Study helps explain how we can sense temperatures

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Scientists at The Scripps Research Institute and the Genomics Institute of the Novartis Research Foundation (GNF) have shed new light on the molecular mechanism that enables us to sense temperature, such as the heat from a sizzling stove. In addition to contributing to our knowledge of basic biology, the findings could one day lead to new therapies for conditions such as acute or chronic inflammatory pain.

The study, which was led by Scripps Research and GNF Professor Ardem Patapoutian, was published in an advance, online edition of the journal Nature Neuroscience on April 22, 2010.

To better understand temperature sensation, the team focused on a protein called TRPV1, which is a member of a small family of proteins known to enable temperature sensation, and is involved in inflammation and the communication of pain to the brain. After producing thousands of mutants of this protein, the scientists were able to identify a region of the protein that enabled temperature sensitivity and to detail some of the molecular mechanisms at work in the molecule.

"Ever since the discovery of these proteins, it has been an outstanding question how they can be activated by temperatures," said Research Associate Jörg Grandl, a member of the Patapoutian lab and first author of the paper. "The new study addresses this question."

"Because our ability to sense temperature is closely linked to our ability to sense pain, some of these ion channels are considered targets to treat

chronic inflammatory and neuropathic pain indications," said Patapoutian. "Understanding these proteins could be crucial in designing future drugs that can either activate or block them."

Hot and Cold

Humans and other vertebrate animals use specialized sensory neurons to detect temperature, pressure, and other physical stimuli on the skin. These neurons are located in the spinal column and are connected to the skin and organs through long extensions known as axons.

On the surface of these axons are ion channel (pore-forming) proteins, which span the axon's membrane, connecting the inside with the outside. Some of these ion channels act like temperature receptors or "molecular thermometers" by opening and closing according to the temperature. At a particular temperature, the receptors open. This allows an influx of ions into the neuronal processes, and this electrical signal is relayed through the neuron to the brain.

The existence of specialized hot- and cold-neurons had been known for years, but the molecules that actually sense the temperatures and signal back to the neuron through the axon were a mystery. That changed in 1997 when a group cloned TRPV1, which is a type of transient receptor potential (TRP) channel. TRPV1, an ion channel, opens when it senses hot temperatures—above 42° C (108° F).

That discovery opened the floodgates for identifying other temperature-detecting proteins. Within a few years, several laboratories—including Patapoutian's—had identified additional temperature-detecting proteins and confirmed that mammals used them to detect temperature.

But how the proteins achieved their temperature-sensing ability remained a mystery. While scientists in the field knew in much detail

how ion channels were activated by chemicals or voltage signals, the molecular structures required for temperature activation remained unknown.

Two competing theories were advanced to explain the activation of ion channels in response to temperature. Drawing on the proteins' similarity to voltage-gated potassium channels, the first theory posited that TRP channels are generating temperature sensitivity because the energies required for voltage activation are very finely tuned. In contrast, the second theory proposed that these channels have a modular structure and therefore possess a specific domain that enables them to be activated by temperature - and postulated the existence of a 'temperature-sensor domain'.

Point by Point

To gain insight into how these ion channels achieve their temperature sensitivity, in the new study the scientists conducted studies of TRPV1, which was not only the first TRP to be discovered but is also the best understood. A previous study in the lab had focused on a related, warm-activated ion channel, TPRV3, but since the biophysics of this molecule is complicated, the team was unable to tease apart its mechanisms.

Using mutagenesis techniques, for the new study the scientists first generated some 8,500 mutants of TRPV1. Then, working with the high throughput equipment available at GNF, the team performed an unbiased screen of these compounds to identify mutations of interest.

"We were looking for mutations in these proteins that would only change the temperature sensitivity of these channels, but would not affect any of the other activation mechanisms," said Grandl. "We were looking for single-point mutations [changes of a single amino acid] where the channel still functioned normally in response to capsacin (the active

ingredient in chili peppers) or pH, but not to temperature."

Indeed, the team found a number of these mutations that affected the molecule's sensitivity to temperature, but not to other cues. Interestingly, the mutations were clustered in one area of the protein, the outer pore region, which provides further support to the existence of the predicted 'temperature-sensor domain'.

Next, with these mutant versions of TRPV1 in hand, the scientists examined what had changed in the molecule to disrupt temperature sensitivity.

In findings new to the field, the team discovered that TRPV1 has two ways of opening its channel—for a brief time, opening for only for a millisecond before returning to its closed resting state, and for a relatively long time, opening for about 10 milliseconds. The team found that the mutations disrupting temperature sensitivity interfered with the long channel openings, but not the short ones.

"This study suggests a potential molecular mechanism that generates extreme temperature sensitivity from two mildly temperature sensitive steps," said Grandl. The team postulates that by stabilizing the open state, the pore domain contributes to thermosensitivity of TRPV1. "We now have a novel working model of how Nature could have evolved such exquisite temperature sensitivity, a hypothesis that can be tested in future work."

More information: In addition to Grandl and Patapoutian, the paper, "Temperature-induced opening of TRPV1 ion channel is stabilized by the pore domain," was authored by Sung Eun Kim and Valerie Uzzell of Scripps Research, and Badry Bursulaya, Matt Petrus, and Michael Bandell of the Genomics Institute of the Novartis Research Foundation.

Provided by The Scripps Research Institute

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