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The extraordinary AFD thermosensor of *C. elegans*

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Abstract

The nematode *C. elegans* exhibits complex thermal experience-dependent navigation behaviors in response to environmental temperature changes of as little as 0.01°C over a >10°C temperature range. The remarkable thermosensory abilities of this animal are mediated primarily via the single pair of AFD sensory neurons in its head. In this review, we describe the contributions of AFD to thermosensory behaviors and temperature-dependent regulation of organismal physiology. We also discuss the mechanisms that enable this neuron type to adapt to recent temperature experience and to exhibit extraordinary thermosensitivity over a wide dynamic range.

Keywords

Thermosensation; *C. elegans*; AFD; receptor guanylyl cyclases; phosphodiesterases; adaptation

The terrestrial nematode *C. elegans* is commonly found associated with decaying plant material and in compost heaps [30,24,22], environments with large localized temperature gradients. Although the laboratory reference strain is derived from animals first isolated in Bristol, England [30], this nematode species is a global citizen; *C. elegans* has been found in diverse locales although largely concentrated within temperate zones [36,1]. Thus, the habitat of *C. elegans* is not only subject to temperatures that fluctuate locally, but that also change daily and seasonally. *C. elegans* is, therefore, a temperature 'generalist', and is able to survive and reproduce in a relatively wide temperature range of about 12°C –26°C [2,73,3,80]. Moreover, these tiny 1 mm long worms are exquisitely thermosensitive, and detect temperature changes of 0.01°C or less across this thermal range [51,67]. Here we review the current knowledge of the molecular and neuronal mechanisms by which a single thermosensory neuron pair, the AFD neurons, regulates this organism's extraordinary thermosensory abilities. The AFD neurons detect additional and ubiquitous physical stimuli including CO_2 gas [10], and possibly magnetic fields [86]. Since little is known about whether or how these functions influence temperature-sensing, these functions will not be discussed here. In addition, while sensory neurons other than AFD have also been shown to respond to temperature, these neurons play more minor roles in temperature-regulated behavioral and physiological responses [42,8,6,60], and are also not further considered here.

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Thermosensory navigation behaviors

When placed on a spatial thermal gradient within the animals' physiological temperature range, worms exhibit one of four distinct behaviors. They move up the gradient towards warmer temperatures (PT; positive thermotaxis), down the gradient towards cooler temperatures (NT; negative thermotaxis), track isotherms perpendicular to the gradient (IT: isothermal tracking), or are insensitive to thermal gradients (atactic) [29]. The specific behavior that will be exhibited is dictated by: a) the worms' temperature experience (T_c), i.e. the temperature to which they were exposed for 3–5h prior to the assay, b) the temperature they experience on the gradient (T), and c) their satiety state [29]. At $T > T_c$, worms exhibit NT; at $T < T_c$, they exhibit PT under a circumscribed set of conditions close to T_c [68,34] or are atactic; and at $T = T_c \pm \sim 2°C$, they perform IT (Figure 1). If T_c is altered, the temperature ranges at which these behaviors are exhibited also shift correspondingly. If animals are starved for 3–5h at a constant temperature, animals are largely atactic [29,68,15]. Thus, in these behavioral assays, *C. elegans* does not exhibit a rigid preferred temperature. Instead, the temperature to which these animals navigate is flexible, and is determined primarily via comparison of their temperature experience with the ambient temperature under well-fed conditions. Simulation of thermoregulatory behaviors in soil-like environments suggests that this T_c-dependent behavioral plasticity may permit *C. elegans* to be robust to temperature changes these animals are likely to experience in their natural environments [68].

Detailed tracking of worm locomotion has described the behavioral strategies that worms employ to navigate spatial thermal gradients. NT behavior is primarily achieved by klinokinesis. In this strategy, the duration of forward movement (or runs) is extended as temperatures fall, and conversely, the frequency of reorientation movements is increased as temperatures rise [70,19,52], resulting in net displacement towards cooler temperatures. In addition, following reorientation maneuvers, animals preferentially bias their runs towards cooler temperatures [52]. In contrast, PT behavior does not employ klinokinesis, but is driven by biasing runs towards warmer temperatures following a reorientation [52].

IT behavior is particularly intriguing. Worms do not actively seek isotherms on a spatial thermal gradient [51,29,70]. However, if they are oriented on an isotherm within the permissive range of $T = T_c \pm \sim 2°C$, the temperature variations detected by the side-to-side movement of their heads is harnessed via unknown mechanisms to maintain forward movement on the isotherm and suppress reorientations [51]. Characterization of the shallowest gradient steepness that permits IT behavior suggests that worms may be able to detect temperature differences of as little as 0.005°C behaviorally in order to track isotherms [70,51].

These behaviors raise several interesting questions. How and where is T_c experience encoded? How do worms sense and compare T with their T_c 'memory' to drive specific behaviors? How do worms detect tiny temperature changes over a broad temperature range to modulate their navigation behaviors?

Temperature responses in the AFD thermosensory neurons

The bilateral pair of bipolar AFD sensory neurons resides in the head of *C. elegans*, with dendrites extending to the tip of the nose, and axons entering into the nerve ring, the major neuropil in the head [89,91]. Physical or genetic ablation of these neurons abolishes IT and severely affects NT/PT behaviors [53,51,88], establishing AFD as the dominant regulator of worm thermosensory behaviors. Temperature-sensing by AFD neurons may also enable worms to navigate toward appropriately humid environments [69].

The AFD neurons are unique in their ability to detect and respond to tiny thermal fluctuations. A recent study monitoring calcium dynamics in dozens of neurons simultaneously showed that activity in only the AFD neurons is strongly correlated with thermal fluctuations in freely moving worms [85]. Such responses are evident not only in freely moving animals traversing spatial thermal gradients [18,83], but also in immobilized animals exposed to time-varying thermal stimuli [35,17,90]. Remarkably, these responses are largely preserved in AFD neurons dissociated from embryos and maintained in culture [38], suggesting that these responses are generated cellautonomously.

The AFD neurons are activated by thermal fluctuations and do not appear to signal during prolonged sojourns at a constant temperature [35,17,19,83]. Such response dynamics are evident in the response to cooling and warming steps that elicit transient decreases and increases in intracellular calcium, respectively [35,17,19] (Figure 2A). Similarly, cooling hyperpolarizes and warming depolarizes AFD by inhibiting and activating a non-selective cation current, respectively [67]. Consistent with activation of this current by a soluble second messenger, tiny and rapid temperature shifts modulate the current with a latency of ~100 ms [67]. How sensitive is AFD to temperature changes? Though imperfect [87], Q_{10} is a common metric used to distinguish the ordinary temperature-dependence expected of biochemical reactions from the extraordinary temperature sensitivity underpinning the function of thermoreceptor molecules and cells like the AFD neurons. The temperature dependence of the thermoreceptor current in AFD is extraordinary, having an aggregate Q_{10} of $>10^{20}$ [67]. Such sensitivity is specific to the thermoreceptor currents, since voltage-activated currents in AFD have a Q_{10} of less than 3 [67]. This extraordinary thermosensitivity reflects the action of a nonlinear amplification cascade (see below) akin to the one that mediates phototransduction and enables vertebrates, including humans, to detect single photons of visible light [28,82,31].

Interestingly, activity in response to thermal fluctuations is observed in AFD only at and above a response threshold (T^*_{AFD}) that is closely correlated with T_c, as determined by imaging AFD calcium dynamics *in vivo* [35,17,8] and *in vitro* [38], and by recording thermoreceptor currents in *ex vivo* preparations [67] (Figure 2B). Shifting animals to a new T_c results in a concomitant shift in T^*_{AFD} [35,17,8,67,38] (Figure 2C), suggesting that behavioral acclimation to T_c is reflected in part via adaptation of T^*_{AFD} [95,67,88,8] as well as AFD synaptic output [8]. A recent study has shown that the T^*_{AFD} acclimation process occurs in two phases [95]. Under the specific conditions used, the first phase is brief and has a time constant of minutes and the second is much longer with a time constant of nearly 5 hours that matches the time required for behavioral adjustments to T_c [95]. In these

experiments, acclimation to temperature downshifts was found to be slower than acclimation to temperature upshifts and could be fit by a single exponential [95,8,35,17]. In electrophysiological experiments, the threshold for warming-evoked currents, was shown to adapt to higher and lower holding temperatures with time constants of ~4 minutes and ~8 minutes, respectively [67]. This pattern and timing is similar to short-term adaptation in calcium signaling, suggesting that a common molecular mechanism is responsible for adaptation on this time scale. Regardless of the mechanism, such adaptation ensures that AFD retains its extraordinary sensitivity to small deviations from T^*_{AFD}, across a wide range of temperatures.

Can temperature responses in AFD alone account for the experience-dependent thermosensory behaviors exhibited by *C. elegans*? This is unlikely to be the case. Responses of AFD to thermal fluctuations overlap with the temperature range at which animals exhibit NT or PT behavior [52,67,35,17]. In addition, the ability of AFD to respond to small sinusoidal thermal fluctuations around T^*_{AFD}, but not at warmer temperatures, enables IT behavior [90]. However, although a few studies have addressed this issue [17,7,59,55], how temperature responses in AFD are translated through the circuit into distinct behavioral strategies at temperatures relative to T_c is not yet fully described. Moreover, T^*_{AFD} adaptation and temperature-modulated responses are unaffected in AFD in starved animals [83,67] even though thermosensory behaviors are abolished, suggesting that circuit mechanisms downstream or in in parallel with AFD modulate thermosensory behavioral output in response to internal satiety state. Together, these results indicate that while the extraordinary thermoresponsive properties of AFD are critical for thermosensory behaviors in *C. elegans*, integration of AFD-dependent signals with additional context-and experience-dependent cues in the circuit likely drive specific behaviors in a T_c experience-dependent manner.

Molecular mechanisms of thermotransduction in AFD

Any thermotransduction mechanisms and pathways in AFD must account for the extraordinary thermosensitivity and broad dynamic range of this neuron type. Diverse sensory systems such as those that detect chemicals and light achieve such feats via multiple molecular mechanisms. These include the expression of a receptor(s) with high affinity for the ligand, amplification of the initial signal via soluble second messengers, and rapid adaptation to maintain sensitivity to stimulus changes even at saturating stimulus levels. It has long been hypothesized that cGMP is likely the major transducer of the thermosensory signal in AFD [20,41,29], such that warming increases intracellular cGMP concentrations and activates a cGMP-gated ion channel. But how do temperature changes regulate cGMP flux in AFD?

The *C. elegans* genome encodes 27 receptor-type transmembrane guanylyl cyclases (rGCs) that catalyze cGMP from GTP [94,62]. Of these, the GCY-8, GCY-18, and GCY-23 rGCs cluster together in the genome and in a phylogenetic tree, are expressed exclusively in AFD, and are localized to their sensory endings [94,33]. Animals mutant for one or two of these AFD-specific rGCs (henceforth referred to as AFD-rGCs) exhibit lower T^*_{AFD}, alter the ability of AFD to follow small amplitude temperature oscillations around T^*_{AFD}, and

disrupt IT behavior or the temperature range in which IT behavior is exhibited [90]. However, NT behavior is only partially disrupted in these animals [33,88], and their AFD neurons retain the ability to respond to a rising oscillatory temperature ramp [90,78]. In contrast, animals triply mutant for all three rGCs are atactic [33,90,88], and temperature changes fail to elicit thermoreceptor current or calcium flux in the AFD neurons of these triple mutants [78,67]. Together, these observations suggest that while the functions of all three AFD-rGCs contribute to precisely shaping AFD thermosensory properties, these rGCs act partly redundantly to mediate thermotransduction in AFD.

Besides being necessary for thermotransduction, might these AFD-rGCs be sufficient to confer thermosensory responses with high Q_{10} onto non-thermosensory cells? GCY-18 and GCY-23, although not GCY-8, was found to confer robust temperature responses upon misexpression in chemosensory neurons in *C. elegans* as measured via imaging of intracellular calcium dynamics [78]. GCY-23 was also sufficient to confer temperature responses onto vulval muscles [78]. Moreover, within the limitations of calcium imaging, quantification of the aggregate Q_{10} value of rGC-conferred temperature responses in chemosensory neurons showed that these molecules are sufficient to confer robust and sensitive temperature responses upon misexpression in non-thermosensory cell types [78]. However, these AFD-rGCs do not exhibit a defined temperature response threshold. Instead, the threshold of temperature response is determined by the individual rGC protein and the cellular context, suggesting that the temperatures at which these proteins become activated are flexible [78]. These experiments suggest that temperature modulates cGMP flux in AFD in part via regulation of rGC activity. Interestingly, the GC-G rGC was recently also shown to be both necessary and sufficient for sensing cool temperatures in the rodent Grueneberg ganglion [12], raising the possibility that rGCs may represent a new and conserved family of thermoreceptor molecules.

Temperature-dependent changes in intracellular cGMP levels in AFD are unlikely to be mediated solely via modulation of rGC activity. As in all signaling pathways, mechanisms must be in place that terminate signaling and allow adaptation. Moreover, since the Q_{10} value of the AFD-rGC-conferred temperature responses on chemosensory neurons is lower than that calculated for AFD via similar methods [78], additional mechanisms may also contribute to AFD thermosensitivity. Temperature-dependent regulation of cGMP hydrolysis is one plausible additional way to fine-tune sensitivity to thermal fluctuations and govern T^*_{AFD}. Indeed, the PDE-2 cGMP-selective phosphodiesterase was shown to be expressed in AFD; animals with a deletion in the *pde-2* gene exhibit thermotaxis behavioral defects under specific growth and assay conditions [88]. Importantly, while the Q_{10} of temperature-evoked currents is not altered, T^*_{AFD} is higher, and thermoreceptor currents are prolonged, in the AFD neurons of *pde-2* mutants [88]. The AFD neurons also express additional PDE genes which may also modulate AFD properties [88,76]. These results suggest that together with the rGCs, PDEs play a critical role in regulating temperature-dependent cGMP levels in AFD, and in shaping the threshold and temporal dynamics of the response. Whether one or more PDEs themselves are responsive to temperature changes remains to be determined.

How are cGMP levels translated into neuronal depolarization? The AFD neurons express multiple cyclic nucleotide-gated channel proteins, a subset of which is essential for

thermotransduction [41,20,29]. While the TAX-4 alpha and TAX-2 beta subunits can form heteromeric channels in heterologous cells, TAX-4 also forms homomeric channels with a remarkably high affinity for cGMP ($K_{1/2}$ - 0.4 μM) [40,63,48]. Loss of function of either protein results abolishes temperature responses in AFD as measured by either calcium imaging or electrophysiology [67,35], and both *tax-2* and *tax-4* mutants are atactic [29,53]. The AFD neurons also express the CNG-3 alpha subunit which is implicated in thermotolerance [16], but a role for this subunit in AFD thermotransduction has not been described. Similar to other sensory neurons in *C. elegans*, the primary TAX-2/TAX-4-dependent calcium influx is expected to be amplified by depolarization-activated calcium channels [25,46,96,11,79]. Whether such channels, calcium release from intracellular stores, or both factors play a role in AFD thermotransduction has not yet been established.

Taken together, the current working model for thermotransduction (summarized in Figure 3) in AFD posits that at $T > T^*_{AFD}$, the rGCs are activated to generate cGMP. Rising cGMP concentrations activate TAX-2/TAX-4 channels to permit cation influx and depolarization. Rising temperatures and cGMP and or calcium concentrations may also activate PDEs such as PDE-2 which subsequently hydrolyzes cGMP to terminate the response. Amplification of the T response by a cGMP-dependent signaling pathway together with the high cGMP affinity of the cyclic nucleotide-gated channels underlies in part the extraordinary thermosensitivity of AFD.

Temperature adaptation mechanisms in AFD

As noted above, adaptation of AFD thermosensory response occurs on both a fast (mins) and slow (hrs) timescale [67,95,7,29,88]. The mechanisms underlying fast adaptation of T^*_{AFD} are not yet fully understood. However, given that this adaptation occurs on a timescale of minutes [88,95,67], this mechanism is likely to be transcription-independent. Calcium buffering was shown to slow adaptation [67], suggesting that a calcium-dependent mechanism regulates this short-term neuronal plasticity. In addition, modulation of intracellular cGMP levels affects T^*_{AFD} adaptation; genetic or pharmacological manipulations predicted to lower or raise intracellular cGMP levels decrease or increase T^*_{AFD}[90,88], respectively. However, whether these perturbations specifically alter short-term T^*_{AFD} adaptation or also affect long-term plasticity has not yet been explored. Nevertheless, these observations suggest that intracellular cGMP and/or calcium feedback terminates signaling and enables adaptation.

The cellular targets of this feedback in regulating rapid adaptation are currently unclear. Animals mutant for the calcium-regulated NCS-1 frequenin-like protein exhibit defects in T^*_{AFD} adaptation [88]. Frequenin promotes phosphodiesterase activity [72] suggesting that PDE-2 may be a potential substrate for regulation [88] (Figure 3). In vertebrate phototransduction, neuronal calcium sensor proteins play a critical role in restoring cellular cGMP levels following a light pulse via interaction with the intracellular domains of retinal rGCs [49,75,74,39]. Calcium-dependent inhibition of AFD-rGC activity via calcium sensor proteins could similarly play a role in rapid T^*_{AFD} adaptation (Figure 3). A subset of these adaptation mechanisms is likely to be AFD-specific. Thus, while AFD-rGCs exhibit T_c-correlated adaptation in AFD, their response thresholds are largely T_c-independent in

misexpressing cells [78]. Moreover, analyses of the response thresholds of chimeric AFD-rGC proteins suggest that the response threshold is partly determined by the rGC intracellular domains [78]. A possible unifying explanation for these observations is that cell-specific levels of intracellular cGMP or calcium concentrations set the response threshold to different values via interaction with AFD-rGC intracellular domains, and that in misexpressing cells, the absence of cGMP/calcium-dependent feedback mechanisms such as those present in AFD fail to shift the response threshold in a T_c-dependent manner. Finally, gating of cyclic nucleotide-gated channels via interaction with calcium/calmodulin or cGMP-dependent protein kinases has been implicated in olfactory adaptation in both *C. elegans* and vertebrates [44,54,13,9,58]; these channels may also represent a target of short-term adaptation mechanisms in AFD (Figure 3).

In addition to the rapid feedback mechanisms to terminate signaling, long-term adaptation of T^*_{AFD} to T_c-correlated values also requires temperature-dependent changes in gene expression. Expression of *gcy-8, gcy-18* and *gcy-23* is 3 to 5-fold higher when worms are grown at 25°C as compared to at 15°C [95]. Animals mutant for the *cmk-1* calcium/calmodulin-dependent protein kinase I (CaMKI) gene exhibit decreased expression of all three AFD-rGC genes that is not further altered upon growth at warmer temperatures [95,71], indicating that CMK-1 plays a key role in upregulating AFD-rGC gene expression upon long-term exposure to a warmer temperature (Figure 3). In *cmk-1* mutants, while T^*_{AFD} shifts at the same rate upon temperature upshift, the magnitude of the shift is significantly decreased [95]. Correspondingly, *cmk-1* mutants exhibit lower T^*_{AFD} regardless of T_c, with the defect being significantly stronger upon cultivation at warmer temperatures [95,38]. These results suggest that upon temperature upshift, both CMK-1-independent adaptation processes such as the feedback mechanisms described above, as well as a CMK-1-mediated increase in the number of AFD-rGC molecules are required to reset T^*_{AFD} to the correct T_c-correlated value (Figure 3). It is likely that the expression of additional genes is also affected in a temperature -dependent manner in *cmk-1* mutants, and that this altered expression further contributes to correct long-term adaptation. The molecular mechanisms by which CMK-1 regulates gene expression in AFD is currently unclear but may in part require the Raf kinase pathway [38], and possibly CREB ([57] but also see [95,38]. In addition to the described mechanisms, temperature-regulated systemic signals from tissues such as the intestine may also fine-tune T^*_{AFD}[77].

Although T^*_{AFD} exhibits both fast and slow adaptation upon temperature shift, behavioral adaptation to T_c experience only occurs on the timescale of hours [29,7]. In other words, animals must be exposed to a new temperature for hours in order to shift the temperature range at which NT, PT and IT behaviors will be exhibited. These observations suggest that adaptation of synaptic output threshold in AFD is linked to the long- but not short-term adaptation of T^*_{AFD}. How is AFD sensory activity coupled to adaptation of its presynaptic output? Loss-of-function mutations in the *dgk-3* diacylglycerol kinase gene were found to decrease the rate of behavioral adaptation as well as adaptation of AFD synaptic output threshold (measured as the response threshold in the AIY interneurons, the major postsynaptic partners of AFD) without altering the rate of T^*_{AFD} adaptation [7]. Similarly, mutations in the *pkc-1* (also called *ttx-4*) protein kinase C gene were shown to alter the operating range of thermotaxis behaviors without affecting temperature response dynamics

in AFD [52,61]. In recent studies, PKC-2 has also been implicated in regulating temperature-modulated synaptic output from AFD [45]. These results imply that adaptation of T^*_{AFD} is translated into changes in synaptic diacylglycerol levels and protein kinase C activity to alter the threshold of AFD synaptic output, and that this presynaptic adaptation occurs on a timescale that resembles the long timescale of T^*_{AFD} adaptation. Thus, the single AFD neuron pair exhibits both short-term transcription-independent, and long-term transcription- and experience-dependent, plasticity mechanisms, features that are generally characteristic of circuits comprised of multiple neurons in more complex organisms [27,32,26].

The specialized sensory endings of AFD shape their thermoresponsive properties

While signal amplification and adaptation are major contributors to the experience-dependent and extraordinary thermosensitive properties of AFD, additional mechanisms are also likely to shape the thermoresponsive features of this neuron type. A major factor is the unique architecture of the AFD sensory endings. Similar to other sensory neurons in *C. elegans*, a microtubule-based short rod-like cilium is present at the dendritic ends of AFD at the nose of the animal [64,21] (Figure 4A). However, unique to AFD, these endings also contain numerous actin-based microvilli [64,21,56] (Figure 4A) whose structures rely on the integrity of surrounding amphid sheath glial cells [5]. Subcellular localization studies have indicated that while TAX-4 cGMP-gated channels are localized to proximal region of the cilium, other thermotransduction molecules including the AFD-rGCs are present in these 'finger'-like microvilli [56] (Figure 4B). The dramatically increased membrane surface area to volume ratio potentially allows for the localization of more rGCs and other signaling molecules than would be possible in endings with a relatively simple structure. Analogous to vertebrate photoreceptors, the concentration and organization of thermotransduction molecules in the specialized sensory endings is likely a major contributor to the extraordinary thermosensitivity of AFD.

Interestingly, AFD microvilli architecture appears to be homeostatically regulated by intracellular cGMP levels such that prolonged high levels of cGMP (for 24h or more) result in dramatic shortening of microvilli via modulation of the actin cytoskeleton [76]. Similar to a subset of rGCs in other systems [43], GCY-8 exhibits basal levels of catalytic activity [76] which must be inhibited upon growth at low temperatures to ensure the correct setting of T^*_{AFD} to low values [90,88]. Animals in which GCY-8 is inappropriately activated, or additional manipulations that increase intracellular cGMP levels, lead to shortened AFD microvilli, particularly at low temperatures [76]. How is basal GCY-8 activity regulated at low temperatures to maintain AFD sensory ending integrity? It has now been shown that GCY-8 catalytic activity is inhibited via binding of Cl- ions to its extracellular domain [76]. Neither GCY-23 nor GCY-18 appear to contain a similar Cl^- binding site in their extracellular domains, suggesting that GCY-8 activity alone may be modulated by Cl^- [76]. In turn, extracellular Cl- ion concentrations are regulated via the KCC-3 K^+/Cl^- cotransporter expressed in the ensheathing amphid sheath glial cells [76,93]. Reduced Cl- concentrations as expected in *kcc-3* mutants also shorten microvilli [76], and affect

thermotaxis behaviors and AFD temperature response properties [76,93]. These experiments raise the possibility that temperature-dependent modulation of the ionic environment by glial cells regulates AFD sensory ending architecture, and may thereby also influence AFD thermosensitivity.

Regulation of systemic temperature responses by AFD

In principle, since all physiological and biochemical processes are temperature-sensitive, and the body temperature of a small ectotherm such as *C. elegans* is not different than the ambient temperature, a dedicated thermosensory system may not be essential to regulate whole body thermal homeostasis. However, work from a number of labs has now suggested that AFD not only directs navigation on thermal gradients in response to temperature changes, but is also important for regulating long-term animal physiology.

In one set of studies, AFD has been suggested to play a critical role in coordinating heat shock responses throughout the body via serotonin-mediated signaling [65,81]. Animals mutant for thermotransduction in AFD fail to mount appropriate heat shock responses in multiple somatic tissues, thereby reducing organismal thermotolerance [65]. Conversely, optogenetic activation of AFD is sufficient to induce HSF1 expression in somatic tissues even in the absence of a heat shock [81].

In a second series of experiments, AFD has been implicated in regulating temperature-dependent longevity. Ectotherms are known to exhibit longer lifespan at lower temperatures [50,23]. Consistent with this notion, *C. elegans* lives longer at cooler temperatures than it does at warmer ones [37,47,84]. Interestingly, AFD was shown to antagonize the heat-mediated reduction of lifespan, such that AFD-ablated animals exhibit an even shorter lifespan than wild-type animals at 25°C [47]. AFD promotes longevity at warmer temperatures by CMK-1-dependent upregulation of the FLP-6 neuropeptide in AFD; FLP-6 in turn regulates insulin and sterol hormone signaling to increase lifespan [14]. In contrast, the cold-dependent promotion of longevity is AFD-independent, and has been suggested to be mediated via TRPA1 channel function in the intestine and elsewhere [92]. Together, these observations suggest that AFD not only signals to synaptically connected neurons to drive behavior, but can also govern systemic temperature responses on different timescales via multiple signaling pathways.

Open questions and future directions

The AFD neurons of *C. elegans* provide a fascinating single neuron system in which to explore the molecular basis of thermosensation and plasticity of behaviors linked to thermosensation. Although there has been much progress on both fronts in recent years, several questions remain to be fully addressed.

1. Are the AFD-rGCs direct thermosensors? Although these molecules are both necessary and sufficient to mediate thermosensation in *C. elegans*, in the absence of successful expression in heterologous systems, is not yet firmly established that these molecules themselves respond to temperature.

2. Why does the AFD neuron require the function of three rGCs? Although all three AFD-rGCs act partly redundantly to mediate thermosensation in AFD, each of these proteins also has unique properties in AFD. For instance, GCY-8, but not GCY-18 and GCY-23, is regulated by Cl^- [76], and single and double AFD-rGC mutants exhibit subtle but distinct phenotypes [90,33].

3. What are the mechanisms by which rapid adaptation to temperature experience is achieved in AFD? How do intracellular cGMP and/or Ca^{2+} homeostatically reset the response threshold of AFD?

4. What is the complete complement of genes whose expression is regulated by T_c experience via CMK-1 to set T^*_{AFD} and the threshold of synaptic output?

5. How does AFD direct the exhibition of distinct behavioral strategies in different temperature regimes relative to the animal's T_c experience? While a role for distinct AFD synaptic outputs in shaping NT and PT behaviors is being described [59,55], little is known about the AFD-driven circuit that regulates IT behavior.

6. How does temperature experience shape the sensory architecture of AFD, and how does this architecture in turn influence AFD thermosensory properties?

Thermosensation in AFD exhibits features remarkably similar to those described previously in mammalian phototransduction. In both systems, signal amplification via cGMP production and hydrolysis, concentration and organization of signaling molecules in elaborate specialized sensory structures, and feedback-mediated adaptation via intracellular calcium levels contributes to their extraordinary sensitivity and response range [66,4,39]. It will be interesting to establish the extent to which principles similar to vertebrate phototransduction, as well as organism-specific mechanisms, shape the unique properties of this sensory neuron and dictate the amazing thermoresponsive behaviors of this animal.

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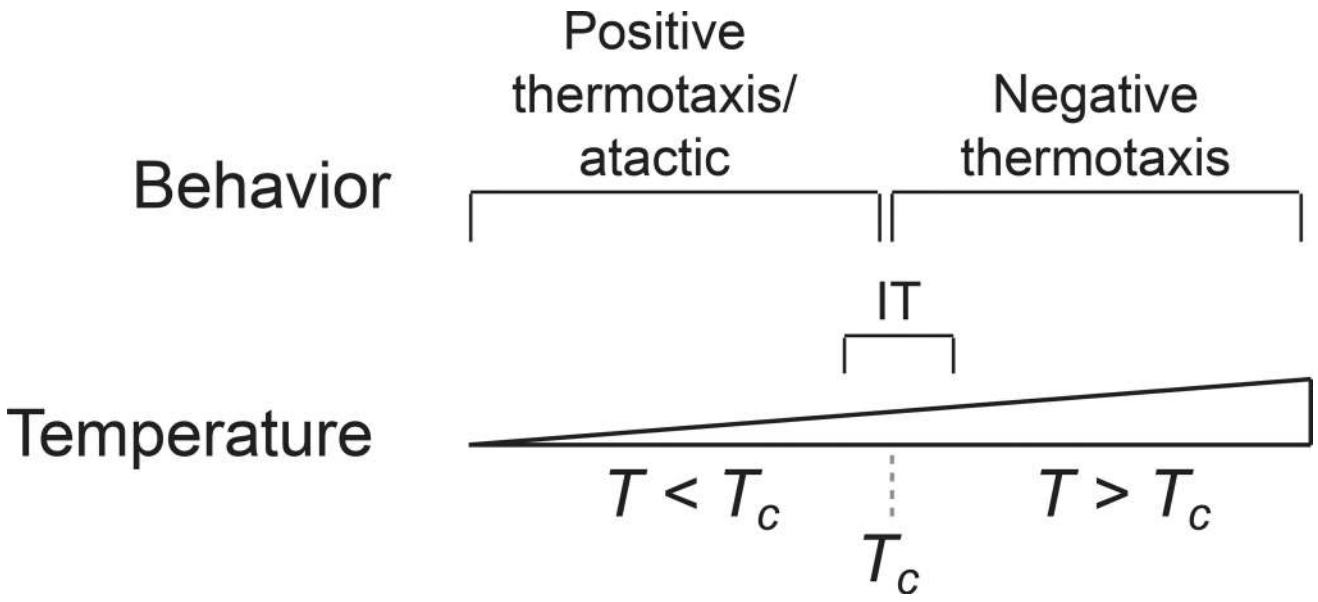

Figure 1.

C. elegans exhibits distinct navigation behaviors at temperatures relative to their recent temperature experience. Positive thermotaxis - movement towards warmer temperatures; Atactic - movement without regard to temperature; Negative thermotaxis - movement towards cooler temperatures; IT - isothermal tracking behavior. T - ambient temperature on spatial thermal gradient; T_c - temperature experienced 3–5h prior to assay. Adapted with permission from [95].

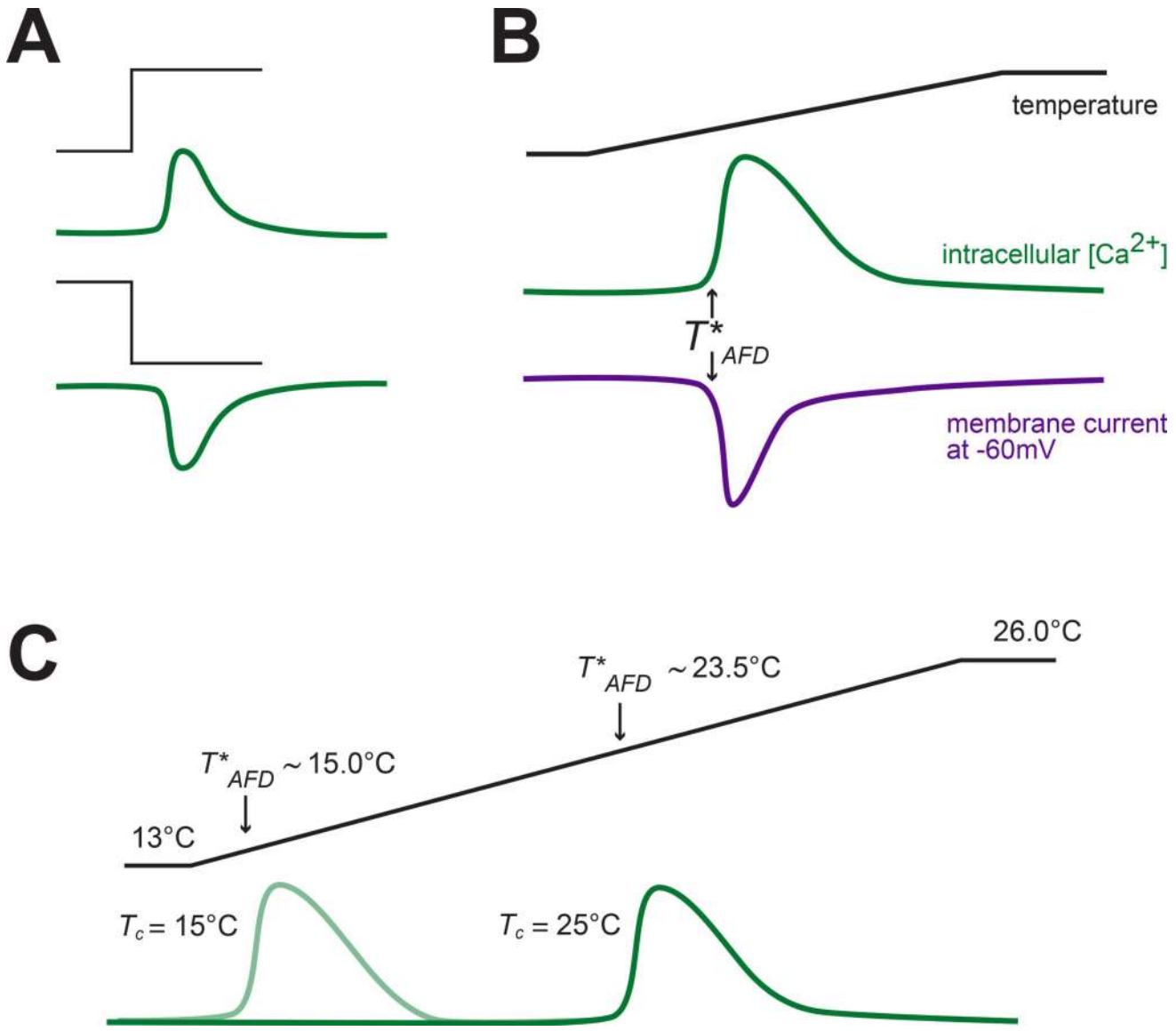

Figure 2.

The AFD sensory neurons are activated by warming and inhibited by cooling. **A**) Idealized calcium transients (green) evoked by thermal up-steps (top) and down-steps (bottom) [35,17]. **B**) Idealized calcium transients (green) and thermoreceptor currents (violet) evoked by a rising thermal ramp [67]. Arrows indicate T^*_{AFD} **C**) Acclimation to a new T_c shifts T^*_{AFD}. Calcium transients are shown in green. Black traces in **A–C** show thermal stimuli delivered to immobilized animals.

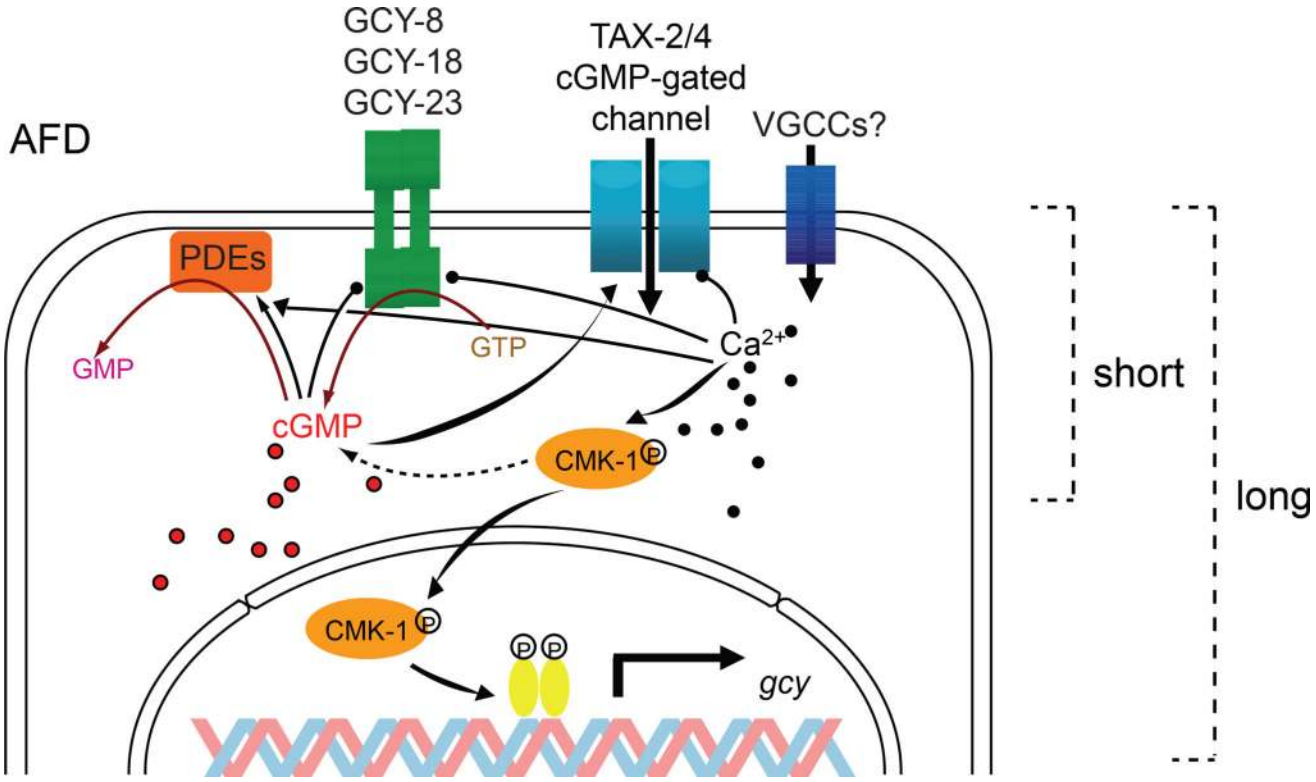

Figure 3.

Model of thermosensory transduction and adaptation pathways in AFD. Warming activates the AFD-rGCs GCY-8, GCY-18 and GCY-23 to increase intracellular cGMP concentrations. cGMP gates TAX-2/TAX-4-encoded cation channels. cGMP hydrolysis is mediated by PDEs such as PDE-2 whose activity may also be temperature-regulated. cGMP and/or Ca^{2+} feeds back to terminate signaling and promote rapid adaptation via inhibition of rGCs, activation of PDEs, and/or decreasing the sensitivity of the TAX-2/TAX-4 channels. Long-term adaptation of T^*_{AFD} also requires CMK-1-mediated changes in AFD-rGC and other gene expression. VGCCs - voltage-gated calcium channels (hypothesized). Adapted with permission from [95].

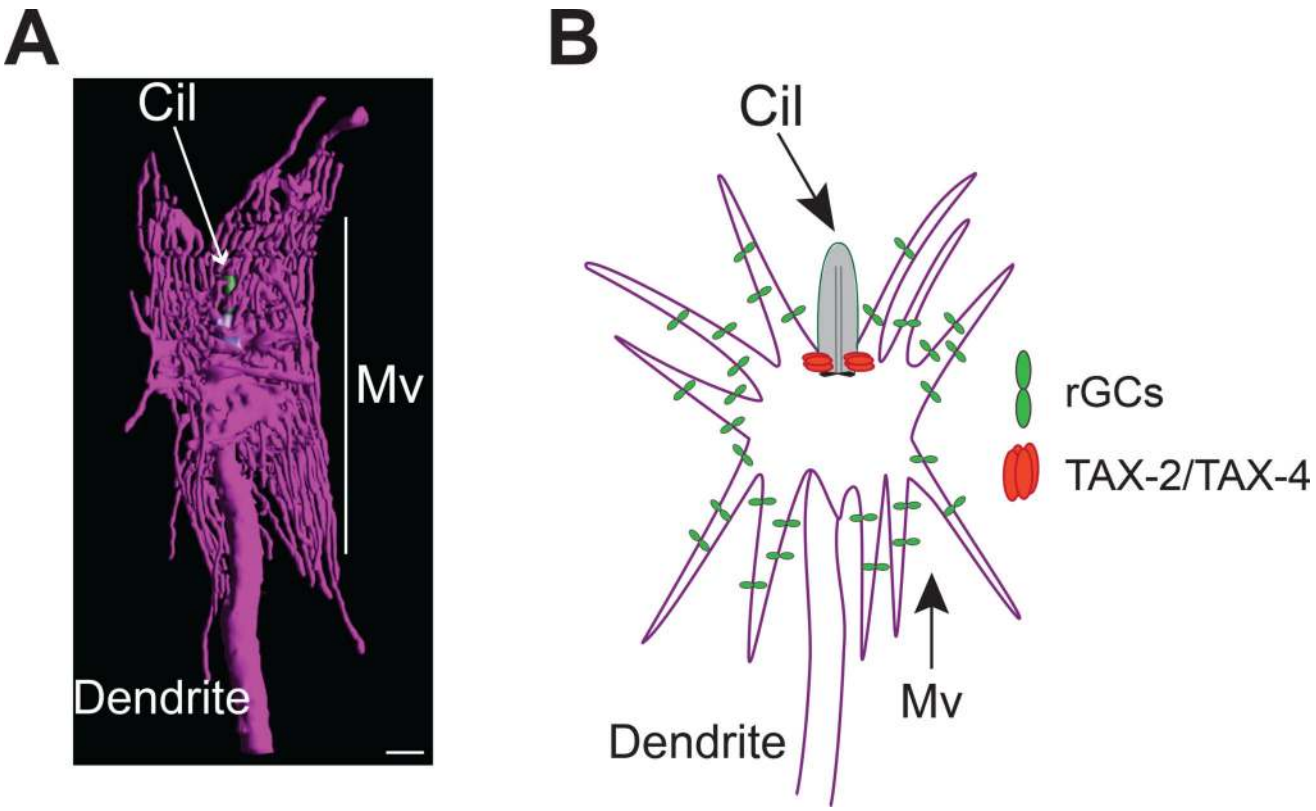

Figure 4.

Thermotransduction molecules are localized to the specialized sensory endings of AFD. **A**) 3D reconstruction model of the sensory endings of an AFD neuron. Cil: cilium (green); Mv: microvilli. Scale bar: 500 nm. Adapted from [21]. **B**) Schematic showing localization of the AFD-rGCs and cGMP-gated channels at the base of the cilium and in the microvilli, respectively. Adapted from [56].