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Authors
Arrigoni, Cristina
Minor, Daniel L

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INVITED REVIEW

Global versus local mechanisms of temperature sensing in ion channels

Cristina Arrigoni[1] · Daniel L. Minor Jr.[1,2,3,4,5]

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Abstract

Ion channels turn diverse types of inputs, ranging from neurotransmitters to physical forces, into electrical signals. Channel responses to ligands generally rely on binding to discrete sensor domains that are coupled to the portion of the channel responsible for ion permeation. By contrast, sensing physical cues such as voltage, pressure, and temperature arises from more varied mechanisms. Voltage is commonly sensed by a local, domain-based strategy, whereas the predominant paradigm for pressure sensing employs a global response in channel structure to membrane tension changes. Temperature sensing has been the most challenging response to understand and whether discrete sensor domains exist for pressure and temperature has been the subject of much investigation and debate. Recent exciting advances have uncovered discrete sensor modules for pressure and temperature in force-sensitive and thermal-sensitive ion channels, respectively. In particular, characterization of bacterial voltage-gated sodium channel ($BacNa_V$) thermal responses has identified a coiled-coil thermosensor that controls channel function through a temperature-dependent unfolding event. This coiled-coil thermosensor blueprint recurs in other temperature sensitive ion channels and thermosensitive proteins. Together with the identification of ion channel pressure sensing domains, these examples demonstrate that "local" domain-based solutions for sensing force and temperature exist and highlight the diversity of both global and local strategies that channels use to sense physical inputs. The modular nature of these newly discovered physical signal sensors provides opportunities to engineer novel pressure-sensitive and thermosensitive proteins and raises new questions about how such modular sensors may have evolved and empowered ion channel pores with new sensibilities.

Keywords Ion channel · Temperature sensing · Heat capacity · ΔCp · $BacNa_v$ · Bacterial voltage gated sodium channel · Coiled-coil · TRP channels

Most ion channels act as sensors that convert various classes of input signals from the environment into electrical activity. One of the remarkable features of this signaling protein class is the variety of signals that can affect function. These inputs range from chemicals, such as neurotransmitters, to proteins, such as G-proteins, to physical forces, including voltage, mechanical force, and temperature. For each type of signal, understanding the architecture that serves as the receiver is intimately tied to understanding how these electrical switches work and how natural inputs, chemical probes, and drugs impact channel activity.

One class of sensor is built from domains that serve as ligand binding sites. Interactions with small molecules and protein ligands drive channel function via binding events that shift channel conformation between the non-conductive, closed and the conductive, open states [44]. As the fundamental event initiating this type of signal response is a physical interaction, channels that respond to such signals have defined structural elements that provide a landing point for the ligand, whether it is a neurotransmitter or a protein (Fig. 1a). Hence, this type of signal input detection can be thought of as a "local" event that is directly tied to the function of a defined and often reconfigurable domain.

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✉ Daniel L. Minor, Jr.
daniel.minor@ucsf.edu

[1] Cardiovascular Research Institute, University of California, San Francisco, CA 94158, USA

[2] Departments of Biochemistry and Biophysics, and Cellular and Molecular Pharmacology, University of California, San Francisco, CA 94158, USA

[3] California Institute for Quantitative Biomedical Research, University of California, San Francisco, CA 94158, USA

[4] Kavli Institute for Fundamental Neuroscience, University of California, San Francisco, CA 94158, USA

[5] Molecular Biophysics and Integrated Bio-imaging Division, Lawrence Berkeley National Laboratory, Berkeley, CA 94720, USA

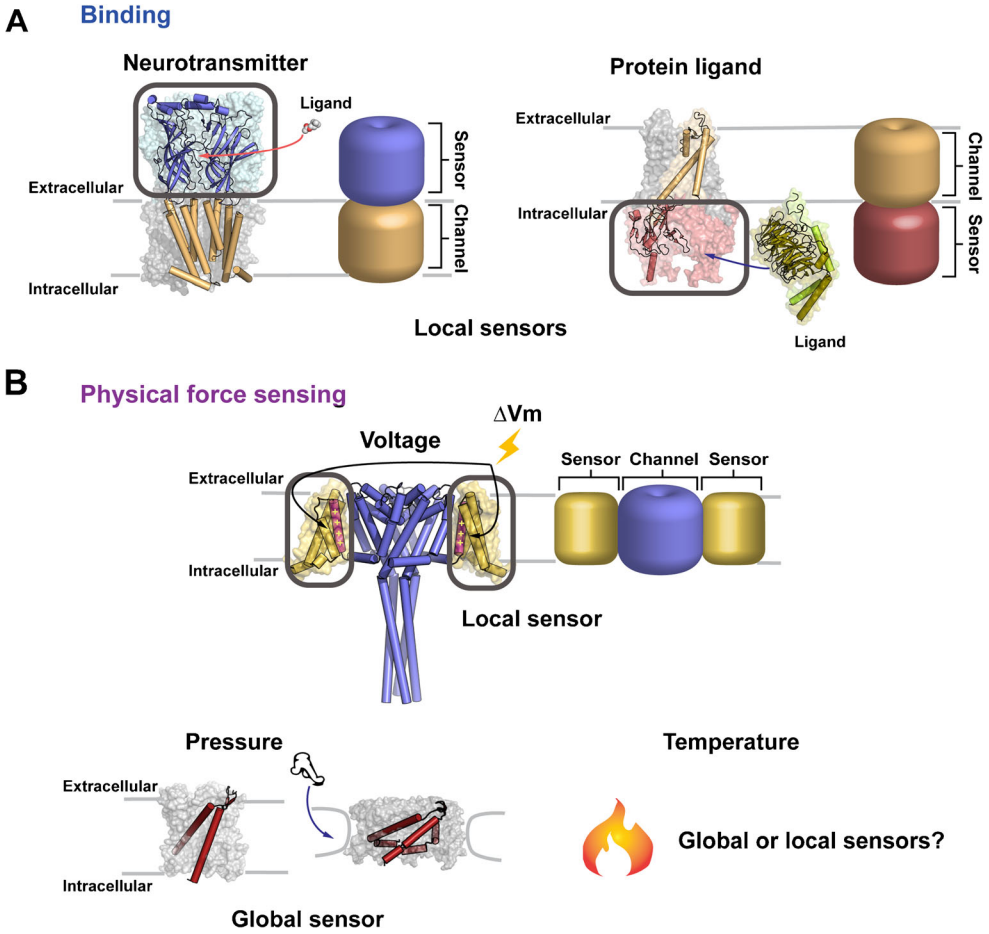

Fig. 1 Ion channel sensor design for ligands and physical forces. **a** Examples of ligand sensors. Left, structural organization of a neurotransmitter ion channel (5KXI) [70]. Ligand sensor domain is blue. Channel domain is orange. The ligand, acetylcholine, and binding site are indicated. Right, structural organization of a protein-gated ion channel (4KFM) [105]. Sensor domain is red. Channel domain is orange. The ligand, the G protein Gβγ subunits, is shown (sand and lime green). Schematics show the general arrangement between the sensor and channel domains. **b** Examples of force sensing ion channels. Top, composite model of a $BacNa_V$ voltage gated ion channel (4LTO [93], 3RVY [78]) [77]. Two of four voltage-sensor domains (yellow) are shown. S4 voltage sensor is purple. Lower left, structure of the closed (2OAR) [96] and model of the open state [97] of the mechanosensitive channel MscL. In **a** and **b**, modular sensor domains are indicated by the gray ovals. Lower right, the issue of how thermosensitive ion channels work is highlighted

Well-characterized examples in which the division of labor is split between a ligand sensor domain and channel pore are found in both neurotransmitter-gated [72, 102] and protein-gated [105] classes of ion channels. This domain-based principle is widely used in biology, particularly in signaling proteins, as it constitutes a powerful way to evolve proteins having novel functions. For example, combining a sensor domain, such as a ligand binding domain, with a domain that carries out a particular function, such as a channel or enzyme, can create a new protein that is regulated by the signal input from the sensor domain [17, 24, 52]. The ability to transplant a sensor domain and its associated function from one channel to another is the ultimate test of sensor domain modularity. Indeed, many protein engineering studies have demonstrated the modular nature of channel sensor domains by swapping in a ligand binding domain and thereby changing the signal response properties of the channel [39, 50, 73]. These sorts of local domain-based ligand sensors are squarely within the larger framework of how many types of signaling proteins are designed [17, 24, 52].

Sensing physical inputs: voltage sensing as a "local" domain-based solution

Understanding how channels respond to physical cues presents a different type of problem from the ligand binding paradigm. In the case of voltage, which is the best understood type of physical signal input for channels, changes in the transmembrane electric field reshape the conformation of a dedicated domain that responds to the "ligand," which is voltage [22, 103]. From the protein architecture point of view, this type of sensor, appropriately called a "voltage sensor domain" (VSD), acts very much like channel domains for sensing chemical and protein signals. There is a defined domain

element, the VSD, that is part of the channel architecture and that serves as the receptor site for the gating ligand (Fig. 1b). Fitting the criterion of an independent module, this domain can be swapped among channels [5, 18], and even between voltage-gated enzymes and channels [10] to transplant function. Hence, this type of voltage sensing is also a very local event, largely confined to driving a response in a defined sensor domain whose conformational changes are then coupled to the pore. It is worth noting that there are other ways to solve the voltage sensing problem, and a number of examples in which the voltage sensing properties of a channel come from the interactions of the permeant ions with the channel [1, 38, 64, 85, 90] or through stabilization of the conformation of the pore region [15, 28, 61]. These latter cases are intimately dependent on changes in the core structure of the channel, most notably, the selectivity filter.

Sensing physical inputs: global and local strategies for force sensing

The way channels sense and respond to the other two types of forces, temperature and pressure, remains much less well understood than the mechanisms for ligands and voltage sensing and is the focus of many current research efforts. The dominant model for pressure sensing involves responses that are a global property of the channel driven by the framework of the "force from lipid" paradigm [8, 43, 56] and the notion that transmembrane parts of the channel are sensitive to forces that stretch, deform, and change the lateral tension in the bilayer. The best understood cases come from the bacterial mechanosensitive ion channels MscS and MscL [43, 79]. For these force-sensitive channels, changes in the tilt of the transmembrane helices in each of the channel subunits serves as the means to respond to changes in membrane tension as the bilayer thins due to pressure-induced deformations (Fig. 1b). This property is not limited to bacterial channels but seems to be shared by some eukaryotic force sensing channels from the K_{2P} [11, 16, 20, 27, 80] and Piezo [80, 98] families. This force sensing response can be characterized as "global" as it arises from an intrinsic property of the complete channel architecture and not from the action of a discrete channel domain.

Interestingly, recent studies of two different types of eukaryotic force sensitive ion channels, NOMPC [53, 111] and Piezo [107, 113], point to the existence of a domain-based solution for pressure sensing that differs from the global mechanisms used by MscS and MscL [4, 111]. In both cases, fusion of the identified force sensor domain to a naïve channel conferred pressure responses to a non-pressure sensitive host channel. The demonstration that two different types of force sensors that have very different protein architectures, one in the membrane [113] and one external to the membrane [111], can transfer this force sensing property to another channel indicates that there is a "local" domain-based solution for building a pressure sensor. Even though the properties of the Piezo force-sensing module clearly require further study [36, 37, 112], the existence of discrete, transferrable, force-sensing domains, indicates that both global and local solutions are viable strategies for pressure sensing by ion channels. These discoveries also highlight that, similar to voltage sensing, there is more than one way for nature to solve this type of physical input detection problem.

Thermal stability and temperature sensing

Temperature sensing mechanisms have been the most vexing of all of the channel signal inputs to unravel. The identification of temperature gated channels from the TRP and K_{2P} channel classes [91, 104] has driven a search for a temperature sensor domain that would be analogous to something like the voltage sensor domain [12, 19, 42]. Much of the difficulty in sorting out the issue of temperature responses is that temperature is an intrinsic thermodynamic property of every molecule. Hence, although only channels with good acetylcholine binding sites can be sensors for acetylcholine signals, every channel will have some sort temperature response. The question is: What sort of temperature-dependent conformational changes constitute a thermal-sensing response, and which elements of the protein in question drive the temperature-dependent transition?

The essence of how to make a thermal sensitive ion channel is intimately tied to the question of protein thermal stability, a subject having many decades of investigation [30, 31]. The heart of the matter is understanding the interactions that contribute to the relative stability of one state over another at a given temperature. The hallmark of every protein conformational change is that some amino acids change their environment as the protein, or protein complex, moves from one state to another. The key factor controlling temperature-dependent changes in stability, enthalpy, and entropy is the thermodynamic parameter describing the change in heat capacity (ΔCp) [14, 82, 83]. Differences in the solvation of hydrophobic and hydrophilic residues between the states in question are a major contributor to ΔCp and are most dramatic in protein unfolding events. The heat capacity difference, which is positive for an unfolding event, comes largely from how water is organized around the protein, particularly the sidechains, and the large entropy gains or penalties that are realized when certain sidechains become buried and liberate the locally organized solvent, or are exposed and induce some local structure in the solvent [82, 83]. Although much of the focus on ΔCp has centered on changes in hydrophobic groups, buried polar residues also impact ΔCp, although with the opposite sign as hydrophobic ones [59, 60]. Moreover, even though changes in hydration are a key factor contributing to ΔCp, protein-protein interactions are also important, and figuring

out which contribution dominates is not straightforward [82]. Because contributions to ΔCp can come from any parts of a protein, it has been pointed out that the thermal response of an ion channel, which is a large protein complex having many moving parts, could arise from elements distributed throughout the channel, and thereby constitute "global" solution that does not depend on the properties of a particular domain [25, 26]. Hence, in principle, a thermosensor domain could be hiding in plain sight by being distributed across a number of parts of an ion channel complex, and driven by changes in solvation of either hydrophobic residues, hydrophilic residues, or both provided that all of the changes sum up to a substantial ΔCp between two states. This situation would be a "global" solution to the temperature sensing problem as it is dependent on changes throughout the channel structure and not a discrete thermosensor domain.

In thinking about thermal sensing, it is instructive to consider how temperature induced changes alter the free energy difference between two states, such as two different conformations of a protein. Regardless of the mechanism for thermal sensing, the relationship between the free energy of stability of two states as defined by the Gibbs-Helmholz equation $\Delta G_0 = \Delta H_0 - T\Delta S_0 + \Delta C_p\left[T - T^0 - Tln\left(\frac{T}{T^0}\right)\right]$ and is parabolic having a curvature set by ΔCp (i.e. larger ΔCp values make a steeper curve) [14, 83]. This relationship has two important consequences. First, there are two temperatures (Tm_{High} and Tm_{Low}) where $\Delta G_0 = 0$ (i.e., the midpoint of the transition between the two states). Depending on the details of the thermodynamic parameters, both Tm_{High} and Tm_{Low} may be in a physiologically accessible range. In such cases, both increases and decreases from room temperature can cause a switch between the two conformations. In protein unfolding reactions, this manifests as heat-induced and cold-induced unfolding (Fig. 2).

The other important fact is that if ΔS and ΔCp are small, as in the unfolding of small protein domains having ~60 amino acids, the ΔG vs. temperature curve becomes relatively broad and ΔΔG ~ ΔTm(ΔS). Consequently, small changes in thermodynamic stability caused by mutations or by changes in conditions, such as ionic strength or pH, result in large changes in Tm [7] (Fig. 2). Such behavior is manifest in studies using the small, 56 amino acid protein, GB1 where single amino acid substitutions that cause modest changes in ΔG of folding (spanning ~2 kcal mol^{-1}) result in a broad range of Tm values, ranging over 25 °C [67, 68]. These studies also show that single amino acid changes and modest free energy perturbations can drastically alter the thermal behavior of a protein in question without causing major changes to ΔCp [68]. This example offers important implications for thinking about how thermal sensitive channels may function particularly as limited amino acid changes in the right context can cause in dramatic shifts in thermal responses [49, 57, 58]. Notably, ankyrin repeats, where a number of point mutant changes affecting temperature responses have been

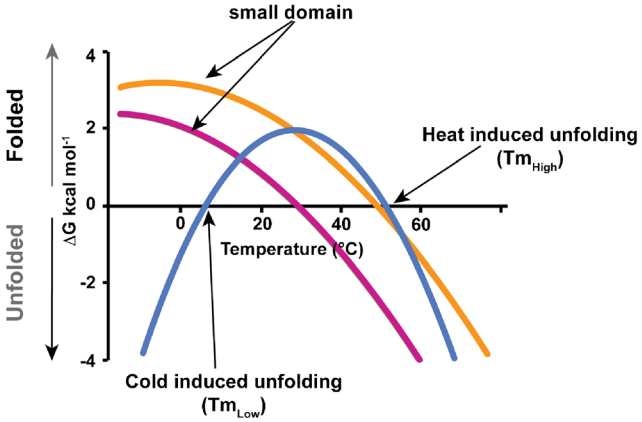

Fig. 2 Exemplar protein stability curves ΔG of unfolding is plotted as a function of temperature using the Gibbs-Helmholtz equation. Orange and magenta curves are for two mutants of the small domain protein GB1 using thermodynamic values from [68], ΔCp = 624 cal mol^{-1} K^{-1}. Blue curve shows a protein having a ΔCp four times larger than GB1, ΔCp = 2400 cal mol^{-1} K^{-1}. Temperatures of cold and heat induced unfolding are indicated. Regions of the plot favoring folded and unfolded forms are indicated

characterized [49, 57, 58], can have ΔCp values similar to GB1 [34]. Thus, in addition to possible changes in coupling [49], single point mutants could be capable of dramatically shifting thermal responses without perturbing ΔCp itself.

Sensing physical inputs: global and local strategies for temperature sensing

How can the thermodynamics of protein stability set the rules for constructing a thermosensitive ion channel? First, since there are temperatures in which one can reach ΔG = 0, whether a channel can sense cold or heat simply depends where Tm_{High} and Tm_{Low} sit relative to a reference temperature. Just as with folding, it is possible to have the same channel act as both a cold and a heat sensor without any need for invoking separate sensors for cold and heat [26]. Second, because the contributions to ΔCp can be driven by changes in the interactions and solvation of sidechains anywhere in the protein, the conformational changes do not have to be restricted to a particular sensor domain and can be driven by changes in residues at multiple sites in the channel [25, 26]. In this case, the thermal sensing is "global." Indeed, such distributed effects have been invoked to explain the difficulty in identifying a "thermal sensor" domain [25, 26] and even used to argue that thermal sensor domains in ion channels may not exist [26]. Although the global thermal sensor strategy can encode temperature dependence [25, 26, 33, 104], the appeal of the possible existence of an authentic temperature-sensing domain that would be analogous to a voltage-sensor domain has persisted [12, 19, 42]. Recently, studies of bacterial voltage-gated sodium channels ($BacNa_Vs$) [77] have provided the first well-defined example of a modular temperature sensing

domain and show that the domain-based strategy is indeed used by nature to build a thermosensitive ion channel [9].

$BacNa_Vs$ are relatives of eukaryotic voltage-gated sodium and voltage-gated calcium channels, assemble into tetramers, and share the six transmembrane architecture found throughout the voltage-gated ion channel (VGIC) superfamily [76, 77, 108]. Besides the common core transmembrane architecture, $BacNa_Vs$ have a long C-terminal tail comprising two domains, a "neck" domain that is proximal to the pore, and a four-stranded coiled-coil [93]. The neck domain is the most diverse element in the family in terms of both amino acid composition and length [77, 81, 93] and contains the domain that functions as a thermal sensor [9]. Studies of the $BacNa_V$ Na_VSp1 revealed strong temperature dependent effects on channel gating that changed the $V_{1/2}$ by ~ 35 mV over the range of 18–35 °C (Fig. 3a). This temperature response is entirely dependent on the structural integrity of the neck domain as either removing the entire C-terminal domain (CTD) or disrupting the neck structure eliminated temperature-dependent gating (Fig. 3b). The strong control of the CTD on $BacNa_V$ gating is further revealed by studies of chimeras in which the CTDs from different $BacNa_Vs$ are grafted onto Na_VSp1 transmembrane core. These chimeras, not only tuned voltage-dependent gating over a range of ~ 65 mV (Fig. 3c), but also had parallel effects on the temperature dependent gating that were either eliminated by disrupting the neck, or absent from a chimera in which the neck domain is disordered (Na_VMs) (Fig. 3c) [9].

The $BacNa_V$ CTD bipartite structure is key to its ability to act as a thermal sensing domain. The C-terminal coiled-coil portion has a hydrophobic core that follows the classic heptad repeat "a–d" packing [63] (Fig. 4a). The core of the neck splays apart slightly relative to the coiled-coil and mostly follows this "a–d" pattern, but is made almost exclusively from hydrophilic, not hydrophobic, residues (Fig. 4a). Buried hydrophilic residues in coiled-coil cores carry an energetic penalty with respect to quaternary architecture stability [63] and such buried polar residues contribute to ΔCp [59, 60]. The neck hydrophilic core along with the constraints provided on each end of the neck by the channel pore and coiled-coil domain, allow the neck to assume a metastable structure that responds to temperature changes by unfolding. The question how sensor domains couple their actions to channel pores is universal has been raised as a particular concern with respect to dissecting thermosensing [35, 49]. Consistent with its location in the channel architecture (Fig. 4b), mutant cycle analysis demonstrates the neck is directly coupled to the channel gate, providing a clear mechanism by which temperature dependent changes in its structure can affect channel opening [9]. These results combined with structural and protein unfolding studies [9] demonstrate that a single domain, the $BacNa_V$ CTD neck (Figs. 4a, b), is sufficient for controlling the temperature-dependent response of an ion channel and describe the first clear example of a defined temperature-sensing ion channel domain that acts by the "local" rather than "global" temperature sensing mechanism.

Besides being found in $BacNa_Vs$ [9, 77, 93], the general channel architecture of pore domain to membrane proximal regulatory domain to coiled-coiled assembly domain is present in many VGICs, occurring in Kv7 [45, 51, 106], TRPM [40, 66, 101], TRPA1 [75], and TRPP [23, 86, 100, 109, 110]. Interestingly, features similar to those in $BacNa_V$ CTDs are found in two other thermoresponsive ion channels TRPA1 [75] and the proton channel Hv1 [99], raising the possibility that the use of coiled-coil domains as thermosensor elements of ion channels may be a general domain-based 'local' strategy in the VGIC superfamily.

Structural comparison shows a remarkable architectural similarity between the tetrameric C-terminal coiled-coil in the thermosensitive channel TRPA1 and the $BacNa_V$ CTD [9] that includes the presence of two layers of buried hydrophilic residues that should be unfavorable for its stability [75] (Fig. 4c). The environment of the TRPA1 CTD is complex, as the large ankryin repeat domains (ARDs) from the N-terminal cytoplasmic domain that are implicated in thermal responses [29, 49] surround it like a cage (Fig. 4c) [75]. Interestingly, exchange of ARD repeats 10–15 from the rattlesnake TRPA1 to the human homolog showed that it was possible to transfer temperature response from one channel to another, demonstrating a role for this module in thermal sensing [29]. Notably, elements from these repeats interact with the coiled-coil at the levels that include the two buried polar residues [75]. Hence, this structural convergence raises the possibility that the reported ARD effects on temperature sensing may be mediated by modulation of structural changes in the CTD and suggests that there is potential for a "local" solution to the thermal sensing problem that has a metastable coiled-coil domain at its center.

The proton channel Hv1 is a relative of VGICs and is a dimer in which each subunit is made from a transmembrane VSD and a cytoplasmic coiled-coil [74] that carries a buried polar interaction made by an asparagine near the VSD/coiled-coil junction [41] (Fig. 4d). Deletion or disruption of the Hv1 coiled-coil at this asparagine decreases the energetic barrier for channel activation and results in faster activation kinetics and a thermoresponse that is shifted to a lower temperature range [41]. Hence, the Hv1 coiled-coil opposes channel activation in a temperature dependent fashion reminiscent of the stabilizing effects that the $BacNa_Vs$ neck has on the channel closed state. The presence of membrane proximal coiled-coil domains bearing buried hydrophilic residues in distantly related thermosensitive VGIC superfamily members ($BacNa_Vs$, TRPA1, and Hv1) suggests that there is a common strategy for building modular channel thermosensor domains based on the coiled-coiled architecture and that a key design strategy is the exploitation of the decrease in stability that buried polar residues bring to coiled-coil assemblies [63]. This tradeoff

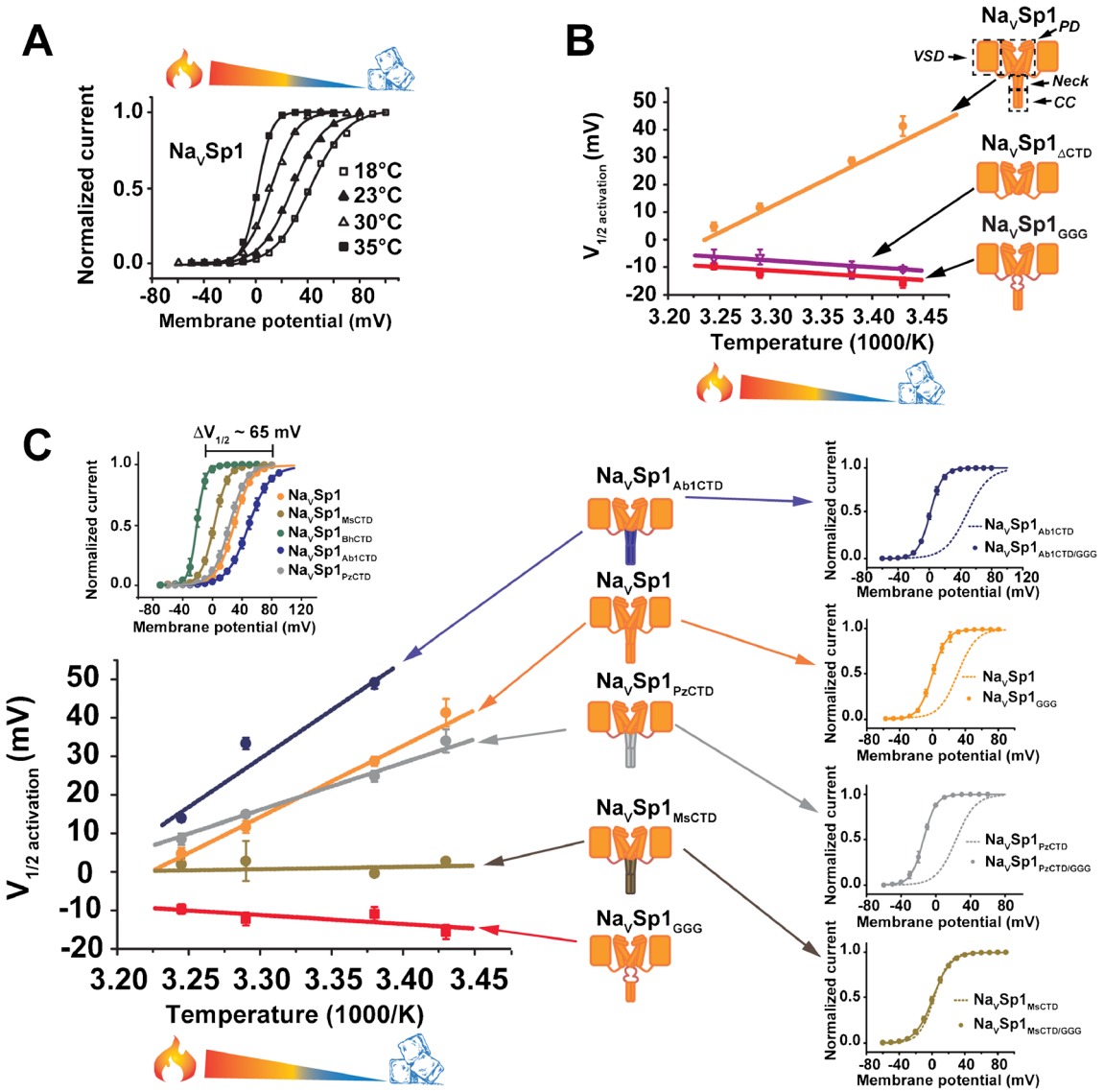

Fig. 3 The BacNa$_V$ modular temperature sensor domain. **a** Temperature-dependence of the activation of the BacNa$_V$ Na$_V$Sp1. **b** $V_{1/2}$ temperature dependence of Na$_V$Sp1, neck mutant Na$_V$Sp1$_{GGG}$, and Na$_V$Sp1$_{\Delta CTD}$. Dashed boxes show the VSD, pore domain (PD), neck, and coiled-coil domain. **c** BacNa$_V$ CTD chimeras tune voltage-dependent gating of the Na$_V$Sp1 transmembrane core. Inset shows the effects on Na$_V$Sp1 and chimeras bearing CTDs from Na$_V$Bh1 (NaChBac), *Bacillus halodurans* [88], Na$_V$Sp1$_{BhCTD}$; Na$_V$Ms, *Magnetococcus sp.* [65], Na$_V$Sp1$_{MsCTD}$; Na$_V$Ab1, *Alcanivorax borkumensis* [94], Na$_V$Sp1$_{Ab1CTD}$; and Na$_V$Pz, *Paracoccus zeaxanthinifaciens* [55], Na$_V$Sp1$_{PzCTD}$. Temperature dependence of $V_{1/2}$ and effects on neck disruption using a triple glycine mutant (GGG) for each channel are shown. All data are from [9]. Temperature dependence in **b** and **c** are shown as van't Hoff style plots

between function and stability has been demonstrated in a number of diverse protein systems [13, 60, 62, 69, 95]. Such metastable domains whose conformational properties can be coupled to the activation of an ion channel pore domain provide an attractive "local" solution for building a thermosensor as well as a means to tune channel thermal responses.

Coiled-coil thermosensors in soluble proteins

Thermal sensing is not only important for ion channels, and has been characterized in a number of other signaling pathways [92]. Interestingly, two such systems, the gene repressor TlpA and the DesK/DesR histidine kinase use coiled-coil domains as thermo-sensitive modules and point to a generalized role for this architectural motif in building modular thermosensors.

TlpA is a *Salmonella typhimuruium* autoregulatory repressor protein involved in intracellular proliferation that is able to perceive temperature changes and modulate the extent of transcription repression [46, 47]. TlpA is composed of a N-terminal DNA binding region and a long homodimeric coiled-coil. TlpA senses temperature through a reversible and rapid thermal induced unfolding transition in the coiled-

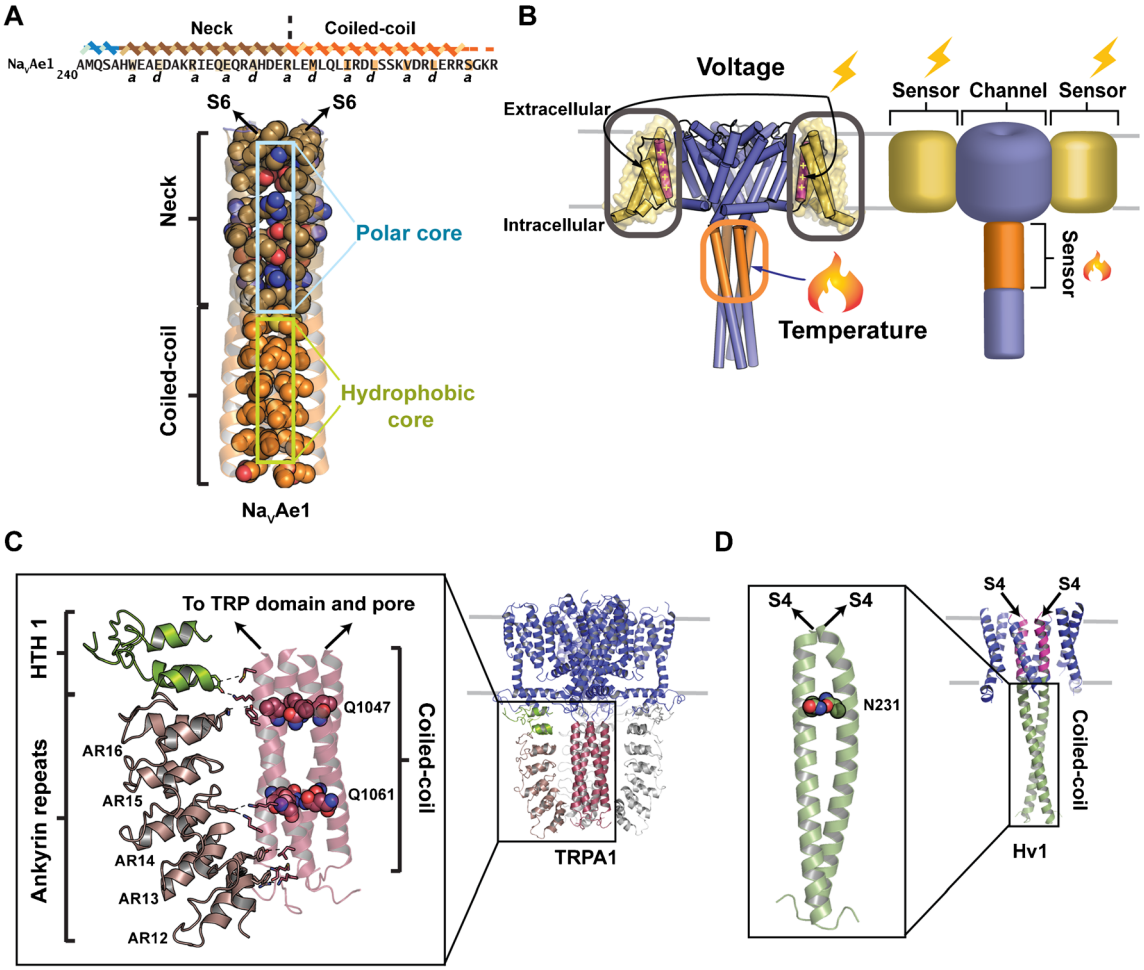

Fig. 4 Coiled-coils in thermal sensitive ion channels. **a** Structure of the *Alkalilimnicola ehrlichii* BacNa$_V$, Na$_V$Ae1 CTD (5HK7) [9]. Sequence of the neck and coiled-coil domain is shown highlighting the "a"- "d" core residues. Cartoon shows the structure of the Na$_V$Ae1 CTD highlighting the polar and hydrophobic cores of the neck (sand) and coiled-coil (orange) domains, respectively. Arrows indicate connection to the pore domain S6 helix. **b** BacNa$_V$ composite model (4LTO [93], 3RVY [78]) [77] highlighting two of four voltage-sensor domains (yellow) and the neck thermal sensing domain (orange) along with a channel schematic indicating the placement of the modular sensor domains. **c** Left, interactions of the TRPA1 Helix-turn-helix (HTH1) (green) and Ankyrin repeats (AR)(brown) with the C-terminal coiled-coil domain (red)(3J9P) [75]. Positions of the buried hydrophilic residues in the coiled-coil are shown in space filling. Dashed lines indicate HTH1 and ANK repeat sites of contact with the coiled-coil. Connection to TRP domain and pore is indicated. Right, TRPA1 structure (3J9P) [75]. Transmembrane domains are blue. Front Ankryin repeat domain is not shown. Non-highlighted Ankryin repeat domains are gray. Coiled-coil is red. **d** Left, structure of the Hv1 coiled-coil (green) (3VMX) [41]. Buried asparagines are shown in space filling. Connection to VSD is indicated. Right, Hv1 structure based on a composite model from 3VMX and 3WKV [99]. Coiled-coil domain is boxed. VSD and S4 segment of the VSD are colored blue and magenta, respectively. Parallel gray lines in **b**–**d** indicate the membrane

coil that results in a non-functional repressor that cannot bind DNA [47, 71]. The folding reversibility and the fast kinetics of assembly of TlpA have recently been exploited to build green fluorescence protein (GFP) based genetically encoded fluorescent thermosensors to visualize thermogenesis in cells [54], demonstrating the potential for modular thermosensitive domains to confer thermal responses to various target proteins.

The *Bacillus subtilis* thermosensor histidine kinase DesK is a cold-activated sensor involved in maintaining membrane fluidity in response to temperature changes. Upon cold activation, DesK switches between a phosphatase-competent state and a kinase-competent state that controls the expression of a lipid desaturase [2, 3]. The nature of the DesK thermosensor has been the subject of a number of investigations that have implicated both the transmembrane and cytoplasmic domains as key players [2, 6, 32, 48, 89]. Although a full-length structure of DesK is lacking, crystal structures of the dimeric cytoplasmic domain in both the phosphatase-competent and kinase-competent states have provided key insights into the thermosensing mechanisms [6]. These studies show that the two helices that connect to the cytoplasmic signaling domain to the transmembrane domain form a coiled-coil in the phosphatase state whose interface is disrupted in the kinase form [6]. Mutational studies support the functional importance of these rearrangements as mutants stabilizing the coiled-coil favored a constitutive phosphatase-competent state, whereas

those that weakened coiled-coil formation caused constitutive kinase activity [89]. Hence, changes in the structural integrity of the DesK coiled-coil appear central to the thermal responses [2]. Together with the TlpA example, these studies underscore the ability of conformational switches in coiled-coil domains to serve as thermosensitive modules in diverse classes of proteins.

Perspectives

There is a rich variety in the types of signals that trigger ion channel activity ranging from chemical neurotransmitters to physical forces. Because sensing physical forces is a fundamentally different problem than responding to signals that are initiated by a binding event to a chemical or protein, channels that respond to voltage, pressure, or temperature have developed a larger repertoire of strategies for making sensors that can respond to these inputs. Although the solution to the ligand sensor problem is often a local modular one involving a specialized domain, two different strategies have been deployed by nature for ion channel physical force sensing. The global mechanism makes use of changes distributed throughout the channel and is used for pressure [11, 16, 20, 27, 43, 79, 80, 98] and temperature [25, 26] sensing. The local domain-based solution for voltage has been long appreciated from a multitude of studies of voltage-sensor domains [22, 103]. Exciting new insights into mechanisms for sensing the two most poorly understood physical inputs now provide examples of local, domain-based sensors for both pressure [53, 107, 111, 113] and temperature [9] controlled ion channels. Identification of local solutions not only sets the physical force sensing question squarely within the general framework regarding the designs of many types of signaling proteins [17, 24, 52] and opens up new questions about how such domains may have evolved, but also offers the electrifying possibility that pressure sensing or a thermosensing modular domains can be co-opted as a tool for channel protein engineering.

The $BacNa_V$ example [9] highlights the role of coiled-coil domains as an adaptable domain-based strategy for controlling channel thermal responses. It is interesting that the $BacNa_V$ unfolding-based thermal sensor neck domain, comprising 60–80 residues depending on the channel subtype, is a size that should a have small ΔCp that would enable small changes in stability by mutation, pH, or ionic conditions to cause large shifts in the Tm [7] and channel response. In the 'design strategy' category, using a small thermal-sensitive domain seems to offer a facile means for endowing an ion channel with varied thermal response setpoints, provided that the unfolding of the domain is coupled to pore opening. In thinking about possible strategies for altering thermal sensing mechanisms, it seems likely that the answers will be similar to how nature makes proteins thermostable. There is no single strategy, as there a many ways to contribute to the thermal stability of the folded state by affecting any of the catalog of interactions available within a protein (i.e., hydrophobic interactions, hydrogen bonds, salt bridges, etc.) [84, 87]. Thus, understanding the details in each specific case in the context of the responsible structures and conformational changes will be important. Notably, making changes to the ΔG of folding by raising or lowering the stability curve and altering ΔCp to flatten the curve are the two most common strategies for shifting the Tm [87] (Fig. 2) and seem to be likely mechanisms by which nature could tune thermal responses within a given thermosensitive channel family.

As other thermosensitive ion channels become structurally characterized, variations on the both global and local strategies are likely to be uncovered. In this regard it is interesting to consider the potential for temperature dependent changes in ligand binding, particularly with respect to the modulation by specific lipids. Such mechanisms may be at play in both thermosensitive K_{2P} channels, where there is evidence for a modular sensor in the channel tail [12], and TRP channels where lipid modulation is important for thermal responses [21]. In the context of exploiting local, domain-based mechanisms to develop channels having new pressure- or thermo-responsive properties, understanding the general question of allosteric coupling and how changes are transmitted through the channel structure remains an important point of investigation [35]. Further, the existence of pressure and thermosensor domains that have been appended to ion channel pores raises the interesting question about the origins of such hybrid proteins and how nature may have used the domain reshuffling approach [17, 24, 52] to construct these fascinating devices that can transform physical inputs into the electrical signals that run the nervous system.

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