'Suicidal' mechanism discovered in ion channel receptors enables the sensing of heat and pain

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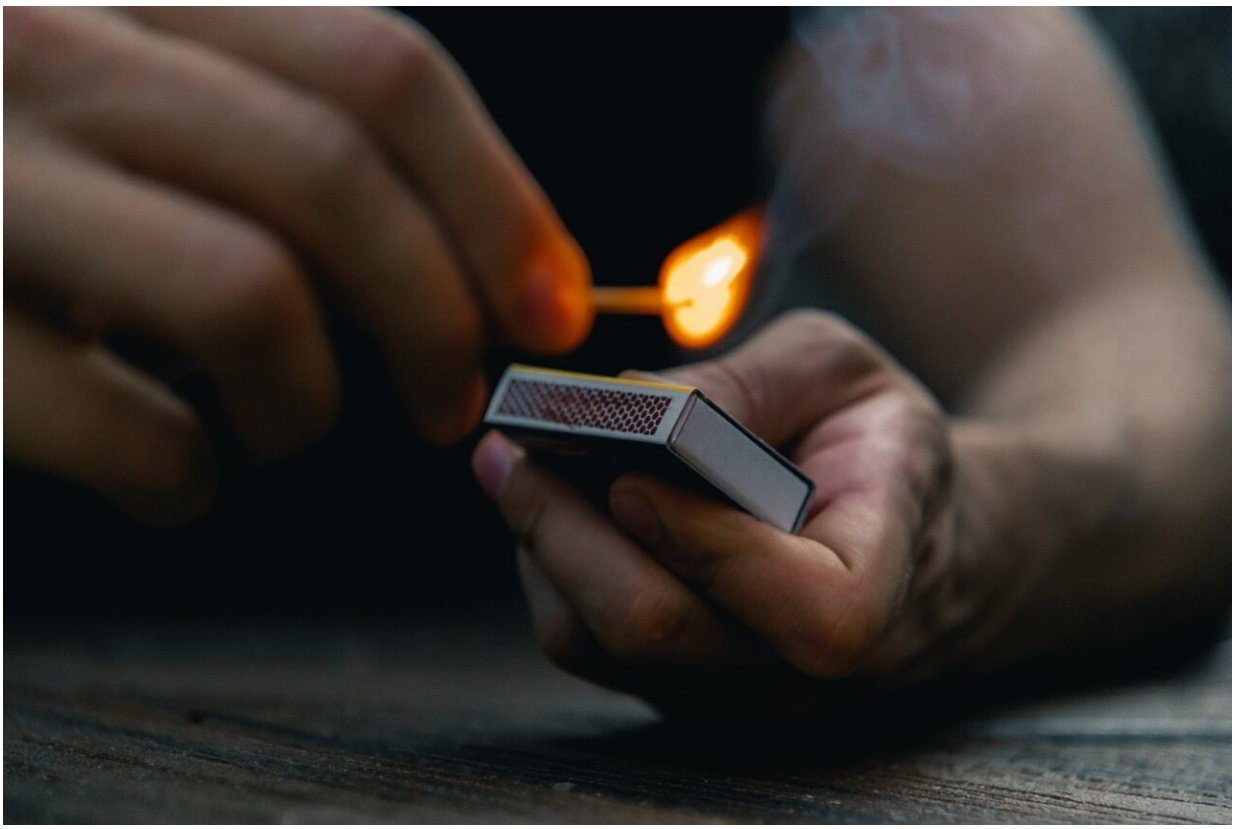

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The ability to accurately detect heat and pain is critical to human survival, but scientists have struggled to understand on a molecular level

exactly how our bodies sense these potential risks.

Now, University at Buffalo researchers have unraveled the complex biological phenomena that drive these critical functions. Their research, published in the *Proceedings of the National Academy of Sciences* on Aug. 28, has uncovered a previously unknown and completely unexpected "suicidal" reaction in ion channel receptors that explains the complicated mechanisms that underlie sensitivity to temperature and pain.

The research could be applied to the development of more effective pain relievers.

Imminent danger warning

"The reason for us to have a high temperature sensitivity is clear," says Feng Qin, Ph.D., corresponding author and professor of physiology and biophysics in the Jacobs School of Medicine and Biomedical Sciences at UB. "We need to tell apart what is cold and what is hot so that we are warned of imminent bodily danger."

It is therefore impossible to separate sensitivity to temperature and to pain.

"The receptors that sense temperature also mediate transduction of pain signals, such as noxious heat," Qin says. "Thus, these temperature-sensing receptors are also among the most critical ones to target for pain management."

For that reason, Qin says that understanding how they work is a first step toward the design of a new generation of novel analgesics with fewer side effects.

The UB researchers have focused on a family of ion channels known as TRP (transient receptor potential) channels and in particular TRPV1, the receptor that is activated by capsaicin, the ingredient that gives chili peppers their spicy heat. These are cutaneous receptors, located at the endings of peripheral nerves in the skin.

But figuring out how to demonstrate how thermosensitive these receptors are has been challenging.

Qin explains that proteins absorb heat and convert it into a form of energy called enthalpy changes, which are associated with changes in a protein's conformation. "The stronger a receptor's temperature sensitivity is, the larger the enthalpy change needs to be," he says.

He and his colleagues had previously developed an ultrafast temperature clamp to detect in real time the activation of a temperature sensor. "We estimated its activation energy to be huge, nearly an order of magnitude larger than that of other receptor proteins," says Qin, noting that the actual total generated by activation is expected to be far higher.

Then they decided to try and measure directly the heat uptake of temperature receptors, a task Qin calls "daunting" as it required the development of new methodologies as well as the acquisition of expensive and sophisticated instrumentation.

Like detonating an atomic bomb

Using the TRPV1 receptor as a prototype, they found that heat induces robust, complex thermal transitions in the receptor on an extraordinary scale. "It's like detonating an atomic bomb inside proteins," Qin says.

The researchers also found that these dramatic thermal transitions of the receptor happen only once. "What we have found is that in order to

achieve their high temperature sensitivity, the ion channel needs to undergo extreme structural changes in their functional state, and these extreme changes compromise protein stability," explains Qin. "These surprising, unconventional findings imply that the channel suffers irreversible unfolding after it opens—that it commits suicide."

What makes the finding all the more remarkable, he continues, is that it defies the conventional expectation that a temperature receptor should be more thermally stable, especially when activated by temperatures in the range that it can detect.

"Our new finding goes against this expectation and the notion of reversibility, which is seen in almost every other type of receptor," he says.

A possible explanation lies in the dilemma between physical principles and biological needs. "The biological need—the strong temperature sensitivity of the receptors—apparently requires a larger energy than what reversible structural changes in the protein can afford," he says.

"Thus, the receptors have to undertake an unconventional, self-destructive means to meet their energy demand. It is remarkable how temperature receptors turn protein unfolding to its advantage using a process generally thought to be destructive to physiological function."

Whether or not new ion channels form to replace the old ones is one of the questions Qin and his colleagues plan to investigate next. He says it could even be possible that neurons may deploy some unexpected way to detect and "rescue" the damaged channels on sites or replenish them with new, synthesized ones.

"It's worth noting that since the high temperature that has been sensed by the receptor may cause tissue damage, the body may not care about the

fate of the destroyed ion channels since the tissue needs to be regenerated anyway," Qin speculates. "This is perhaps the 'smart' strategy that nature has figured out to best fulfill the high temperature sensitivity demand for the channel."

UB co-authors are Andrew Mugo, Ph.D.; Ryan Chou; Beiying Liu, MD and Qiu-Xing Jiang, Ph.D. Felix Chin of the University of Pennsylvania is also a co-author.

More information: Andrew Mugo et al, A suicidal mechanism for the exquisite temperature sensitivity of TRPV1, *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2300305120

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