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INVITED REVIEW

TRPs et al.: a molecular toolkit for thermosensory adaptations

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Abstract
The ability to sense temperature is crucial for the survival of an organism. Temperature influences all biological operations, from rates of metabolic reactions to protein folding, and broad behavioral functions, from feeding to breeding, and other seasonal activities. The evolution of specialized thermosensory adaptations has enabled animals to inhabit extreme temperature niches and to perform specific temperature-dependent behaviors. The function of sensory neurons depends on the participation of various types of ion channels. Each of the channels involved in neuronal excitability, whether through the generation of receptor potential, action potential, or the maintenance of the resting potential have temperature-dependent properties that can tune the neuron's response to temperature stimuli. Since the function of all proteins is affected by temperature, animals need adaptations not only for detecting different temperatures, but also for maintaining sensory ability at different temperatures. A full understanding of the molecular mechanism of thermosensation requires an investigation of all channel types at each step of thermosensory transduction. A fruitful avenue of investigation into how different molecules can contribute to the fine-tuning of temperature sensitivity is to study the specialized adaptations of various species. Given the diversity of molecular participants at each stage of sensory transduction, animals have a toolkit of channels at their disposal to adapt their thermosensitivity to their particular habitats or behavioral circumstances.

Keywords Thermosensation · Molecular adaptations · Ion channels · TRP channels · Neuronal excitability

Introduction

Environmental information is detected by sensory primary afferents that innervate the skin and is transmitted through central projections to the spinal cord and the brain. The cell bodies of the somatosensory neurons reside in the dorsal root ganglia (DRG) that innervate the body and in trigeminal ganglia (TG) that innervate the face. Somatosensory neurons express a combination of multiple channel types that determine their ability to detect and transmit specific sensory stimuli. Primary sensors generate a graded depolarization in response to a stimulus. The receptor potential activates an inward current through voltage-dependent sodium channels to generate the upstroke of an all-or-none action potential. Subsequently, potassium channels conduct an outward current to create the down-stroke and after-hyperpolarization of the action potential. Action potentials are only generated if the cellular depolarization reaches a certain threshold. The proximity of the cell's resting membrane potential to this threshold contributes to how easily the cell can fire in response to stimuli. The resting potential is determined by activities of several types of ion channels and pumps (Fig. 1).

Much attention has been paid to temperature-sensitive receptor channels, but there are a growing number of studies that show that other types of channels play a critical role in the detection and transmission of temperature information. A full understanding of the molecular mechanisms of thermosensation

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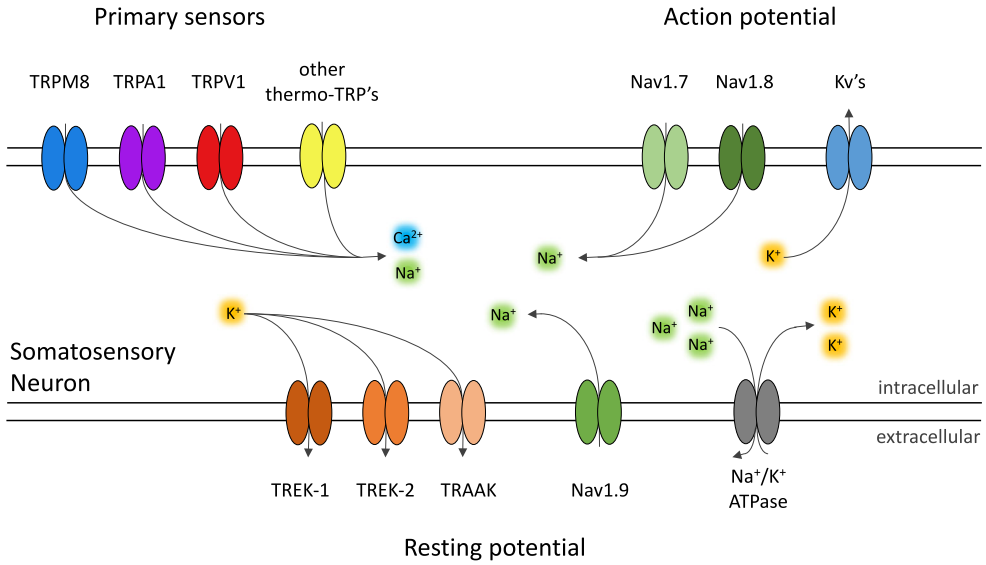

Fig. 1 Diagram of molecular participants in thermosensory excitability. Multiple-channel types contribute to the function of thermosensory neurons. Primary sensors of temperature are non-specific cation channels (TRPM8, TRPA1, TRPV1, and other thermo-TRP's). Action potentials in thermosensitive neurons are mainly conducted by voltage-gated sodium channels (Nav1.7 and Nav1.8) which promote excitability. Voltage-gated potassium channels (Kv's) provide a counteracting current that limits excitability. Nav1.9 is a regulator of the resting potential and amplifier of subthreshold depolarization. The resting potential of thermosensory neurons is also regulated by thermo-sensitive leak potassium channels (TREK-1, TREK-2, and TRAAK) which counteract excitability. Another contributor to the resting potential is the Na^+/K^+-ATPase, which sets up the ionic gradients across the membrane

requires an investigation of all channel types at each step of thermosensory transduction. Comparative studies demonstrated that molecular components of the thermosensory system can be altered through evolution to confer temperature adaptions in animals with different thermosensory needs. In this review, we will discuss the involvement of primary temperature sensors, channels that generate and propagate action potentials, and channels that maintain the resting potential in regulation of temperature sensitivity across different species.

Primary temperature sensors

A group of temperature-sensitive receptor channels that have been studied extensively is the TRP (transient receptor potential) family [100]. TRPs are non-selective cation channels, many of which are polymodal, meaning they generate transient depolarizing potentials in response to multiple types of sensory stimuli. Thus, most of the thermosensitive TRP channels (thermo-TRPs) can be activated by changes in temperature and also by various chemicals, some of which evoke similar temperature-like sensations [61]. The activity of the known thermo-TRPs covers the whole range of physiologically relevant temperatures, from painful heat, and intermediate warmth, to cold. For some of the thermo-TRPs, their function in vitro agrees well with their role in the detection of the relevant temperature ranges in sensory neurons and in vivo, while for most such a link has not been firmly established. In addition to thermo-TRPs, a number of other channel types have been shown to be gated by temperature and may play a role in thermosensation.

The temperature-evoked currents of thermo-TRPs increase in a steep but graded manner across their temperature activation range, as the channel open probability increases with changes in temperature. Thermosensitivity is typically quantified using two measures, Q_{10} and temperature threshold. Q_{10} refers to the relative change in current amplitude when the temperature increases by 10 degrees. While all reaction rates are dependent on temperature and all channels have a Q_{10}, thermosensors usually have a Q_{10} of > 5 (for heat sensors) or < 0.2 (for cold sensors) [146]. By plotting the logarithm of the current response versus the inverse of the temperature in Kelvin (Arrhenius plot, Fig. 2), the Q_{10} can be calculated from the slope of the resulting curve. The intersection of two lines that lie tangent to each end of the Arrhenius plot points at the apparent temperature activation threshold (Fig. 2). However, the temperature threshold should not be misinterpreted as an absolute threshold of channel activation, but rather as a marker of the detectable temperature-sensitive range.

TRPM8

TRPM8 is the receptor for cold temperatures and chemicals that elicit cooling sensation, such as menthol (found in mint leaves) and the synthetic compound icilin [96, 115]. In cell lines and neurons, mammalian TRPM8 exhibits gradual activation upon cooling below 30 °C. TRPM8 knockout mice

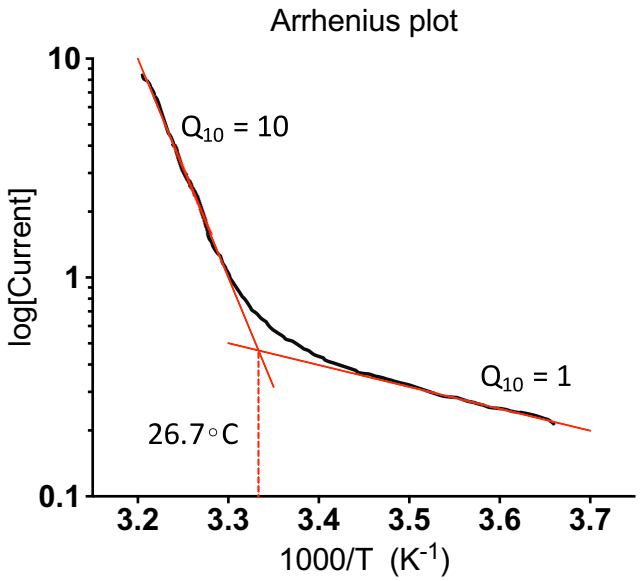

Fig. 2 Arrhenius plot of a hypothetical temperature-sensitive channel. The Arrhenius plot depicts the current amplitude evoked by changes in temperature on a log scale on the y-axis, versus the inverse of temperature in degrees Kelvin on the x-axis. The slope of the resulting curve reports the Q_{10} of the channel at different temperatures. While all proteins have some dependence on temperature, thermosensitive channels usually have a $Q_{10} > 5$. A typical method of quantifying the temperature threshold is to find the intersection point of two lines that lie tangent to the beginning and end of the curve (red lines). This apparent activation threshold marks the start of a detectable increase in channel activity in heterologous and native systems, which increases at a steep rate over the channel's activation range

show significant deficits in temperature preferences in the cooling range (10–20 °C), but retain responses to painful cold below 10 °C [17, 37]. Some reports, however, demonstrated deficits in noxious cold sensing even at 5 °C [71]. Genetic or pharmacological ablation of TRPM8-expressing cells, rather than the TRPM8 gene alone, causes deficits in the whole testable cold range [72, 119]. This indicates that there is an additional TRPM8-independent mechanism for sensing temperatures below 10 °C (Fig. 3).

Within its role as a cold sensor, there is a diversity of TRPM8 sensitivities among different animal species. When heterologously expressed in oocytes, rat TRPM8 has a half-maximal activation of 24 °C, a few degrees below the rat's preferred ambient temperature of 28 °C [80]. On the other hand, frogs (*Xenopus laevis* and *Xenopus tropicalis*) have a notably shifted TRPM8 half-maximal activation to 13.9 °C, which would allow these species to detect cold below their tolerable temperature range of 14–32 °C [21]. The half-maximal activation of chicken (*Gallus gallus domesticus*) TRPM8 is 29.4 °C [105]. For effective cold sensation, it seems that TRPM8 activity is tuned to the relative body temperature of the species. In animals with lower or more variable body temperatures, such as ectothermic animals, whose core body temperature adjusts to ambient levels, it would be detrimental to activate the cold receptor at cool ranges that are frequently experienced (Fig. 4a).

An extreme example of changing body temperature occurs in hibernating animals. Mammals that hibernate exhibit a mixture of endothermic and ectothermic phenotypes, actively maintaining a stable body temperature during the active state, and adjusting body temperature to ambient levels during the torpid state [49]. For example, the core body temperature of a 13-lined ground squirrel (*Ictidomys tridecemlineatus*) can drop to 2–4 °C [98], and that of an arctic ground squirrel (*Spermophilus undulatus*) can drop as low as − 2.9 °C during hibernation [15]. In order to tolerate extended periods of time at such temperatures, these animals must be able to modify their sensation of noxious cold, a sensory mechanism that is not yet fully understood. Furthermore, while transitioning between the active and torpid states, they experience severe hypothermia that would be intolerable to other endothermic animals. The results of a recent study support the possibility that modifications of TRPM8 contribute to cold tolerance in hibernators. The TRPM8 orthologs of two hibernating species, the 13-lined ground squirrel and the Syrian hamster (*Mesocricetus auratus*), respond weakly to cold, especially in the range of 10–20 °C, while retaining chemical sensitivity to icilin and menthol. Six amino acids distributed across the transmembrane core of the channel were found to be important for this modality-specific modification, and replacing these amino acids with the corresponding residues from the

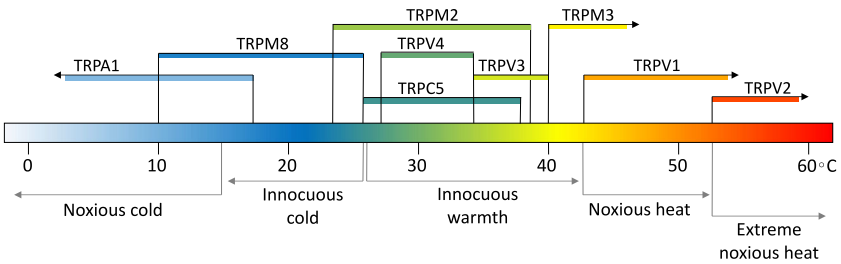

Fig. 3 Temperature range of mammalian thermo-TRPs. Depicts the temperature-sensitive range of each thermo-TRP. TRPA1 (< 17 °C), TRPM8 (10–26 °C), TRPM2 (23–28 °C), TRPC5 (26–38 °C), TRPV4 (27–34 °C), TRPV3 (33–40 °C), TRPM3 (> 40 °C), TRPV1 (> 42 °C), TRPV2 (> 52 °C). These overlap with psychophysical temperature ranges of noxious cold (< 15 °C), innocuous cold (10–25 °C), innocuous warmth (25–42 °C), noxious heat (42–52 °C), and extreme noxious heat (> 52 °C)

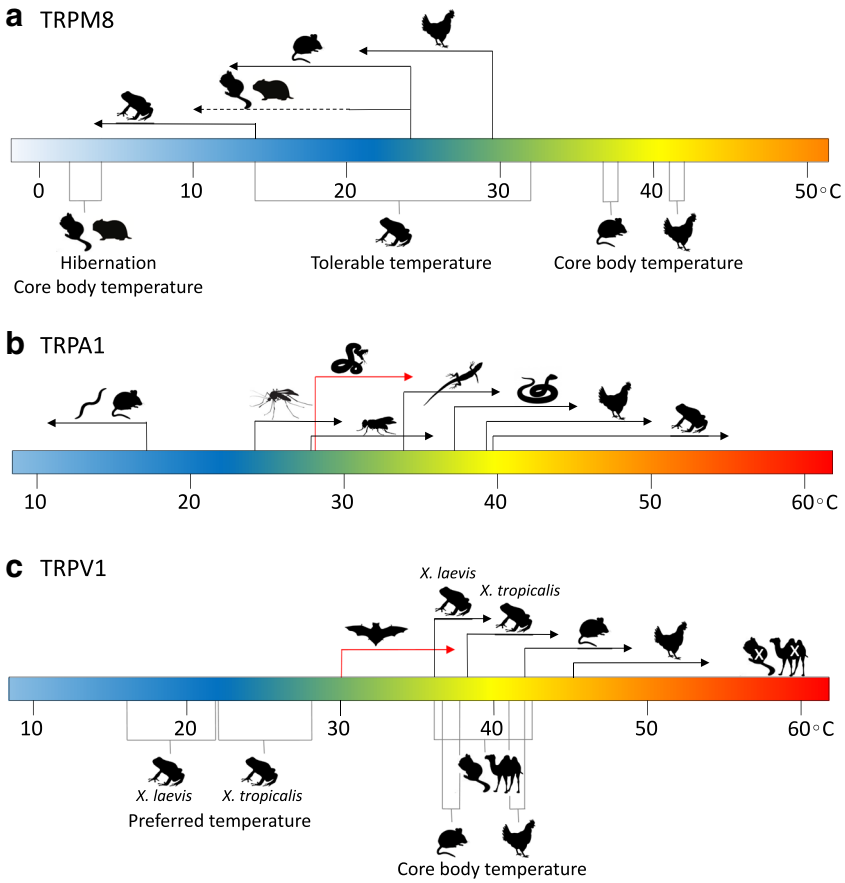

Fig. 4 Species-specific temperature ranges of TRPM8, TRPA1, and TRPV1. **a** Half-maximal activation temperatures of TRPM8 from chicken (29.4 °C), rat (24 °C), and frogs (13.9) correlate with the body temperature of chicken (41–42 °C) and rat (~ 37 °C), and the tolerable temperature of frogs (14–32 °C). The body temperature of hibernating 13-lined ground squirrels and Syrian hamsters drops as low as 2–4 °C, which these animals may be able to tolerate due to reduced TRPM8 sensitivity in the range of 20–10 °C (denoted by dotted line). **b** TRPA1 apparent activation threshold of mouse (< 17 °C), worm (< 17 °C), mosquito TRPA1-B (24.8 °C), fruit fly TRPA1-B (27.8 °C), rattlesnake (32.7 °C), green anole (33.9 °C), rat snake (37 °C), chicken (39.4 °C), and frog (39.7 °C). Red arrow denotes specialized use of TRPA1 in snake pit organs as a radiant heat sensor. **c** TRPV1 apparent activation threshold of frog *Xenopus laevis* (36 °C), frog *Xenopus tropicalis* (38 °C), mouse (> 42 °C), and chicken (> 45 °C), which correlate with the preferred temperature of *Xenopus laevis* (16–22 °C) and *Xenopus tropicalis* (22–28 °C), and the body temperature of mouse (~ 37 °C) and chicken (41–42 °C). Extremophiles 13-lined ground squirrel and wild Bactrian camel tolerate a greater variation of body temperatures, and their TRPV1 homologs are not sensitive to heat. Red arrow denotes specialized use of TRPV1-S isoform as a heat sensor in pit organs of vampire bats (30 °C)

cold-sensitive rat channel is sufficient to restore cold sensitivity in squirrel TRPM8 [95].

TRPA1

TRPA1 is a polymodal channel that responds to a variety of stimuli in different species [78]. A commonly used chemical agonist of TRPA1 is allyl isothiocyanate (AITC), the pungent compound in mustard, radish, horseradish, and wasabi [13, 16, 26, 59]. TRPA1 can be activated by numerous other noxious chemicals, including naturally derived compounds from cinnamon, garlic, oregano, and olive oil, irritants in smoke and tear gas, and endogenous inflammatory factors. TRPA1 orthologs of different species have a diversity of functions, which show the evolutionary flexibility of this molecule [78].

Some, but not all mammalian orthologs of TRPA1 are cold-sensitive (Fig. 3) [28, 75, 97, 101, 102, 138]. Human TRPA1 is activated by cold in a lipid bilayer, suggesting that cold sensitivity is intrinsic to the channel [102]. In mice, TRPA1 also mediates physiological sensitivity to cold after injury and in pathological conditions [36, 77]. In *C. elegans*, TRPA1 is a cold sensor and is required for avoidance of acute cold shock at 15 °C [27]. Moreover, TRPA1 has been implicated in the process of cold-induced longevity in worms [154]. Interestingly, deficits in the cold avoidance in TRPA1 knock-out worms could be partially rescued by the mouse ortholog [27]. On the other hand, in birds, reptiles, amphibians, and insects, TRPA1 is activated by heat (Fig. 4b) [51, 66, 73, 123–125, 149].

The remarkable flexibility of TRPA1 temperature responses might be explained from a thermodynamic

standpoint. Thermodynamic considerations dictate that a channel with a sufficiently large change in molar heat capacity between open and closed states will exhibit a steep temperature dependence of its equilibrium constant of opening [31]. Furthermore, the equilibrium constant will have a non-linear U-shaped dependence on temperature. It would follow from this that all thermo-TRP's are actually both heat and cold sensors, but only reveal one "arm" of the activation curve in the physiologically testable range. A change in the molecular interactions within the protein could produce a shift in the activation curve along the temperature axis, placing the other arm of the activation curve into the physiological "window." This will effectively switch a channel's temperature sensitivity from heat to cold and vice versa, without requiring changes to the temperature sensing elements of the channel [31]. Indeed, a U-shaped temperature dependence was shown for human TRPA1; while in mouse TRPA1, the intrinsic directionality of temperature responses can be reversed by a single point mutation [58].

The versatility of TRPA1 makes it a good target for the evolution of specialized functions. Snakes have adapted TRPA1 to detect the heat emission of warm-blooded prey. Three groups of snakes (pit-vipers, boas, and pythons) have specialized structures on their faces—pit organs—that are enriched with TRPA1-expressing trigeminal sensory fibers. The rattlesnake (*Crotalus atrox*) has the highest sensitivity to infrared radiation. In addition to having a 400-fold higher expression of TRPA1 in TG than in DRG neurons, rattlesnake TRPA1 has a lower apparent heat activation threshold near 28 °C. By comparison, other pit-bearing snakes, python (*Python regius*) and boa (*Corallus hortulanus*), have thresholds of 32.7 and 29.6 °C, respectively; whereas a non-pit snake, Texas rat snake (*Elaphe obsoleta lindheimeri*), has a threshold near 37 °C. The increased thermosensitivity of snake TRPA1 channels may come at the expense of chemical sensitivity. Compared to the heat-insensitive rat TRPA1 whose half-maximal effective concentration (EC_{50}) for AITC is 11 μM, the EC_{50} of rattlesnake and rat snake is ≥ 500 μM (Fig. 4b) [51].

Fruit flies (*Drosophila melanogaster*) have multiple TRPA1 isoforms, effectively expanding the repertoire of TRPA1 functions. Drosophila TRPA1 (dTRPA1) has been shown to have at least four distinct splice isoforms expressed in different sensory organs in order to distinguish between innocuous heat, noxious heat, and noxious chemical stimuli. The dTRPA1-A isoform is activated by the chemical agonist AITC, but shows a very muted temperature response above a threshold of 29.7 °C. dTRPA1-A is expressed in the chemosensors of the proboscis, where it triggers regurgitation upon ingestion of noxious chemicals. Its reduced thermosensitivity avoids regurgitation in response to innocuous heat [65]. Another isoform, dTRPA1-B, is activated by temperature with an apparent threshold of 27.8 °C and various chemical agonists, including AITC. dTRPA1-B has a much steeper response to temperature, with a Q_{10} of ~ 116, compared to dTRPA1-A's Q_{10} of ~ 9. This isoform is expressed only in thermosensors of the fruit fly head where it is secluded from external chemicals. Therefore, dTRPA1-B mainly senses internal and external temperature and is likely responsible for thermal preferences in the innocuous range of 18–32 °C [65]. Two additional isoforms, dTRPA1-C and dTRPA1-D, have been shown to contribute to noxious heat sensation. Unlike the dTRPA1-A and B isoforms, dTRPA1-C and D are expressed in neurons that detect painful stimuli that mediate the fly's response to noxious temperatures. However, the apparent properties of these isoforms do not fully explain the fly's noxious heat threshold of 39 °C. dTRPA1-D has a relatively high thermal threshold of 35 °C. dTRPA1-C did not have a detectable thermal response within the testable range up to 42 °C, but is nevertheless required for the typical behavioral response to noxious heat [158].

A possible mechanism for indirect sensation of noxious temperature was recently suggested in a study of planarian flatworms (*Schmidtea mediterranea*). Planarian TRPA1 is similar to the *Drosophila* ortholog dTRPA1-C in that it is necessary for avoidance of noxious heat > 30 °C, but it is not directly activated by temperature when expressed heterologously. Instead, it was suggested that planarian heat-insensitive TRPA1 activates in response to early indicators of tissue damage from heating, such as H_2O_2, a known TRPA1 agonist [9].

Drosophila has additional TRPA homologs, Painless and Pyrexia, which are more closely related to basal TRPA's than to the TRPA1 clade [66]. By the same phylogenetic analysis, *C. elegans* TRPA1 is also more closely related to basal TRPA's [66]. Painless and Pyrexia are activated by noxious heat [57, 81, 136, 144]. Additionally, Painless responds to AITC and similar chemicals and noxious mechanical stimulation [5, 57, 144]. The thermosensory system of flies alone demonstrates several evolutionary mechanisms to create a variety of functional temperature sensors, through gene duplication and through alternative splicing.

Mosquitos (*Anopheles gambiae*) also use TRPA1 in a crucial thermotaxis behavior. To seek hosts for a blood meal, mosquito females use a variety of cues, including temperature. Their host-seeking thermotaxis involves attraction to warm stimuli, but avoidance of heat that exceeds the typical temperature of a host. The avoidance of heat above 50 °C requires TRPA1 [32]. Similar to the fruit fly, mosquitos produce isoforms TRPA1-A and B, with similar chemosensitivity, but much higher thermosensitivity in TRPA1-B [65]. These isoforms are conserved in other mosquito species (*Aedes aegypti* and *Culex quinquefasciatus*) and lice (*Pediculus humanus corporis*) [65], demonstrating the evolutionary conservation of this function. Across vertebrates and invertebrates, TRPA1 has a wide range of temperature sensitivities, displaying its evolutionary versatility as a polymodal molecular sensor.

TRPV1

TRPV1 is a receptor for noxious heat in mammals (> 42 °C), as well as for the spicy compound capsaicin (found in hot chili peppers), low pH, and multiple inflammatory mediators [24, 35, 61, 143]. TRPV1 knockout mice show significant behavioral deficits in temperature discrimination above 50 °C [22]. However, deletion of TRPV1-positive cells abolishes temperature sensitivity at all testable temperatures above 37 °C [99, 119]. This suggests the existence of additional heat sensors in TRPV1-containing neurons (Fig. 3).

The activation of heat sensitive ion channels also appears to correlate with the relative body temperature of different species. In mice and rats, TRPV1 activation occurs several degrees above their core body temperature near 37 °C. Along with birds' higher core body temperature of 41–42 °C, chicken TRPV1 has an activation threshold of > 45 °C [60]. In frogs, which are ectothermic and have a much lower preferred temperature range, TRPV1 activation is tuned according to the frog's preferred environment. *X. tropicalis*, which has an optimal temperature range of 22–28 °C, has a TRPV1 heat threshold of 38 °C. *X. laevis*, which has a slightly lower optimal temperature range of 16–22 °C, has a TRPV1 heat threshold of 36 °C [110]. Zebrafish (*Danio rerio*), with a tolerable temperature range of 14–33 °C, has an even lower TRPV1 threshold of 32.9 °C [50]. This ortholog is essential for heat avoidance behavior in zebrafish (Fig. 4c) [48].

Animals that live in extremely hot environments also require modifications of TRPV1. Small diurnal rodents, such as ground squirrels and chipmunks, that occupy a wide geographical range from California deserts to Minnesota, can tolerate prolonged heat exposure [56]. Consistent with this, ground squirrels do not avoid noxious temperatures up to 55 °C in a temperature preference test, but they do show nocifensive responses to capsaicin or chili oil. Electrophysiological studies also show that squirrel TRPV1 is sensitive to capsaicin, and pH, but not heat within the testable range up to 48 °C [79]. Another temperature extremophile, the wild Bactrian camel (*Camelus ferus*), that occupies the Gobi Desert, is faced with a similar problem of surviving high-environmental temperature and has evolved a similar adaptation in TRPV1 to help tolerate these conditions by their somatosensory system (Fig. 4c). Remarkably, TRPV1 sensitivity can be modulated by a single amino acid substitution in both species [79].

Bats have an adaptation to the opposite extreme that makes them especially sensitive to heat. Vampire bats (*Desmodus rotundus*) feed on the blood of mammals and identify target blood vessels by detecting radiating heat with specialized pit organs, localized on their face [74]. The specialized function of their pit organs comes from a differentially expressed splice isoform of TRPV1. The truncated (TRPV1-S) isoform is activated at 30 °C and is expressed exclusively in trigeminal fibers innervating the pit organ, while the full length (TRPV1-L) is activated at 40 °C and is expressed in the rest of the body. To prevent the constant activation of the TRPV1-S by its own body heat, the pit organs are insulated by a thick layer of tissue [50]. The shifting of TRPV1 activation thresholds across species demonstrates the importance of precise heat sensation, and the ability to adapt to species' specific circumstances (Fig. 4c).

Other thermo-TRPs

Several other members of the TRP family are considered to be involved in temperature sensitivity. TRPV3 [52, 103, 134, 155], TRPV4 [53, 151], and TRPM2 [141] were implicated in sensing intermediate innocuous warmth (25–42 °C), TRPM3 [147]—noxious heat (> 42 °C), TRPV2 [3, 23, 85]—extreme noxious heat (> 52 °C), and TRPC5 [160]—innocuous cold (25–15 °C). In addition, TRPM5, which is involved in taste perception, is also gated by temperatures spanning the innocuous cool and innocuous warm ranges [140]. The temperature sensitivity of some of these channels has been confirmed by knockout studies, such as TRPM3 which caused deficits in noxious heat sensing [139, 147], and TRPM2 which altered temperature preference in the innocuous range of 23–38 °C [141]. Some thermo-TRPs are interesting candidates for temperature-specific adaptations. For example, TRPV4 mRNA was found to be downregulated in the Japanese grass lizard (*Takydromus tachydromoides*) in the hibernation state [106]. Whether TRPV4 acts as a warm sensor in reptiles is unknown, but the changes of TRPV4 expression may be representative of a general reduction of the thermosensitive components during hibernation.

Other channels

TRPs are a well-established group of thermosensors; however, there are several other temperature sensitive channels that may act as primary sensors or modulators of thermosensitivity. The calcium-activated chloride channel anoctamin (ANO1) depolarizes sensory neurons at temperatures > 44 °C, and deletion of this channel reduces responses to noxious heat [29]. Cold temperature activates epithelial sodium channels (ENaC) and potentiates the activity of other members of the DEG/ENaC family [10].

Rhodopsins (Rh), whose canonical function is photodetection, play a role in temperature sensation. In fruit flies, TRPA1 was shown to function downstream of a G-protein-coupled signaling cascade [76]. Similar to phototransduction in the fruit fly eye, this cascade is initiated by rhodopsins. In mid-third-instar larvae, thermal preference within the tolerable range of 18–24 °C requires Rh1 [131], while the switch to a strong preference for 18 °C in late-third-instar larvae requires Rh5 and Rh6 in TRPA1-expressing neurons [135]. Rhodopsin-mediated thermotaxis was

independent of light; however, it is not yet clear if rhodopsins are intrinsically temperature sensitive.

Recent studies of *Drosophila* temperature sensitivity also revealed channel paralogs of taste receptors that are involved in thermosensation. The gustatory receptor paralog GR28B(D) is activated by heat and is required for rapid negative thermotaxis, away from high temperatures toward innocuous warmth [107]. Interestingly, this channel is expressed in a separate set of neurons from dTRPA1-B and controls a distinct behavior. Several ionotropic receptors (IR), a group that has been well studied in relation to chemosensation, were found to mediate cool sensation and avoidance of cool temperatures. Usually, a modality-specific IR acts in combination with a more widely expressed co-receptor [1, 122]. IR21a in combination with IR25a and IR93a is responsible for activation of the fruit fly's dorsal organ cold cells [108]. However, IR25a and IR93a mediate humidity sensation when expressed in combination with different IR channels [69, 70].

C. elegans also illuminates many molecular components of thermosensation, including non-channel proteins involved in processes such as cGMP signaling and neuron morphology. While TRP channels are involved in the sensation of noxious temperatures in the hot and cold range [27, 86], thermotaxis in the innocuous range is mostly mediated by CNG and cGMP channels [8].

This is not an exhaustive list of receptor channels with temperature sensitivity. Other suggested members are the ATP receptor P2X3 [67, 132, 137], and the calcium channel modulator STIM1 [153], and the list will surely grow to include many more channels in the future. As the multitude of receptor channel types and species-specific adaptations demonstrates, primary temperature sensors are one of the tools available for fine-tuning thermosensitivity.

Action potential

Action potential firing depends on two principal types of opposing ion currents. Inward sodium currents rapidly depolarize the cell and generate the upstroke of the action potential. Counteracting the inward currents are outward potassium currents that drive the falling phase of the action potential and repolarize the cell (Fig. 5) [63]. Temperature can alter channel properties in multiple ways, such as changing the kinetics of opening and closing, shifting the voltage-dependence of activation and inactivation, which can change the resting potential, input resistance, and electrogenic properties of the cell. Even in neurons that do not express known thermosensitive receptor channels, the transmission of sensory information is affected by temperature. Depending on the ion channel subtypes expressed, and the differential effect of temperature on these channels, various populations of sensory neurons have different responses to changes in temperature [97, 129, 145].

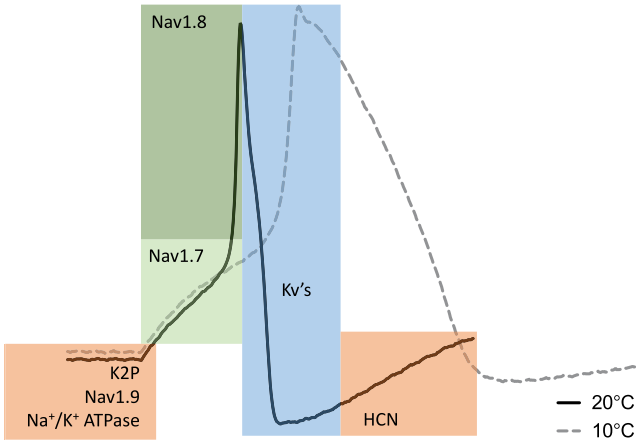

Fig. 5 Main molecular components of the action potential. Shown is the typical shape of an action potential in a mouse DRG neuron at room temperature (black trace) along with major electrical conduits. Colored regions denote the areas of contribution of the indicated channels' activity to the different phases of the action potential. Nav1.7 contributes to the early depolarization and upstroke (light green). Nav1.8 contributes to the rapid upstroke (dark green). Kv's repolarize the cell in the falling phase (blue). K2P's, Nav1.9, and Na^+/K^+-ATPase regulate the resting potential of the cell, and HCN channels drive the return of the resting potential from the after-hyperpolarization (orange). At cold temperature, the action potential becomes much slower and broader due to temperature dependent changes of the underlying channel activity (dashed gray trace)

Observations of excitability in mouse and rat somatosensory neurons at different temperatures demonstrate a diversity of cellular responses to temperature changes. In response to cooling, although most cells were not activated directly by cold, about half of the cells increased their excitability by increasing the number of action potentials fired and/or lowering the rheobase (current threshold) in response to stepwise current injections. Other cells were minimally affected or decreased their excitability at cold temperatures by decreasing the number of spikes and/or increasing the rheobase [62, 128]. It is noteworthy that the cells sampled in these studies were mostly small diameter neurons, likely neurons that transmit noxious information, not just of the temperature variety. Cold temperature can indeed change the perception of pain, in some cases numbing, in other cases exacerbating it, especially after injury conditions.

Nav1.8

Nav1.8 is one of several voltage-gated sodium channel (Nav) homologs expressed in dorsal root ganglion neurons. Nav1.8 is resistant to tetrodotoxin (TTX-R) and is a major component of the action potential upstroke in sensory neurons and is required for robust and sustained action potential firing [4, 152]. The critical role of Nav1.8 in pain sensation (nociception) is demonstrated by numerous single point mutations in human Nav1.8. Gain-of-function mutations lead to severe pain hypersensitivity disorders [19, 44].

Studies of sodium currents in sensory neurons at various temperatures have shown that all sodium currents are somewhat reduced and slowed down by cooling [62, 128, 159]. However, compared to the TTX-sensitive Nav1.7 (see below), Nav1.8 is relatively resistant to the effect of cold, with a reduction in current density of only ~50%, with a minimal effect on the voltage-dependence of fast and slow inactivation at 10 °C compared to 30 °C [159]. This has led to the interpretation that Nav1.8 is required for sending cold temperature information, as the main carrier of the action potential. Consistent with this hypothesis, neurons from Nav1.8 knockout mice did not fire action potentials in response to current injections at 10 °C and knockout mice did not show nocifensive responses to a 0 °C cold plate (159). Recently, a gain-of-function mutation of Nav1.8, called "Possum," was identified in mice. These animals have severe neurological abnormalities and exhibit significant hypersensitivity to cold when compared to wild-type mice [20].

Nav1.8 is an important evolutionary target for altering the sensitivity of nociceptors. Although an adaptation to temperature specifically has not yet been demonstrated, the case of the grasshopper mouse (*Onychomys torridus*) shows how alterations in Nav1.8 properties can turn off a pain modality. The grasshopper mouse feeds on the bark scorpion (*Centruroides sculpturatus*) which can deliver a debilitating painful sting. The toxin in the bark scorpion venom targets a different sodium channel, Nav1.7, to induce pain [91]. However, the grasshopper mouse has amino acid variants in Nav1.8 that bind to the bark scorpion toxin and inhibit Nav1.8 activation, thereby stopping the transmission of the pain signal [121].

Other animals might use a similar strategy to alter sensitivity to temperature as well. As noted earlier, hibernators endure extremely cold external and internal temperatures for extended periods of time [15, 98]. Modifications of Nav1.8 that reduce its activity at cold temperatures could be one mechanism to confer cold tolerance in these animals. For example, in a hibernating snail (*Helix pomatia*), Nav1.8-like channel expression is downregulated in the central nervous system during the hibernation state. In this mollusk, Nav1.8-like currents are also significantly reduced during hibernation [68]. As a major contributor to the robust firing of sensory neurons, Nav1.8 is poised to be an evolutionary target to alter sensitivity at the transmission step of thermal signaling.

Nav1.7

Nav1.7 is sensitive to inhibition by TTX (TTX-S) and is also a major component of the action potential upstroke. Nav1.7 is frequently co-expressed with Nav1.8 in small diameter DRG neurons [41, 127, 142]. Nav1.7 is activated at more hyperpolarized voltages than Nav1.8, thus Nav1.7 initiates the rapid inward current of an action potential, whereas Nav1.8 is needed to propagate robust, repetitive firing (Fig. 5) [30]. Nav1.7 is also critical for nociception, and single point mutations in human Nav1.7 are linked to severe pain hypersensitivity or complete pain insensitivity disorders [33, 34, 45, 54]. Several other sodium channels, Nav1.1, Nav1.2, and Nav1.6, are also expressed in some sensory neurons and can contribute to the TTX-S current in DRGs [25]. These Nav subtypes may also contribute to nociception, as has been shown for Nav1.1 which has a modality-specific role in mechanical pain but not in thermal pain [111]. Total TTX-S current and heterologously expressed Nav1.7 current amplitudes are strongly reduced by cold, by ~90% at 10 °C compared to 30 °C [159]. Nav1.7 has a large hyperpolarizing shift in slow inactivation, which could explain the strongly reduced current density in cold temperature at a normal neuronal resting potential near − 80 mV [159]. In rat TG and DRG, cells with only TTX-S current usually have a reduced firing rate at cold temperature, firing only a single action potential or several aborted action potentials, which shows that the small amount of remaining TTX-S current cannot support sustained firing [62, 128].

Nav1.7 is also an important evolutionary target for the modulation of nociception [157]. Although not specifically related to temperature sensation, the African naked mole-rat (*Heterocephalus glaber*) is an example of a species that uses alterations in Nav1.7 to block a pain modality. Among many interesting features, these animals are resistant to hypoxia, which allows them to live in densely populated underground burrows under high CO_2 conditions [112]. In many other animals, hypoxia is life threatening and perceived as painful due to the sensation of internal acidification. Instead of changing the function of acid sensors (ASIC's and TRPV1), the naked mole-rat has altered Nav's that are more strongly inhibited by protons. Naked mole-rat sodium currents were decreased by 63%, compared to mouse sodium currents which were decreased by 42%, at pH 6.0. Although the naked mole-rat's primary acid sensors can depolarize the neuron, signal transduction is blocked at the level of sodium channels and action potential initiation and propagation. This study found that the culprit of this phenomenon is Nav1.7, which has amino acid variants that render this channel more sensitive to block by protons [133].

Similar variants of Nav1.7 were found among other groups of animals that live in high CO_2 conditions, including several families of hibernators, which experience internal acidification and high CO_2 during torpor due to reduced respiration. However, this was not the case for all hibernators examined [87]. For example, the 13-lined ground squirrel amino acid residues are more similar to mouse than to naked mole rat. A similar mechanism could also be responsible for noxious cold tolerance in hibernators, in which increased block of Nav1.7 by cold prevents the propagation of signals in cold-sensitive neurons. Furthermore, action potential block by a pervasive signal such as internal acidification can lead to a more generalized analgesia. In the naked mole-rat, low pH also blocked other pain modalities, such as mechanically and electrically evoked firing of nociceptors [133].

Voltage-gated potassium channels

Several low threshold voltage-gated potassium channels contribute to the falling phase of action potentials. In nociceptors, they are mainly Kv1.4, Kv4.1, Kv4.3 (A-type K+ currents), and KCNQ2/3 (M-type K+ currents) [18, 113, 117, 120, 148, 150]. These channels are involved in modulating the shape of the action potential, membrane repolarization, action potential threshold, and repetitive firing. Since outward potassium currents act in opposition to the inward sodium currents of the rising phase of the action potential, larger potassium currents are thought to restrict neuronal excitability. Both the A- and the M-type currents are reduced, and the kinetics are slowed at cold temperature [62, 128]. The interaction between these currents and different types of sodium channels helps to explain the differential effect of cold on different populations of sensory neurons. In small-diameter somatosensory nociceptors that contain TTX-R sodium currents, which are relatively resistant to cold, the cold-induced reduction of potassium current has the expected result of lifting a brake and increasing the firing rate of these cells. In cells with only TTX-S sodium current, however, the cold-induced slowing of potassium current kinetics has the effect of impairing membrane repolarization which prevents the full recovery from inactivation of the sodium channels, leading to only single firing or aborted action potentials [128].

Cold-induced slowing of potassium channel kinetics that leads to suppression of repetitive firing presents a challenge for species that live in extremely cold habitats. Polar octopi were found to have a very interesting mechanism for altering potassium channel function. Instead of adapting through mutations in the genetic code, the octopi changed the sequence of a Kv1 homolog through RNA editing. Amino acid residues in the pore region were highly edited in an Antarctic octopus (*Pareledone* sp.), but were mostly unedited in a tropical octopus (*Octopus vulgaris*). The RNA-edited amino acid changes accelerated the deactivation of the channel, thus shortening the refractory period and increasing repetitive firing. Among eight different species of octopi, the proportion of edited channels correlated remarkably with the temperature of the species' habitats, pointing to the possibility that this RNA-editing mechanism is temperature dependent [47]. The temperature-dependence of the molecular drivers of action potentials can have large effects on an animal's temperature sensitivity, because the blocking of firing can override the activity of temperature sensitive receptor channels. For widely expressed channels that participate in the firing of many different cell types, it is important to maintain functionality at temperatures appropriate to the species' habitat.

Resting potential

Another determinant of neuronal excitability is the resting membrane potential. The resting potential is the set-point from which the neuron has to reach the voltage threshold for action potential firing (Fig. 5). A depolarized potential sets the cell closer to the firing threshold; however, more depolarized potentials also inactivate more voltage-gated channels, which decrease the cell's ability to fire action potentials. The excitability of a neuron depends on a combination of the expression and availability of different types of channels, the resting membrane potential, the action potential threshold, and other electrogenic properties, such as the input resistance, which represents how easily the membrane potential can be changed. It is also crucial to be able to return the cell to the correct membrane potential from the hyperpolarization after an action potential to ensure the continuation of robust firing. Observations in mouse and rat somatosensory neurons showed that the resting potential becomes more depolarized at colder temperatures and that the input resistance increases [62, 128].

The resting potential is determined by the relative concentration of charged particles on each side of the membrane. Several ion channels and pumps that contribute to the distribution of ions across the membrane have been shown to have temperature-dependent activity. These include background sodium channels and potassium channels that allow the passive flow of ions along their concentration gradient, and active sodium-potassium pumps that use ATP or sodium gradients to transport the ions against their concentration gradient [43, 46, 118]. Temperature influences the function of these proteins, which can alter the excitability of sensory neurons by changing the set-point at rest or changing the speed of recovery from the after-hyperpolarization.

Nav1.9

Nav1.9 conducts a persistent inward sodium current at hyperpolarized voltages and is considered to contribute to setting the resting potential of the cell. Nav1.9 is resistant to TTX and is frequently co-expressed with Nav1.8 in small-diameter DRG neurons [7, 38, 40]. Like Nav1.7 and Nav1.8, Nav1.9 is considered to be crucial for pain sensation [54]. There are several single point mutations in human Nav1.9 that are linked to pain disorders, including an interesting gain-of-function mutation that unexpectedly leads to pain insensitivity [39]. The mutant channel is hyperactive at the resting potential, causing sustained depolarization that progressively inactivates other Nav's, thus leading to impaired generation of action potentials and aberrant synaptic transmission in nociceptors [83].

As a modulator of neuronal excitability, Nav1.9 was found to be required for sensing noxious cold [82, 90]. Although Nav1.9 seems not to be a major component in the generation of action potentials, it may act as a subthreshold amplifier of sensory information. Nav1.9 knockout mice have impaired sensation of noxious cold stimuli, without altering temperature responses in the warm range [90]. As a modulator of cold sensation, Nav1.9 is another possible evolutionary target for species with

noxious cold tolerance. Though an ortholog of this channel was not downregulated in the hibernating snail [68], the functional properties of this ortholog remain to be investigated, and a potential role in hibernating mammals remains to be determined.

K2P

Two-pore potassium channels (K2P) provide a voltage-independent potassium leak that is essential for setting the resting membrane potential [42]. A greater potassium efflux through these channels hyperpolarizes the membrane and thus suppresses excitability [2]. Several members of the K2P family have been shown to be gated by temperature [130]. K2P's are also gated by mechanical stimuli and play a role in various sensory processes [11, 12, 14, 55, 84, 88, 89, 92, 94, 114, 126].

The main thermosensitive K2P's that have been studied are TREK-1, TREK-2, and TRAAK. These channels are silent at 14 °C and dramatically increase their activity to a maximum at > 40 °C [6, 64, 93, 109, 116]. TREK-1 and TRAAK are often expressed in TRPV1-positive neurons [156] and act in opposition to the heat-activated TRP channel via elevated potassium leak. In contrast, decreased potassium leak causes neurons to depolarize and is expected to increase excitability. Consistently, TREK-1$^{-/-}$, TRAAK$^{-/-}$, or double knockout mice show increased firing of nociceptive fibers, and hypersensitivity to noxious heat [6, 109].

Interestingly, deletion of TRAAK alone did not change cold sensitivity, but TREK-1$^{-/-}$ or TREK-1/TRAAK double knockout mice were also hypersensitive to cold [109]. This is consistent with the observation that TREK-1, TREK-2, and TRAAK are co-expressed with TRPM8 [156]. However, a different K2P, TASK-3, is especially enriched in a population of TRPM8-positive neurons. The deletion of TASK-3 led to increased thresholds and cold hypersensitivity in mice [104]. Although TASK-3 had been shown to be only weakly thermosensitive [12, 64], it acts as a break on the excitability of cold-sensitive neurons. The ability of channels that regulate the neuronal resting potential to influence the response of temperature sensitive neurons makes them evolutionary targets for thermosensory modifications. Though TREK-1 from 13-lined ground squirrels retains temperature sensitivity similar to the mouse ortholog [79], species-specific temperature-dependence of K2P's has not been systematically explored, but they may play an important role in the diversification of thermosensory function.

Conclusion

The coordinated activity of multiple channel types is required for the transduction and transmission of thermal information. The high number of molecular participants provides a toolkit of adaptable channels for species with different thermosensory needs. The diversity of functions illustrates how each channel can contribute to the tuning of temperature sensitivity relative to optimal temperatures, as seen for TRPM8 and TRPV1 orthologs from mammals, birds, amphibians, and fish. In addition to sensing internal and environmental conditions, TRPs can be adapted for very specialized behavioral functions, such as acute heat sensitivity for hunting in snakes and bats. Sensory modalities can also be tuned independently, as seen in the differences in temperature and chemical sensitivity of TRPA1 between different species, and between splice isoforms of TRPA1 in fruit flies and mosquitos. Aside from the primary temperature sensors, the channels that participate in firing action potentials and setting the neuronal excitability play crucial roles in determining temperature sensitivity. Temperature-dependent changes in the function of voltage-gated sodium, voltage-gated potassium, and potassium leak channels can determine whether or not temperature information is relayed to the central nervous system. Evolutionary examples of Nav adaptations that block pain sensation, as in grasshopper mice and naked-mole rats, may also apply to tolerance of noxious temperatures in certain species. Furthermore, temperature-dependent adaptations may be needed in animals that live in extreme temperature habitats not only for the sensation of temperature, but also for the maintenance of neuronal function, as was illustrated by potassium channels in the polar octopi. A restricted study of only a small number of model species would miss many of the nuanced aspects of channel function and adaptability that is revealed by investigating multiple evolutionarily distant species. We expect that future studies will bring to light many more players in the complex molecular machinery of temperature sensation.

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