealed that Pirt interacts with yet another molecule in the cell, a so-called acidic phospholipid, allowing access to TRPV1. According to Dong, through this phospholipid Pirt somehow changes the TRP channel, perhaps by opening it wider, or maybe by causing it to stay open longer. And the result is elevated pain sensitivity.

Exactly how Pirt regulates the TRPV1 channel isn't yet clear, says Dong. "The goal is to find molecules that specifically affect the pain pathway, but not other nerves," he says. "We're looking for genes specifically turned on in pain-sensing neurons. If we find them and can target them with new drugs, we will be able to treat pain without unfavorable side effects."

Source: Johns Hopkins Medical Institutions