ION CHANNELS

Temperature sensitivity is voltage dependent

There is already evidence that certain transient receptor potential (TRP) cation channels are important in discriminating between a wide range of temperatures in the mammalian sensory system. Now, research published in *Nature* brings us closer to understanding the mechanism by which gating (opening and closing) occurs in temperature-sensitive TRP channels (thermoTRPs). There are six known thermoTRPs, and they respond to different temperature ranges: four of these, TRPV1, TRPV2, TRPV3 and TRPV4, are activated by heating, and two, TRPM8 and TRPA1, by cooling, although there has been some dispute about the temperature sensitivity of TRPA1.

Voets *et al.* showed that activation of thermoTRPs is not governed by a single temperature threshold but strongly depends on transmembrane voltage. Using whole-cell patch-clamp experiments, they found that at depolarized potentials TRPM8 is activated at higher temperatures than at more negative potentials. Similarly, at depolarized voltages TRPV1 is activated at significantly lower temperatures than at hyperpolarized voltages.

TRPM8 and TRPV1 are both voltage-dependent channels that are activated on depolarization. Just as they showed that temperature sensitivity depends on transmembrane voltage, Voets *et al.* also found that the voltage dependence of activation of these thermoTRPs is affected by cooling and heating, which explains how they open and close in response to changes in temperature. TRPV1 has previously been shown to be heat activated in cell-free patches, and Voets *et al.* showed the same to be true for activation of TRPM8 by cooling, indicating that the temperature sensitivity of both types of channel is membrane delimited. This might not be the case for all thermoTRPs, however, as TRPV4 is not heat activated in cell-free patches.

Voets *et al.* calculated that the rate of channel opening of TRPM8 showed only shallow temperature dependence, but that the closing rate was steeply temperature dependent. They also showed that the opposite applied to TRPV1, for which the opening rate was steeply temperature dependent and the closing rate had only shallow temperature dependence. They concluded that temperature sensitivity results when there is a sufficient difference between the activation energies that are required for channel opening and closing.

As well as functioning as temperature sensors, TRPM8 and TRPV1 are also ionotrophic receptors for various chemicals that cause cooling (TRPM8) or burning (TRPV1) sensations. Voets *et al.* showed that the cooling agent menthol and the pungent compound capsaicin mimic thermal responses by shifting the voltage dependence of activation of TRPM8 and TRPV1, respectively. This explains why low, subactivating doses of these compounds cause an increased temperature sensitivity, whereas higher doses lead to direct activation of these thermoTRPs.

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References and links

ORIGINAL REFERENCE PAPER Voets, T. *et al.* The principle of temperature-dependent gating in cold- and heat-sensitive TRP channels. *Nature* **430**, 748–754 (2004)