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Researchers uncover ion channel trio that mediates painful heat sensing

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Researchers at VIB and KU Leuven have uncovered a trio of complementary ion channels in sensory neurons that mediate detection of acute, harmful heat. Having three redundant molecular heat-sensing mechanisms provides a powerful fail-safe mechanism that protects against burn injuries. The seminal findings have been published today in *Nature*.

Although the sensory neurons involved in acute pain signaling in mammals were described more than a century ago, the molecular mechanisms whereby these neurons detect harmful signals have remained largely unresolved.

A research team jointly led by prof. Thomas Voets (VIB - KU Leuven) and prof. Joris Vriens (KU Leuven) used genetic knockout models to pinpoint which molecular partners are involved. "We already knew several potential molecular heat sensors, but none of them, when deactivated, resulted in severe loss of acute noxious heat sensing," explains Ine Vandewauw, postdoctoral scientist in the lab of Thomas Voets.

The researchers started by eliminating two different heat-activated TRP ion channels, including one known to be also activated by capsaicin, the active component of chili peppers. But this only resulted in very mild deficits in heat sensing. Interestingly, most residual heat-sensitive neurons in the double knockout mice also responded to allyl isothiocyanate, responsible for the pungent sensation of mustard, radish

and wasabi.

This chemical selectively activates a third TRP channel, which prompted the scientists to go one step further and generate a triple knockout. Mice with all three TRP channels eliminated showed a complete loss of heat-induced pain responses. Reintroduction of the receptors via transient transfection restored sensitivity to heat, and conversely, heat responses could also be suppressed by an inhibitor cocktail for all three TRP channels. The signaling was specific for the pain response to heat, as the animals responded normally to other painful stimuli such as cold, pressure or pinpricks, and their overall thermal preference was not affected.

This triple knock out mouse represents the first demonstration in mammals of elimination of the pain response to a physical stimulus at the level of the signal-transducing ion channel.

"Acute pain in response to heat is a crucial alarm signal in all mammals," explains Thomas Voets. "The presence of three redundant molecular heat-sensing mechanisms with overlapping expression in pain-sensing neurons creates a powerful fail-safe mechanism. It ensures we avoid dangerous heat, even if one or even two heat sensors are compromised."

Next, the researchers want to investigate how these channels can be targeted to treat chronic pain. Thomas Voets says, "Millions of people worldwide suffer from ongoing, burning pain caused for instance by nerve damage or inflammation, and the currently available drugs to treat chronic pain often don't work well or cause addiction. In such conditions, the three heat-activated TRP channels can get deregulated, signaling painful heat even when there is no risk of burning. By developing new drugs that specifically temper the activity of these molecular heat detectors, we hope to be able to provide effective and safe means to treat chronic pain in patients."

More information: A TRP channel trio mediates acute noxious heat sensing, *Nature* (2018). nature.com/articles/doi:10.1038/nature26137

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