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# Feel the Burn

*The linked sensations of temperature and pain come from a family of membrane proteins that can tell neurons to fire when heated or hot-peppered*

Gina M. Story and Lillian Cruz-Orengo

Imagine a brilliant day in bluegrass country: A sip of a minty-cool julep counters the hot sun beating down, and water from a cold spring soothes feet that marched across the broiling pavement of summer. The evening features piquant foods and dancing, and although you pay for these indulgences, the night's unwelcome legacy yields to an antacid and a pungent balm for sore muscles.

The delights of this day come courtesy of a family of molecules that enable our senses to detect temperature and a handful of chemical cues. These molecules stand at the intersection of pleasure and pain, and under normal conditions they direct sensory inputs accordingly. But when they go wrong, even innocuous sensations and mild temperatures seem excruciating.

**On Pain**

A man we talked with outside a clinic associated with our research center, the Washington University Pain Center at Barnes-Jewish Hospital in St. Louis, Missouri, told us a story that is typical of people who experience chronic pain. A car accident left him with three slipped discs in his neck, causing dramatic changes in the way he experiences physical sensations in that area. Outwardly, he's fine—he can walk, use his arms, turn his head—but the simple passage of cool air across the nape of his neck now elicits stabbing pain. His neural damage has caused a condition called *cold allodynia:* Normally innocuous cool sensations have become painful. Unfortunately, the options for treating his pain are limited.

We sense temperature and pain through nerve endings in the skin and joints and in the mucous membranes of the nose and mouth. These scattered nerve endings stretch out from nerve fibers terminating in a row of cell clusters called the *dorsal root ganglia,* which lie next to the spinal cord. There are two ganglia per vertebral segment, one on each side. Cells in the ganglia relay information about the environment from the skin to the spinal cord, where another neuron conducts it to the brain. There are different categories of sensory nerves, and neuroscientists think that so-called *C-fibers* and *Aδ-fibers* transmit information about heat and cold or mechanical pressure.

The ubiquity of pain and the drawbacks of current treatments have fueled intense study of the physiological basis for this category of sensation. Chronic pain accompanies many medical conditions, including nerve injury, diabetes and cancer. Existing drugs for pain management have undesirable side effects, including tolerance and, in some cases, addiction.

Some scientists who study pain (including members of our research group at Washington University in St. Louis) focus on the peripheral neurons in which these sensations begin. Our collective hope is that it might be possible to block the detection of pain by inhibiting the molecules that activate pain-sensing, or *nociceptive,* neurons. This strategy promises to avoid some of the side effects of analgesic drugs that act on the central nervous system. We now know some of the molecules that transduce hot and cold stimuli and are learning how inflammation and injury cause peripheral neurons to become pathologically sensitive to temperature and touch.

**A Spicy Family**

Until recently, scientists understood little of how peripheral neurons detect thermal and pain stimuli. In 1997, Michael J. Caterina, then a postdoctoral fellow in David Julius's laboratory at the University of California, San Francisco, reported the discovery of the cellular receptor for capsaicin—the chemical responsible for the "heat" in jalapeños, habaneros and other hot peppers. The capsaicin receptor is a protein channel that sits in the outer membrane of specific nerve cells and allows a flood of calcium ions to enter the cells when capsaicin is present. The characteristic burning sensation comes from the excitation of these cells, which are a subgroup of nociceptive neurons. With continued exposure, the neurons become less sensitive, which accounts for the analgesic effect of topical capsaicin. Patients initially experience burning that is difficult to tolerate; continued application usually brings relief as the nociceptive neurons desensitize.

The capsaicin receptor turned out to be the first mammalian member of a family of similar proteins called *transient*

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**Figure 1. The linked sensations of taste, temperature and pain arise from a single family of cellular receptors. Among the chemical compounds that activate these receptors are ones found in hot peppers, mint, garlic, mustard and horseradish, some of which can be purchased at this spice market in Istanbul. (Photograph courtesy of Susan E. Hough.)**

*receptor potential,* or TRP, *channels.* TRP ion channels exist in many kinds of organisms, from insects to fish to people. They also perform a remarkable variety of jobs, most of which are linked to the senses. In dozens of studies, TRP channels enable vision, taste, olfaction, and the sensations of mechanical stress (pressure or stretching) and temperature.

Since 1997, scientists have discovered five other thermosensitive TRP channels (thermo-TRPs) in mammals, each tuned to a specific range of temperatures. The proteins in this group all have six transmembrane domains, and the physical channels or pores they form are four-part complexes (tetramers) made up of one or possibly more types of TRP-channel proteins.

The founding member of the family became known as TRPV1 because it recognized a "vanilloid" molecule (the class of chemicals to which capsaicin belongs). In the initial report of its discovery, the investigators showed that the channel could also be opened by noxious heat. Cultured cells that contained the channels had a thermal threshold of about 42 degrees Celsius or 108 degrees Fahrenheit (in this article, all temperatures are given in degrees Celsius). The 42-degree threshold is similar to the native heat responses of isolated neurons from dorsal root ganglia.

In addition to TRPV1, three other TRPV subfamily members are activated by heat or warmth, each with a distinct thermal threshold. TRPV2 is activated by very high heat (52 degrees), whereas TRPV3 and TRPV4 open under milder conditions (33 degrees and a range of 27 to 42 degrees, respectively). Two distantly related thermoTRPs respond to cool or cold stimuli: TRPM8 is active at or below room temperature (25 degrees), and TRPA1 is thought to open at temperatures near the point at which cold becomes painful (15 degrees). Some scientists disagree about the cold sensitivity of A1, and it's an area of active study.

The thermoTRP channels are also sensitive to different plant-derived and synthetic compounds, many of which "feel" hot or cold. The sources of these phytochemicals are famously pleasant and often pungent, including menthol,

cinnamon, garlic and horseradish in addition to chili peppers. ThermoTRPs also mediate unpleasant sensations by becoming oversensitive in response to nerve injury. The channels are regulated by some of the ingredients in the "inflammatory soup" of chemical signals cooked up by our own bodies in response to injury or infection. A few of the same signals can alter the quantities and biophysical properties of thermoTRPs in peripheral nerves and skin, leading to conditions such as *hyperalgesia* (greater sensitivity to painful stimuli) and *allodynia* (feeling pain from normally painless stimuli, as discussed above).

**High Heat**

The capsaicin receptor TRPV1 remains the best-studied of the thermoTRPs. In addition to its presence in superficial nerves such as those in the skin and joints, the channel also exists in neurons buried in the viscera, urinary bladder and airways. TRPV1 also shows up in the brain, specifically the part of the hypothalamus that regulates core temperature and metabolism—explaining, perhaps, why capsaicin lowers body temperature. TRPV1 channels in cells of the bladder appear necessary for proper bladder reflexes.

Two teams of scientists have made targeted deletions of the gene that encodes the TRPV1 protein in mice. Both groups found that the resulting "knockout" mice seemed not to experience pain after contact with capsaicin. In the laboratory, sensory neurons taken from these mice and kept alive in cell cultures did not admit calcium ions in response to capsaicin. These results suggest that TRPV1 is the sole receptor for capsaicin. However, this channel is probably not the only means of perceiving heat, as the responses of knockout mice to noxious heat stimuli were blunted but not absent. Only at temperatures greater than 50 degrees did the mutant mice show less sensitivity than normal mice. Such findings argue that heat sensation is more than just TRPV1 activation.

Indeed, the perception of temperature is only one dimension in which to consider the physiological roles of TRP channels. There are also chemical sensitivity and potential for adaptation to think about. And there are at least three experimental paradigms in which to observe each dimension: living animals, cultured neurons and cultured nonneuronal cells that artificially produce channel proteins. Typical of all scientific endeavors, this biological and experimental complexity often generates conflicting or inexplicable results that can take years to understand. For example, despite the normal perception of noxious heat in TRPV1 knockout mice, these mutants never develop the kind of thermal hyperalgesia that is triggered by inflammation. The authors of the study—and many other scientists in this hypercompetitive field—are trying to understand exactly why this is.

The answer may have to do with the cross-modal sensitivity of TRP channels. In the case of TRPV1, painful heat and capsaicin aren't the only triggers. The channel is highly sensitive to resiniferatoxin, an ultra-potent capsaicin analog, and its tendency to open is dictated by *p*H, becoming much more active under acidic conditions, such as those produced by tissue injury. Furthermore, ingredients in the inflammatory soup can sensitize the channel so that it becomes active at body temperature, providing a plausible mechanism for heat hyperalgesia.

Inflammation also seems to increase the amount of TRPV1 protein in sensory neurons. The extra protein is transported specifically to nerve endings in response to inflammation. People who have inflammatory bowel disease (IBD) show a similar increase in TRPV1 in visceral nerves, which may explain the abdominal pain associated with this condition. TRPV1-knockout mice never became hypersensitive to normal colon distension as do patients with IBD. The capsaicin receptor is further implicated in a variety of human diseases, including osteoarthritis, gastrointestinal reflux disease, vulvodynia and inflammatory disorders of the airways and bladder.

Unlike V1, TRPV2 doesn't respond to capsaicin, but it does respond to heat with a threshold higher than that of V1 (52 degrees) in cultured cells. Repeated activation of the TRPV2 channel makes it more sensitive, not less, which has led to speculation that neurons containing these channels contribute to neuropathic pain by becoming too sensitive to low-threshold mechanical stimuli. However, a direct role for TRPV2 in pain sensation has not been proven, and the data from experiments with knockout mice, which

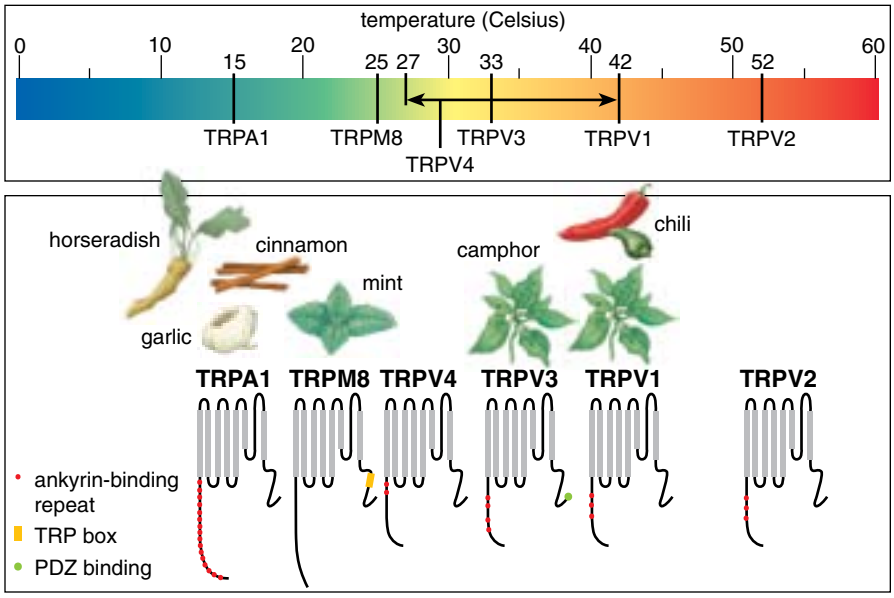


**Figure 2. Certain transient receptor potential, or TRP, ion channels mediate the sensation of temperatures from extreme cold (TRPA1) to extreme heat (TRPV2). The channels also open or close in response to certain botanical compounds. Mint-derived menthol (a TRPM8 activator) is cooling, whereas chili-derived capsaicin (a TRPV1 activator) causes a sensation of heat. Paradoxically, the "burning" sensations of horseradish, cinnamon and garlic are thought to arise from activation of TRPA1, a neural riddle not fully understood. Each channel has six segments that span the cell membrane *(gray)* with a loop between the fifth and sixth segments that is thought to form the actual passageway for ions. Both ends of the proteins reside within the cell, where they interact with other cellular proteins (such as ankyrin, which anchors membrane proteins) through specific regions. The number, type and locations of such regions vary considerably.**

ought to provide important insights, haven't yet been published.

**Nice and Warm?**

It's obviously important to be able to detect dangerously hot conditions but less obvious that animals need to perceive innocuous temperatures. The latter ability is essential, however, for properly regulating body temperature and maintaining comfort level. Animal studies in which nerve fibers are teased out from the surrounding tissue but left connected to the skin show that two kinds of fibers carry the perception of warmth, both of them distinct from the neurons that detect uncomfortable heat. These warmth neurons are active at normal skin temperature (30 to 34 degrees) and become more active as temperatures rise: One peaks at 41 degrees and the other at 47 degrees. Curiously, warmth-activated responses rarely appear in cultured neurons. As with light-touch stimuli, pleasantly warm sensations at injured or inflamed sites can be perceived as painful—an example is the scalded feeling you get stepping into a warm shower after being sunburned.

In cultured cells, TRPV3 and TRPV4 act within the same temperature ranges as these warmth-sensitive fibers. As we hinted above, you might assume that the warmth-sensing neurons fire at these thresholds because they con-

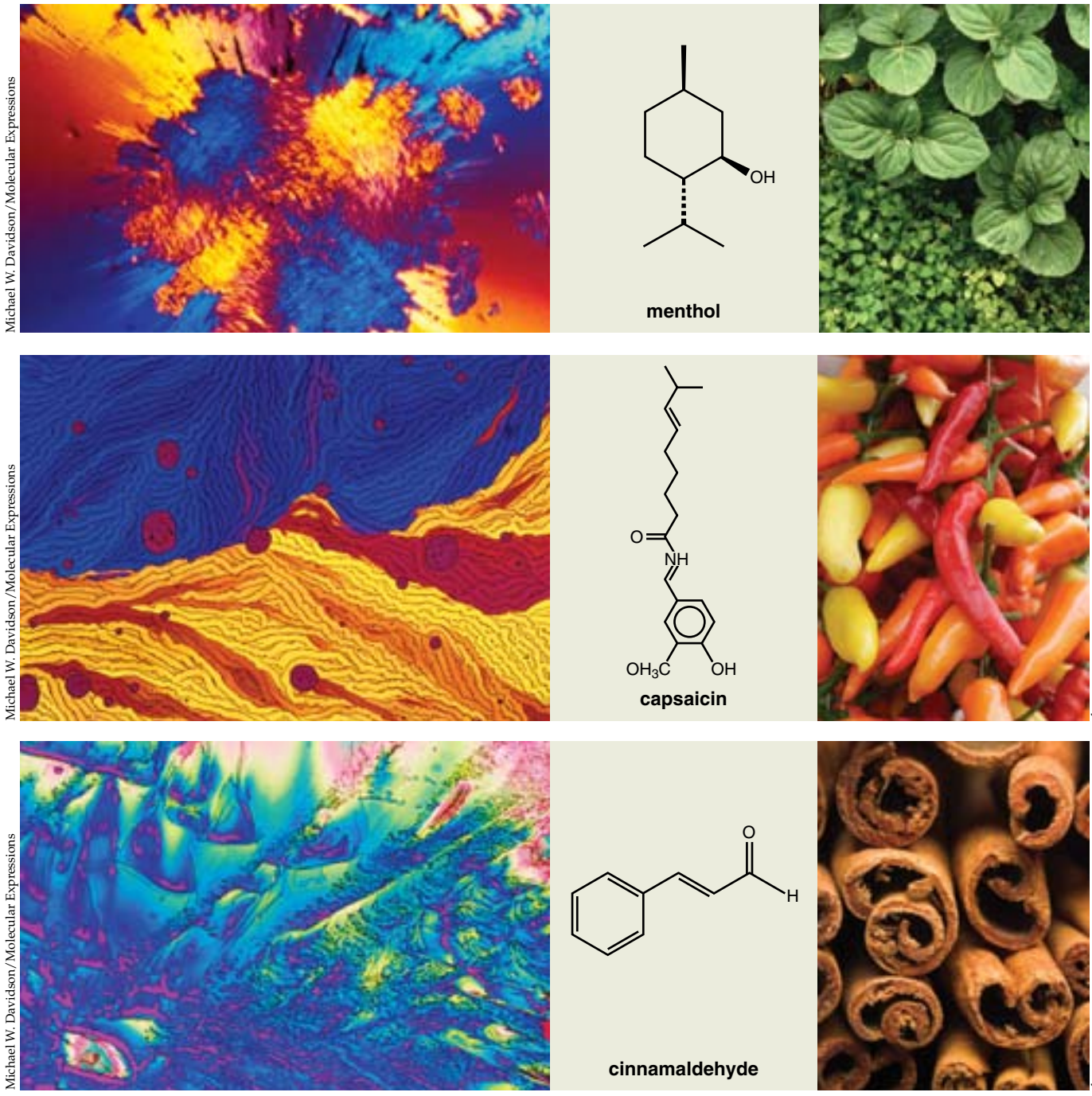


**Figure 3. The polarized-light micrographs at left show crystals of cooling menthol, spicy hot capsaicin and "burning" cinnamaldehyde. The center and right panels show their chemical structures and the foodstuffs from which these chemicals are derived (mint, pepper and cinnamon). (Photo of mint courtesy of Michael Thompson/U.S. Department of Agriculture.)**

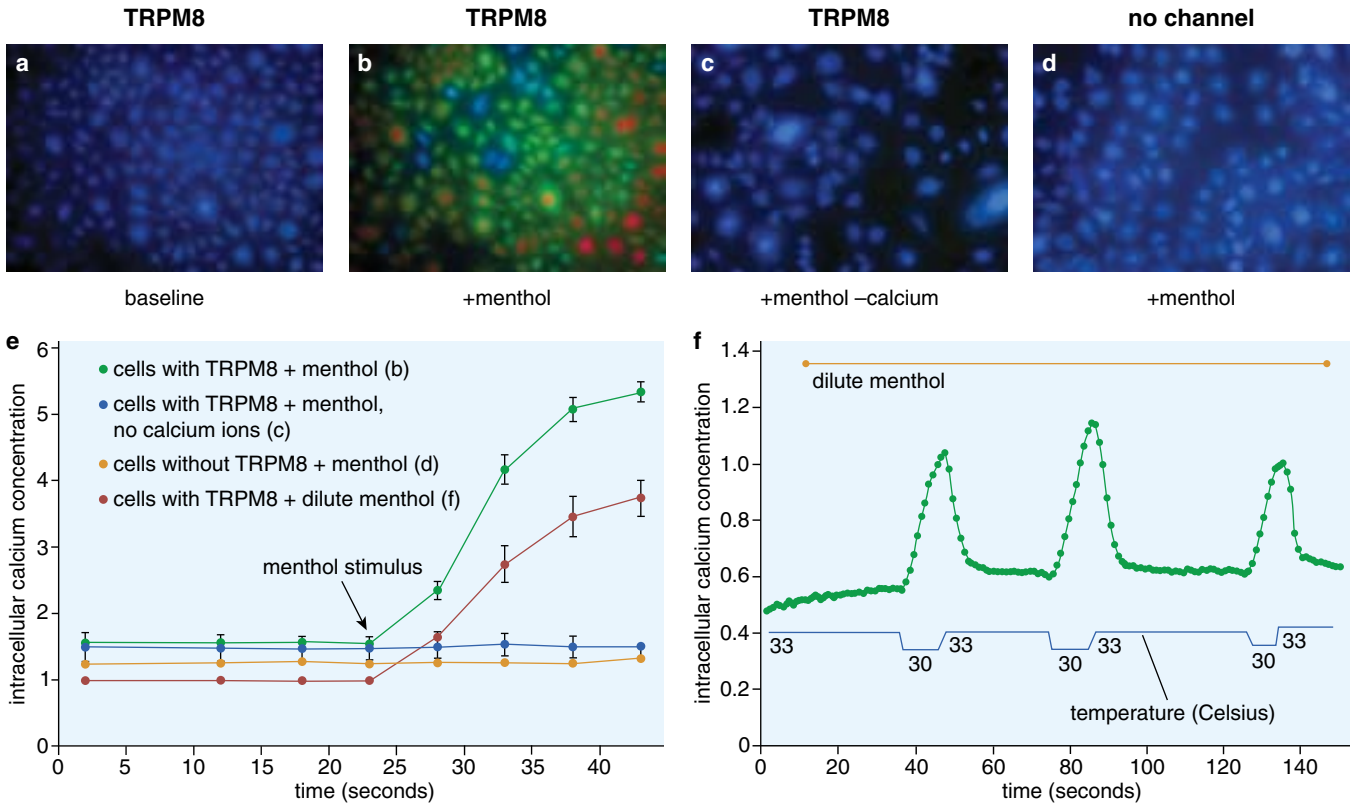


**Figure 4. A fluorescent dye used to measure intracellular calcium shows the entry of calcium ions through menthol-activated TRPM8 channels. Images a–d depict cultured cells filled with the indicator dye Fura-2, which changes its spectral properties depending on the concentration of calcium ions. Frames a–c contain cells programmed to make TRPM8 channels; the cells in d are the same type but do not have TRPM8 channels. In this false-color scheme, the cells give off a blue glow when calcium levels are low; warmer colors correspond to higher concentrations. Without menthol, the TRPM8 cells contain little calcium *(a)*, but the application of menthol causes a flood of calcium ions to enter the cells *(b)*. The omission of calcium from the surrounding medium prevents this change *(c)*, as does the absence of TRPM8 channels *(d)*. These data are shown graphically in e. Separately, neither dilute menthol nor 30-degree temperatures activate TRPM8, but together they can open the channel *(f)*. (Adapted from Peier *et al.* 2002. Micrographs courtesy of Ardem Patapoutian.)**

tain warmth-sensitive V3 and V4 channels, but this turns out to be not quite right. In a curious turn of events, the channels don't always show up in the neurons; some studies find them, and some don't. What is undisputed is that these two TRPV channels are abundant in skin cells. This observation raises the interesting possibility that the skin itself, rather than being an inert protective layer, has its own active role in thermosensation and pain. This is an attractive topic of research because of its potential to redefine our understanding of peripheral sensation itself. TRPV4 probably has a physiological role apart from thermosensation, as the protein can also be detected in the brain, blood vessels, kidney and inner ear.

Like TRPV2, V3 becomes sensitized with repeated heat stimuli, and such responses increase at temperatures greater than 33 degrees. The properties of the TRPV4 channel are more complex. V4 opens under warm conditions (in the range of 27 to 35 degrees) and becomes increasingly active as temperatures reach 42 degrees. But the flow of ions through the channel decreases if temperatures rise past that point. This channel desensitizes under repeated stimulation. V4 is also uniquely sensitive to extracellular *osmolarity*—the concentration of salts and soluble compounds outside the cell. When the concentration is unusually low, as is the case when physical damage causes swelling of an injured site, V4 channels are more likely to open with mild heat.

TRPV3 and TRPV4 also bind and are regulated by natural and synthetic chemicals. V3 opens in response to the aromatic plant compound camphor, which feels warm on the skin. Camphor is widely used in analgesic ointments, an apparent nod to the function of V3 in nociception. However, Haoxing Xu and Nathaniel T. Blair in David E. Clapham's laboratory at Harvard Medical School reported in 2005 that concentrated camphor also activates and strongly desensitizes TRPV1. Therefore camphor, similar to capsaicin, could trace its analgesic properties to a desensitization of V1. TRPV4 is activated by several of the body's own molecules, including arachidonic acid (a fatty acid that acts as a key cellular messenger) and an endogenous cannabinoid called anandamide. (Exogenous cannabinoids are found in marijuana plants.) In both cases, thermal and chemical (and osmotic) stimuli act together on the channel. Thus, V3 becomes cross-sensitized by repeated stimulation with either heat or camphor. V4 performs a kind of molecular computation by integrating its diverse signals—temperature, osmolarity, the presence of certain chemicals—through distinct modules of the protein.

Overall, the biophysical properties of each heat-sensing channel are unique, with different thresholds and chemical sensitivities. But the ranges of temperatures over which these channels are active are somewhat overlapping. The significance of this overlap remains unclear, but it underpins several outstanding questions, including: How does activation of thermoTRPVs enable us to

perceive fine distinctions in temperature? Can these channels functionally compensate for one another? Do they use the same signaling pathways over the range of temperatures? Do they use the same signaling pathways during normal thermosensation and heightened thermosensation as a result of inflammation? These are difficult questions. Because animals with deletions in the genes that encode the various TRPV channels retain partial thermosensation, several research groups are undoubtedly pursuing combinatorial knockout approaches by breeding one mutant line with another.

**From Cool to Cold**

Moderately cool stimuli, such as the breeze from a fan, are usually pleasant. Very cold temperatures are obviously painful, but this pain is qualitatively different from the pain from a very hot stimulus. Thus, touching a hot stove causes a reflexive withdrawal, but there is no corresponding reflex for touching an icy cold surface. Cold pain is complex—a burning, pricking or aching feeling, with acute, stabbing components and rising discomfort. Yet our ability to discern increments of cold as small as 1 degree is well developed across a range of temperatures. The threshold of pain in healthy people is around 15 degrees. But for people with a neuropathic condition that makes them hypersensitive to cooling stimuli (the aforementioned cold allodynia), temperatures between 15 and 30 degrees are painful. Two distantly related thermoTRP channels, TRPM8 and TRPA1, are thought to enable the detection of innocuous and painful cooling temperatures.

In 2003, two independent studies with different experimental approaches reported the discovery of a new channel called cold and menthol receptor 1 (CMR1). The name of the channel was later changed to TRPM8. Ardem Patapoutian at the Scripps Research Institute in La Jolla, California, and David Julius were the respective laboratory directors, and one of us (Story) was among the contributors to this novel finding.

In cultured cells, the research groups found that menthol and cool temperatures (with a threshold of 25 to 28 degrees) both activate TRPM8. The channel seems to adapt to prolonged cold stimuli, and its threshold shifts to a warmer range when menthol is present, suggesting that the stimuli act synergistically. Besides menthol, eucalyptol and spearmint as well as artificial compounds such as the "ultracooling" *icilin* act on this channel.

Just as capsaicin evokes the sensation of heat by activating TRPV1, and camphor induces a sensation of warmth by activating TRPV3, so menthol produces a cool feeling by opening TRPM8 channels. Yet many of the physiological functions of the M8 channel are still being worked out. Most investigators agree that TRPM8 sensory neurons are distinct from those cells containing other types of TRP channels. But the properties of these neurons are poorly characterized, and the cells themselves are hard to study in culture—perhaps because they begin expressing other TRPs under culture conditions. The cul-

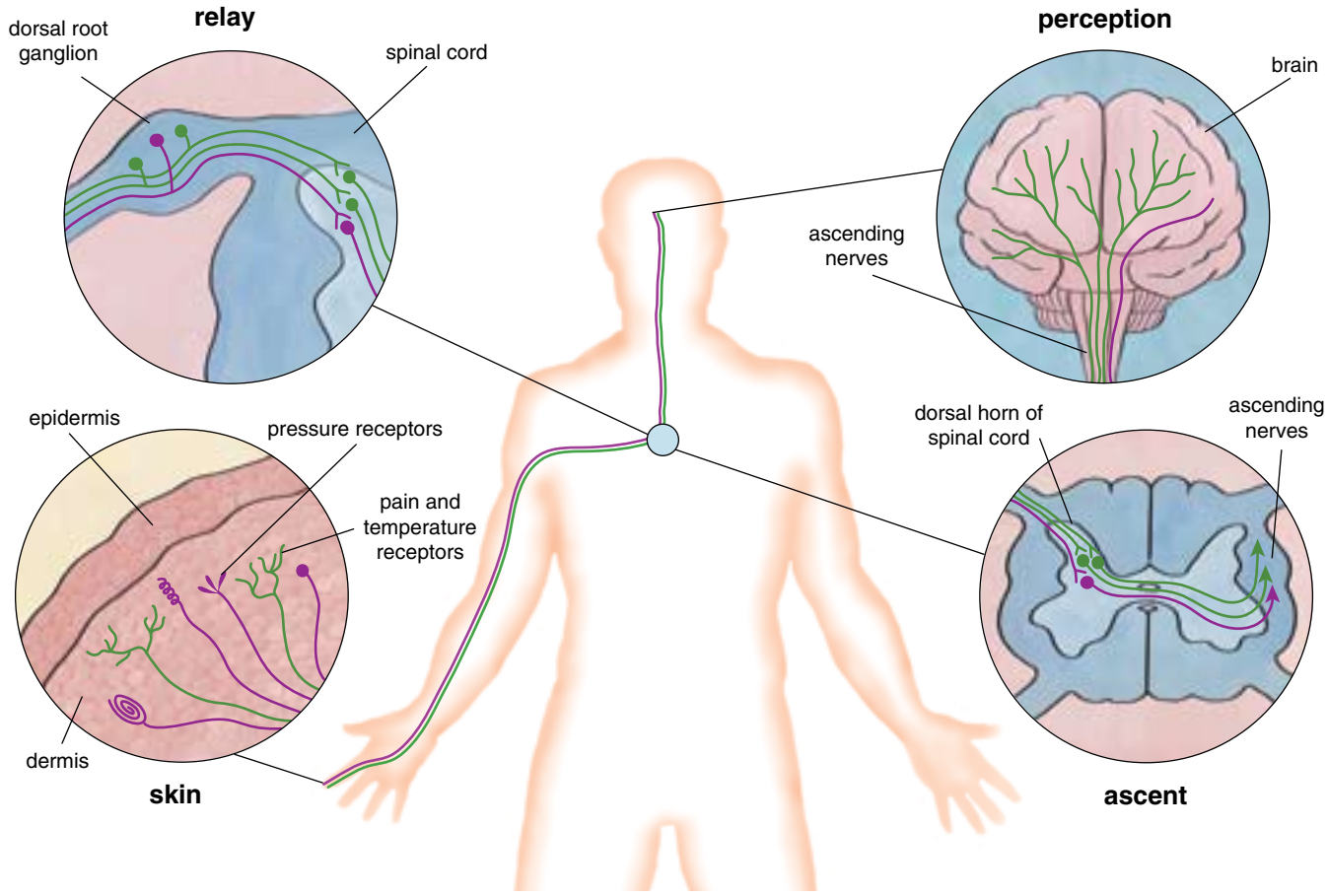


**Figure 5. Tiny nerve endings in the skin of the right hand detect mechanical sensations *(purple)* and thermal and pain stimuli *(green)*. Signals from these nerve endings travel to the dorsal horn of the spinal cord, where they activate relay neurons that cross from the right to the left side of the cord and ascend, carrying information about environmental stimuli to specialized regions of the brain where it is decoded and perceived.**


**Figure 6. Over-the-counter and prescription pain rubs can contain capsaicin or camphor, which dulls arthritis pain through its desensitizing effect on TRPV1 channels. As a result, the pain-sensing neurons that contain these channels become less active.**

tured-cell experiments initially generated some excitement that cells containing TRPM8 and TRPV1 might sense both painful cold and painful heat, thereby explaining the phenomenon of "paradoxical cold," in which cold-sensing neurons are activated by high heat. This hypothesis has since wilted in the face of several studies of intact tissue that fail to detect TRPM8 and TRPV1 proteins in the same cells. One lesson learned from this discrepancy is that despite the power and utility of experiments that use cultured cells, they don't always provide the final word on TRP function in living organisms.

At this time, scientists still don't know whether TRPM8 transduces painfully cold stimuli in addition to cooling sensations. Menthol is not normally painful, but a recent study says that concentrated menthol can cause cold pain at warmer temperatures and intensify pain at colder temperatures. It's not clear that this effect is because of TRPM8 activation, but either way, menthol could prove useful in the study of cold allodynia. One interesting detail about the M8 channel is that a few stimuli affect it and TRPV1 in an opposite manner. Acidic conditions and a specific cellular messenger called bradykinin activate or sensitize the TRPV1 channel; the same stimuli inhibit TRPM8.

Two independent groups (Patapoutian's and another at Johnson & Johnson led by Raymond W. Colburn and Ning Qin) recently reported the creation of TRPM8-knockout mice. Knockout mice were less likely to avoid cool surfaces (similar to humans, mice prefer a pleasantly warm surface over a cold one), suggesting that TRPM8 is involved in cold sensation. The same studies indicated that TRPM8 could play a role in cold-induced pain in healthy animals and ones with injury or inflammation.

**Burning Cold**

Whereas all available data conclude that TRPM8 is a key player in cold sensation, the physiological role of TRPA1, the channel attuned to the coldest temperatures, is still a prickly issue. One of us (Story) spearheaded the identification of this channel in Patapoutian's laboratory. When we put the DNA encoding TRPA1 into cultured cells, the channel proteins were active over a broad range of temperatures with an average of about 17 degrees—close to the 15-degree threshold for cold pain. The A1 channel opens in response to concentrated icilin but not menthol. Intriguingly, camphor and menthol inhibited the passage of ions through A1. Thus, these chemical signals regulate more than one thermoTRP channel, hinting at a potential mechanism for their analgesic affects.

The nerve fibers that contain TRPA1 (or at least its RNA) are different from those with TRPM8. Rather, the A1-containing neurons are a subset of TRPV1 nerve cells. This detail suggests two interesting conclusions: First, TRPM8 and TRPA1 convey different information about cold stimuli, and second, a neuron with TRPA1 and TRPV1 might be some sort of "polymodal" nociceptor, one that responds to noxious cold and heat along with other painful chemical and mechanical stimuli.

Several familiar, pungent substances contain chemicals that activate TRPA1, including mustard (allyl isothiocyanates), cinnamon (cinnamaldehyde) and garlic (allicin). Acrolein, a highly toxic component of air pollution, also opens the channel. These substances can produce painful, burning sensations. Although it's not certain that A1 is involved in the perception of painful cold under normal circumstances (the data are conflicting), this channel does seem to contribute to the oversensitivity to noxious cold (cold hyperalgesia) caused by inflammation or injury.

Using mice with a targeted deletion of the gene for TRPA1, two studies showed that this channel is the major action site for allyl isothiocyanate, an irritating, potentially toxic component of mustard oil. This substance is the source of the culinary bite in food garnishes such as wasabi and horseradish, but in larger quantities it causes acute pain and inflammation. Unlike normal mice, TRPA1-deficient mice will drink water that contains mustard oil (albeit in lesser quantities than plain water). And the mutant mice don't appear to perceive the topical application of mustard oil to be as painful as it is for normal animals. Studies of TRPA1 knockout mice also confirm that this channel contributes to the development of the mechanical and thermal hyperalgesia that accompanies inflammation.

**The Dimension of Pain**

Scientists continue to learn more about the biophysical properties of these channels and the mechanisms that enable them to integrate so many types of stimuli. Early studies identified the region of TRPV1 that responds to capsaicin by comparing the mammalian protein with that of birds, which are insensitive to that compound. (This detail suggests that capsaicin evolved in pepper plants to deter mammals in favor of birds; we must be poor seed dispersers compared to our feathered friends.) Another recent study indicated that swapping portions of the TRPV1 and TRPM8 channels also switched their thermal sensitivity, inflammatory modulation and distinctive biophysical signatures. Different domains of the TRPM8 channel also confer sensitivity to menthol, according to another report. Two research groups, noting a common trait among the myriad of TRPA1 activators, showed that cysteine amino acids at key regions of the channel protein are necessary for ligand potency. We cannot dive into all of the interesting biophysical characteristics of thermoTRPs here, but they certainly prove the remarkably complexity of these channels. There is no shortage of unanswered questions.

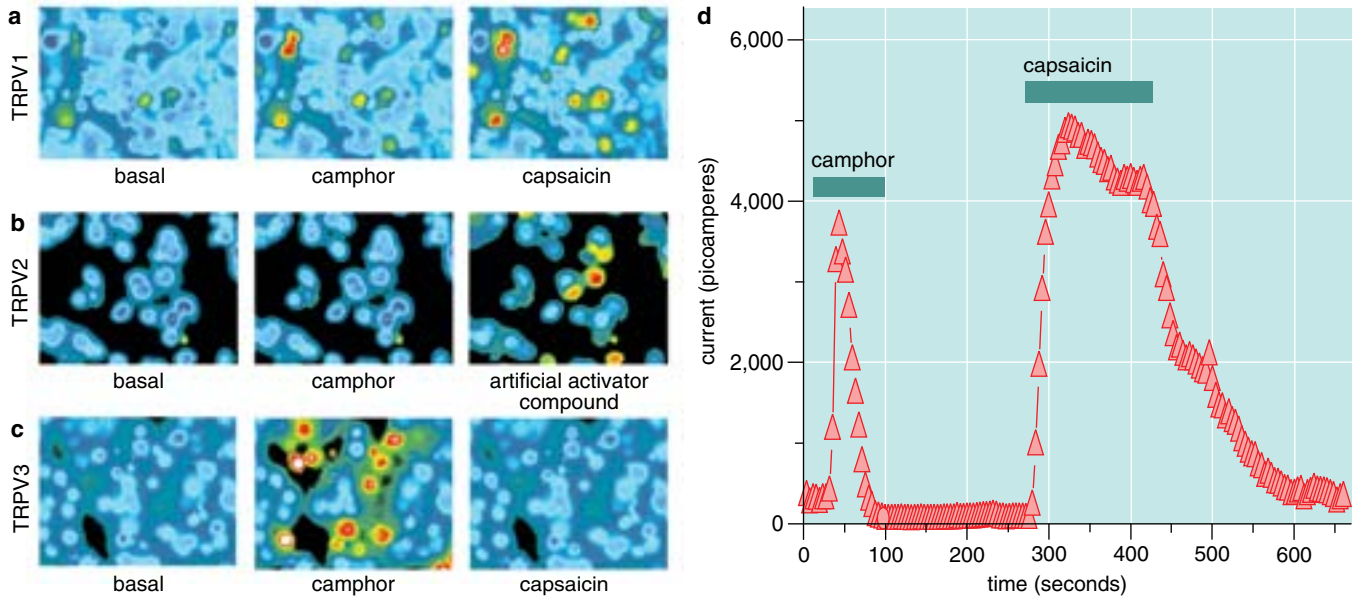


**Figure 7. In the images in a–c, a calcium-sensitive dye shows which compounds open warmth- and heat-sensing channels in cultured cells. In this false-color scheme, blue indicates low concentrations of calcium and red denotes high levels. Cells that are programmed to make TRPV1 protein *(a)* show an influx of calcium ions in response to camphor and capsaicin. When the same cell type contains TRPV2 channels *(b)*, camphor does not cause a calcium rise; a synthetic TRPV2 activator proves the channels are in place. Cells with TRPV3 *(c)* open with camphor but not capsaicin. Another way of measuring whether ion channels are open or closed is to measure the current flowing across the cell membrane. In TRPV1-producing cells in culture, camphor and capsaicin cause a spike in the current, followed by a decline as the channels become desensitized *(d)*. (Adapted from Xu *et al.* 2005)**

The solid link between thermoTRPs and temperature sensation doesn't rule out the possibility that other means of feeling heat or cold might still exist. One recent paper showed that warming temperatures (increasing from 15 to 35 degrees) activated TRPM4 and TRPM5, channels long thought to be insensitive to temperature. TRPM5 is found on taste-receptor cells on the tongue, enabling the perception of sweet, bitter and umami flavors. According to this study, TRPM5 modulates neurons from sweet-sensitive taste buds. This property could explain why people report that sweet flavors are more intense at warm temperatures. The question of whether M4 or M5 (or both) enable gustatory neurons to act as thermosensors is an exciting new area of investigation.

We are at the threshold of understanding the normal and pathological functions of thermoTRP channels. These studies are first steps in understanding pain. We must also learn how the nervous system amplifies pain signals in allodynia and hyperalgesia, and how the pattern of signals in sensory neurons affects the perception of pain high within the brain.

Yet the uncertainties in this field are disappearing at a remarkable rate. A ground-breaking paper is published every week, it seems. The mysteries of pain, linked as they are with temperature and touch sensation, are flickering into view as the fire of our knowledge burns brighter.

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