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Role of Adaptation in *C. elegans* thermotaxis. Focus on “Short-Term Adaptation and Temporal Processing in the Cryophilic Response of *Caenorabditis elegans*”

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From honeybee foraging to bird migration, the orientation of animals in their environments is vital for survival and provides opportunities for studying the neural mechanisms that underlie the perception and processing of sensory information. Temperature is a ubiquitous environmental variable that affects both the rate and the nature of the chemical reactions in and around a cell. Animals have developed sophisticated thermosensory systems that help them to avoid the physiological catastrophe caused by extreme temperatures and to seek out optimal temperatures at which they can thrive.

One of the best-characterized examples of thermosensory behavior is exhibited by the soil-dwelling nematode *Caenorhabditis elegans*. As initially described by Hedgecock and Russell (1975), *C. elegans* exposed to a thermal gradient migrate from higher temperatures toward the temperature at which they were previously cultivated, which constitutes the thermotactic set-point (T_s). Within 2–3°C of T_s , the worm is also capable of tracking a narrow isotherm of $\leq 0.05^\circ\text{C}$ for dozens of body lengths (several cm) over the course of 1–2 min (Hedgecock and Russell 1975). The plasticity and precision of worm thermotactic behavior raises many questions. What mechanism sets the T_s ? How does the T_s govern navigation behavior? Once near the T_s , how does the worm track an isotherm? A flurry of recent work, including the paper by Clark et al. in this issue of the *Journal of Neurophysiology* (p. 1903–1910) has begun to dissect the molecular and neural bases of these remarkable feats of sensory processing.

C. elegans thermotactic behavior is impressive, and the anatomical and experimental features of the worm make this behavior a promising model for studying how sensory information is processed. *C. elegans* has a nervous system of only 302 neurons for which a nearly complete wiring diagram is available (White et al. 1986). Combined with the highly developed state of *C. elegans* molecular genetics, the worm is a powerful system for investigating the neural and molecular basis of behavior. Classic studies have taken advantage of both the wiring diagram and the molecular genetics to map out significant portions of the neural circuit for thermotaxis (reviewed in Mori 1999).

Recently, the introduction of highly quantitative assays for thermotactic behavior and the direct examination of thermosensory neuron activity have led to the further refinement of models for the neural basis of thermotaxis (Biron et al. 2006; Clark et al. 2006; Kimura et al. 2004; Ryu and Samuel 2002). A simple working model consistent with much of the current data (summarized in Fig. 1A) would be that *C. elegans* ther-

motaxis involves the interaction of two key neural pathways. One pathway involves an interneuron called AIZ. The AIZ pathway drives the animal toward lower temperatures (causes cryophilic behavior) whenever it is active. A second pathway involves the thermosensory neuron AFD and its synaptic target, the interneuron AIY. The AFD/AIY pathway acts as a switch that determines when the AIZ pathway is active, presumably acting via synaptic connections between AIY and AIZ. T_s information flows through the AFD/AIY pathway and reflects a weighted average of the worm's recent temperature experiences. T_s appears to alter the thermosensory function of AFD. When $T > T_s$, AFD is active, potentially inhibiting AIY and, in turn, permitting the AIZ pathway to drive the animal down the temperature gradient. When $T < T_s$, however, AFD is inactive and AIY inhibits AIZ, shutting off cryophilic behavior and rendering the worm atactic at lower temperatures. Together the AIZ and AFD/AIY pathways allow the worm to avoid temperatures above their T_s .

Cryophilic behavior is very interesting from the perspective of sensory processing because it is a critical factor in thermotaxis toward T_s and it requires the worm make robust behavioral responses to subtle gradations in thermal stimuli. Worm locomotion on thermal gradients (either spatial or temporal) involves forward runs interspersed with turns that reorient the animal, and previous studies have shown that cryophilic movement involves a biased random walk (Ryu and Samuel 2002). Cryophilic behavior does not involve alterations in either run speed or orientation. Rather animals lengthen their runs as they move down the thermal gradient by extending run duration, and they shorten their runs as they move up the gradient by decreasing run duration (Ryu and Samuel 2002).

Clark et al. extend this analysis by providing a detailed analysis of the adaptation of cryophilic behavior (Clark et al. 2007). As noted in the preceding text, animals lengthen their runs as they move down the thermal gradient and shorten their runs as they move up the gradient. Clark et al. demonstrate that these responses are transient and that run lengths return to their initial values after the temperature has been elevated or reduced (Fig. 1B). As one would expect, such adaptation permits the worm to retain exquisite sensitivity to temperature fluctuations (as little as $0.01^\circ\text{C}/\text{s}$) over a relatively wide temperature range ($\sim 5^\circ\text{C}$). Interestingly, the authors also find that although the behavioral responses to increases and decreases in temperature are the opposite of one another, the two responses are of similar magnitude and adapt with similar kinetics. These properties are predicted to allow the system act as a band-pass filter that would be less sensitive to temperature fluctuations occurring on a time scale significantly faster or slower than the time needed for adaptation. The authors proceed to demonstrate that

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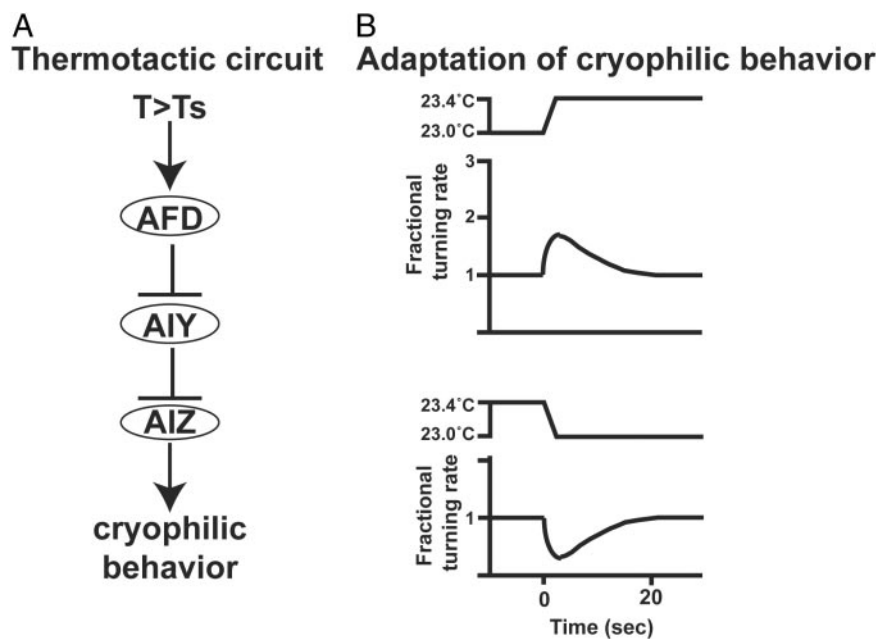


FIG. 1. A: simplified diagram of the operation of the *C. elegans* thermotaxis circuit. See text for details. B: adaptation of turning response to a stepwise increase or decrease in temperature. Modified from Clark et al. (2007).

the response amplitude is indeed maximal when the temperature is fluctuating with a periodicity near the time required for adaptation (~ 15 s in response to a 0.4°C temperature upshift or downshift). This result is consistent with the system filtering out very rapid and very slow temperature fluctuations. A second interesting observation is that adaptation times are similar to the duration of the average run time of a crawling worm on a thermal gradient. The authors suggest that such a rate of thermotactic adaptation is well-suited for determining the orientation of an average run on a temperature gradient.

As the authors note, their current analysis of worm thermotactic behavior raises possible parallels to the orientation behavior of a single-celled organism, the bacterium *Escherichia coli*. The movement of *E. coli* toward chemical attractants and away from repellents also involves a biased random walk, and this behavior is both adaptive and bidirectional. In fact, > 20 yr ago Block et al. performed a similar analysis to Clark et al., examining the adaptation of *E. coli* to chemosensory stimuli (Block et al. 1982). Block et al. also found that the chemosensory system of *E. coli* was optimized to respond to changes over the course of an average run, while filtering out very transient or very slow fluctuations in chemical concentrations. Although the physical hardware of the worm and the bacterium are very different, the Clark et al. paper brings to the fore the potential for diverse organisms to exploit similar system properties to solve a similar problem, namely the problem of responding robustly to subtle gradations in an external stimulus.

Although worm thermotactic behavior is increasingly well-characterized, there remain critical gaps in current knowledge at the molecular level, in particular regarding the identity of the thermal sensors. One promising group of thermal sensors belongs to the TRP family of cation channels. Some TRPs are activated by temperature (Patapoutian 2005), and TRP proteins are important for thermotaxis in both flies and mice (Lee et al. 2005; Moqrish et al. 2005; Rosenzweig et al. 2005). There are > 20 TRP channel genes in *C. elegans*, and loss-of-function mutations are available for an increasing number of these loci,

which will permit an assessment of their roles in thermotaxis in the near future. Whether the worm uses TRPs or other types of temperature-responsive factors, this will not be the end of the story as these factors are likely to be just one element in a larger thermosensory apparatus. Such an apparatus presumably includes multiple modulators and effectors of heat-responsiveness that together permit the worm to respond to temperature fluctuations of $\sim 0.01^\circ\text{C/s}$ across a range of baseline temperatures. Although such thermal sensitivity is impressive, it is not unprecedented. For example, single fibers from the thermosensitive facial pits of vipers exhibit an $\sim 50\%$ increase in spiking frequency on temperature increases of just 0.003°C (Bullock and Diecke 1956). That animals are sensitive to such subtle alterations in the vibrational and translational energy of matter is stunning and remains largely unexplained. One anticipates that with the combined forces of molecular genetics, physiology, neural circuit analysis, and structural biology focused on the problem of thermosensation, plenty of exciting biology will arise from the attempt to explain what remains one of the least-understood sensory modalities.

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