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How do humans and plants feel the heat?

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The 2021 Nobel prize was awarded for the discovery of the animal thermosensory channel TRPV1. We highlight notable shared features with the higher plant thermosensory channel CNGC2/4. Both channels respond to temperature-induced changes in plasma membrane fluidity, leading to hyperphosphorylation of the HSF1 transcription factor via a specific heat-signaling cascade.

The 2021 Nobel prize in Medicine and Physiology was shared by David Julius and Ardem Patapoutian for the discovery of the thermosensory ion channel TRPV1 and the mechanosensitive ion channel component 2, PIEZO2, in vertebrates (https://www.cell.com/nobelprize#:~:text=in%2DChief%2C%20Patterns-,Nobel%20Prize%20in%20Physiology%20or%20Medicine%202021,receptors%20for%20temperature%20and%20touch). In the current context of human-aggravated global warming, it is important to gain knowledge beyond the vertebrates, on how plants, fungi, protozoa, bacteria, and archaea perceive sudden changes of ambient temperature and react in a timely manner to establish various defenses to avert and repair damages from upcoming environmental stresses. Interestingly, the findings on the human heat sensor provide valuable clues on how land plants may similarly perceive a rise in the ambient temperature and establish comparable molecular defenses, by accumulating a conserved set of heat-shock proteins (HSPs), conferring thermotolerance to both vertebrates and plants [1].

The animal thermosensory channel TRPV1 forms a tetrameric transmembranal ion channel, which at resting low temperature is in a closed polarized state, poised to readily respond to a temperature increase. Cholesterol is a membrane-rigidifying molecule that was found to control membrane phase transitions at the heat-activating temperatures for TRPV1 [2], suggesting that the heat-shock response depends both on the intrinsic thermo-responsive characteristics of the channels, as evidenced by temperature-sensitizing mutations [3], and on the presence of molecules, such as cholesterol or saturated/unsaturated lipids affecting the fluidity of the plasma membrane in which TRPV1s are embedded (Figure 1, left). Under heat shock, the TRPV1 channel transiently opens and mediates the entry of extracellular Ca^{2+} ions, which bind, recruit, and activate calmodulins associated with the N and C terminal cytosolic domains of TRPV1 [4]. This initiates a specific cellular signal that ends in activation of the heat shock transcription factor 1 (HSF1). The widely accepted model for animal cells is that at low temperature, HSF1 is maintained inactive in the cytosol by bound HSP70 and HSP90 molecules. Under heat shock, the chaperones are observed to dissociate, while HSF1 concomitantly becomes hyperphosphorylated and active; therefore, it is generally thought that some unknown thermolabile proteins, that presumably aggregate, can titer away the repressor HSP70s and HSP90s from the HSF1 complex. Consequently, the activated HSF1 is unleashed to translocate to the nucleus, where it recruits RNA polymerase to synthetize HSP mRNA [5]. The consequent massive accumulation of HSPs, many of which are molecular chaperones, establishes effective protective mechanisms against heat damages in thermolabile proteins and membranes.

The heat-depolarized TRPV1 channel soon closes and does not further allow translocation of external Ca^{2+} ions, despite the ongoing heat stimulus. As demonstrated for TRPV3 [6], hours at non-heat shock temperature are necessary for TRPV-type channels to revert into an initial heat-responsive state, poised to respond again to an upcoming heat stimulus. Binding of the agonist capsaicin to TRPV1 induces a localized nociception of heat. Both activation by heat or the binding of capsaicin at 37°C produces a similar profile of HSP accumulation [7]. Because capsaicin is a potent TRPV1 agonist, it is used, somewhat counterintuitively, in anesthesiology [8]. Conversely, and demonstrating that TRPV1 is a central thermo-sensor of human cells, pretreatments of cells with TRPV1 RNAi, or the TRPV1 antagonist capsazepine, or EGTA that chelates external Ca^{2+}, all prevent the heat-induced accumulation of HSPs [7].

Noticeably, higher plants similarly contain specific thermosensory channels, called cyclic nucleotide gated channels (CNGC2/4s) [9–11] (Figure 1, right), which, like TRPV1, form at low-temperature transmembranal ion channels that are closed. This closed polarized state is poised to readily respond to a heat-induced increase in the fluidity of the surrounding plasma membrane. Like TRPV1, upon heat exposure, the heat-responsive CNGC2/4 channels transiently open and mediate the controlled entry of external Ca^{2+} ions, which bind to calmodulins that are associated with the cytosolic C terminal domain of the channel [12]. This triggers a specific heat-signal cascade involving kinases that ultimately phosphorylate and activate HSFA1 [13].

Moreover, like neurons, which by way of propagating the rapid entry of Ca^{2+} ion along axons can transfer a heat signal from a distant organ to the human brain and elicit an escape reaction, plants too may transfer an initial heat signal from a heated leaf to neighboring leaves, by way

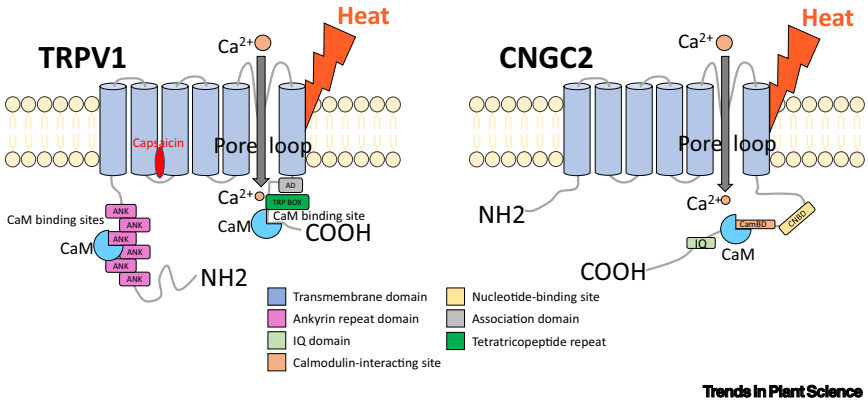

Figure 1. Plant and animal heat sensors are very similar in structure and function. Domain organization of heat-sensory channels. Vertebrate TRPV1 (left) and plant CNGC2 (right) are tetrameric channels in the plasma membrane. Their subunits are composed of six transmembranal helices with a pore loop between helix 5 and 6. Both channels bind calmodulins in their cytosolic C terminal. The N terminal of TRPV1 contains six ankyrin domains that also bind calmodulins. Higher temperature increases the fluidity of the plasma membrane. This, or capsaicin-binding to TRPV1, induces the transient opening of the channels and the binding of extracellular calcium to channel-associated calmodulins on the cytosolic side, which in turn sends a specific signal to activate heat-shock transcription factors and produce protective heat-shock proteins.

of an observed propagation of Ca^{2+} ion entry along the vasculature [14]. Noticeably, the plant vasculature is composed of both dead hollow xylem cells and of live phloem sieves (Figure 2). Interestingly, like animal axons that are highly differentiated live cell extensions fostered by neighboring glial cells, phloem sieves are highly differentiated live cell extensions fostered by companion cells. Whereas the hollow dead xylem cells lack a source of energy to carry out the observed rapid heat-induced propagation of calcium ions (in the order of 20 seconds) against the water flow down the petiole of an arabidopsis (*Arabidopsis thaliana*) leaf (Figure 1B), live phloem sieves could, in principle, use energy from ATP hydrolysis to do so by a mechanism yet to be determined.

Yet, at variance with TRPV1-expressing vertebrates with brains and muscles, for which evolution may have found an advantage in developing nociception to escape heat damages, CNGC-expressing plants lack brains and muscles. Therefore, although similar to vertebrates, plant tissues sense heat and react by producing HSPs and by sending a heat signal to neighboring organs, unlike animals, plant have a sessile lifestyle. Plants cannot escape heat damages and, therefore, it is unlikely that evolution has developed nociception as an effective warning system to prompt plants to escape heat stress.

Thus, despite the similarities of sensing and of the signal transduction pathways between the TRPV1 thermo-sensors and the heat CNGC thermo-sensors, it is unlikely that plants feel pain. Yet, being complex organisms and serving as the main food source for the ever-expanding human population of the planet, plants deserve more research to understand their functional

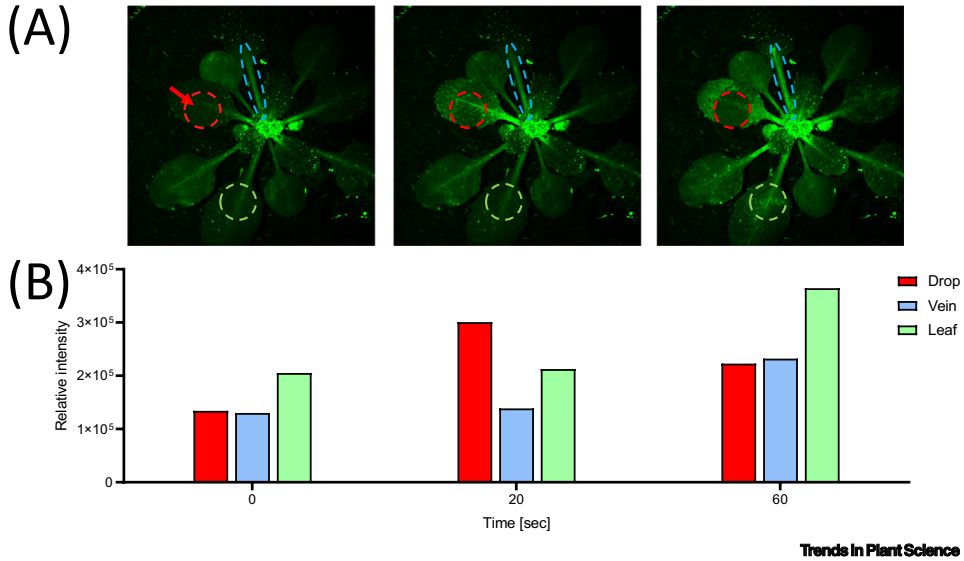

Figure 2. A local heat stress elicits a calcium-dependent heat signal between leaves. (A) Transgenic *Arabidopsis thaliana* plants that constitutively express the calcium-dependent GCaMP3 fluorescent reporter [15]. The time laps (0, 20, and 60 s) following the deposition of a hot drop of water at 45°C on one leaf (red arrow and circle). Grey circles indicate high calcium concentrations in the live tissues of distal vasculature and leaves. (B) The time laps (at 0, 20, and 60 s) fluxes of Ca^{2+} in relative intensity calculated with ImageJ by measuring GFP fluorescence.

characteristics and potential adaptation to global warming, as well as our gratitude and respect [15].

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Declaration of interests

The authors have no conflict of interest.

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