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Temperature sensation in *Drosophila*

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Abstract

Animals use thermosensory systems to achieve optimal temperatures for growth and reproduction and to avoid damaging extremes. Thermoregulation is particularly challenging for small animals like the fruit fly *Drosophila melanogaster*, whose body temperature rapidly changes in response to environmental temperature fluctuation. Recent work has uncovered some of the key molecules mediating fly thermosensation, including the Transient Receptor Potential (TRP) channels TRPA1 and Painless, and the Gustatory Receptor Gr28b, an unanticipated thermosensory regulator normally associated with a different sensory modality. There is also evidence the *Drosophila* phototransduction cascade may have some role in thermosensory responses. Together, the fly's diverse thermosensory molecules act in an array of functionally distinct thermosensory neurons to drive a suite of complex, and often exceptionally thermosensitive, behaviors.

Temperature sensation in *Drosophila*

Temperature affects all aspects of physiology, and animals use their thermosensory systems to achieve optimal temperatures for growth and reproduction and to avoid damaging thermal extremes[1]. Thermoregulation is particularly challenging for small animals like the fruit fly *Drosophila melanogaster* (weighing < 2 mg), which can reach undesirable body temperatures within seconds of environmental temperature fluctuation or sunlight exposure[2, 3]. *Drosophila* thermosensory responses are sensitive and robust, with milli-degree per second temperature changes triggering readily assayed behavioral responses[4]. The availability of clear behavioral readouts, together with *Drosophila*'s genetic toolkit and the quantitative nature of temperature as a stimulus, make fly thermosensation a powerful system for studying fundamental issues in sensory processing and behavior. In fact, the developing fly (the larva) and the adult fly provide two complementary systems. Both are exquisitely thermosensitive[5, 6], but the cells, neural pathways and loco-motor strategies involved are different. Each has unique features: the larva's simpler anatomy aids analysis of circuitry and behavioral strategy, while the adult's rich behavioral repertoire facilitates studying the integration of temperature with other inputs.

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Like other animals, flies possess multiple classes of thermoreceptors[7-9]. Thermoreceptors fall into four basic classes: warm receptors respond to innocuous (moderate) warming, cool receptors to innocuous cooling, high-temperature nociceptors to noxious (damaging) heat, and low-temperature nociceptors to noxious cold. Flies have at least three classes of thermoreceptors[7-9] (cold nociception awaits analysis), and multiple subtypes of some classes[10]. This complexity raises several questions. What molecular mechanisms underlie the thermosensitivity of various thermoreceptors? How is thermoreceptor input processed to yield coherent responses? How can thermosensation be modified by experience, physiological status or other sensory input to sculpt appropriate responses? In this review, we focus on progress made toward answering these questions.

Innocuous thermosensation in the adult: multiple sensors driving diverse responses

Flies continually encounter innocuous temperature variations that affect their body temperature and can have significant long-term survival impacts [11]. Four sets of neurons that act as innocuous thermosensors have been identified in the adult fly, two warm-responsive and two cool-responsive, and together they mediate multiple aspects of thermosensory behavior [8-10, 12] (Fig. 1).

The Anterior Cell (AC) neurons inside the head[8] and the Hot Cell (HC) neurons in the arista[9] both function as innocuous warmth sensors, responding to temperatures above ~25°C (the fly's preferred temperature)(Fig. 1). These cells sense temperature via different mechanisms and drive distinct behaviors. At the molecular level, the AC neurons detect warming using the Transient Receptor Potential (TRP) protein TRPA1[8]. TRPs are an evolutionarily conserved family of cation channels, of which a subset, the thermoTRPs, function as thermoreceptors from flies to humans[13-15]. TRPA1 mediates the warmth-activation of AC neurons above ~25°C [8], and can act as a warmth-activated ion channel in heterologous cells[8, 16, 17]. The AC neurons also exhibit a second, TRPA1-independent warmth response at temperatures above ~32°C[18]. This second response is non-cell-autonomous and requires input from as yet unidentified antennal warmth sensors. Thus the AC neurons act both as thermosensors as well as interneurons that integrate thermosensory input.

The HC neurons sense warmth differently than the AC neurons, relying on the Gustatory Receptor (Gr) Gr28b(D), rather than a thermoTRP, to drive warmth responses[10]. Gr's conventionally participate in insect chemoreception[19], but ectopic Gr28b(D) expression confers warmth-sensitivity upon multiple cell types, indicating Gr28b(D) is a thermoreceptor[10]. At a mechanistic level, some Gr's act as ion channels, but others signal through G proteins[20, 21]. The breadth of cell types in which Gr28b(D) mediates warmth-sensing suggests it may be a warmth-responsive channel, but more concrete proof awaits Gr28b(D)'s successful expression in heterologous cells.

The HC and AC neurons detect similar temperatures, but project to distinct brain regions[8, 9, 22] and drive distinct behaviors. The peripheral HC neurons mediate rapid (<1 minute) warmth avoidance on steep thermal gradients (e.g., 5°C/cm)[10], while the internal

AC neurons mediate the slow (over ~20 minutes) warmth avoidance elicited by shallowerthermal gradients (e.g., 0.5°C/cm)[10]. Thus, HC neurons may primarily sense changing external thermal environments, and the AC neurons internal body temperature. In addition, the AC neurons mediate the aversive associative memory formed by pairing warmth with odor[12]. Such memory formation involves a cluster of ~20 dopaminergic neurons in the fly protocerebrum, which appear to be contacted and potentially regulated by the AC neurons[12]. Together, these findings begin to reveal surprising complexity in how warmth is sensed and affects behavior in the fly.

Drosophila also contain two sets of neurons responsive to innocuous cooling: the Cold Cells (CCs), which form thermosensor pairs with the HCs in the arista, and the Sacculus Cells (SCs), located in a pouch within the antenna called the sacculus[9] (Fig. 1). These antennal cool sensors are important for innocuous cool responses, as their inhibition or surgical removal disrupts cool avoidance[9],[8]. Three TRP channels, Brivido1 (Brv1), Brv2 and Brv3, participate in cool sensing, as *brv* family mutants disrupt cool avoidance and reduce CC neuron cool-sensitivity[9]. However, attempts to demonstrate thermoreceptor function of Brvs via ectopic expression were unsuccessful[9], suggesting they may not be thermoreceptors. (Many TRPs are not thermoTRPs, but support neuronal function in other ways[13].). At the circuit level, innocuous cooling stimulates dopaminergic neurons [23] and dopaminergic signaling in the mushroom bodies is critical for cool avoidance[24], suggesting that cool-sensing and warmth-sensing both act through modulating dopaminergic signaling in the mushroom bodies. As thermal preference exhibits circadian variation, input from the circadian clock may also interact with these pathways[25].

Innocuous thermosensation in the larva: from sensors to navigational strategies

As in the adult, innocuous warmth sensation in the larva relies on TRPA1[26]. TRPA1 was initially found to mediate warmth avoidance of temperatures over ~30°C[26], and subsequently as low as ~20°C [27, 28]. Surprisingly, in the lower temperature range, mutants in *Drosophila* phototransduction proteins, including rhodopsin and its G protein/phospholipase C cascade, exhibited behavioral phenotypes similar to *TrpA1* mutants[27, 28]. But as the thermoreceptor neurons controlling larval warmth avoidance are unknown, whether TRPA1 and/or rhodopsin function in thermoreceptors and to what extent they affect warmth detection versus another process is unclear.

While direct involvement in temperature detection remains uncertain, rhodopsin's involvement in thermotaxis has generated interest in possible similarities between thermo- and photo-transduction. In one scenario, the rhodopsin pathway would detect temperature and TRPA1 would act as a transduction channel[27, 28]. However, this notion is controversial[29]. Not only are rhodopsins reported to be highly thermostable, thermally isomerizing an estimated once per ~1000 years at 24°C[29], ectopic expression of rhodopsin has not been demonstrated to confer thermosensitivity or to activate TRPA1. An alternative would be TRPA1 as thermosensor. While TRPA1 can function as a warmth-responsive thermoTRP[8, 1617], the temperatures yielding robust responses in oocytes are several degrees warmer than the lowest temperature driving thermotaxis[30]. However, thermoTRPs do not

have discrete or fixed temperature thresholds[31], but rather exhibit graded responses to temperature modulated by cell signaling[13]. In addition, other factors contribute to a thermoreceptor neuron's response properties, including the cell's intrinsic excitability and its level of thermoTRP expression. Thus, TRPA1 could act as a thermoTRP in this system, with rhodopsin dynamically modulating its thermal sensitivity. Whether the rhodopsin pathway, TRPA1 or another molecule provides the thermosensor, interesting biology is emerging from the analysis of warmth sensing.

The molecular basis of larval innocuous cool detection is also largely unknown. Multiple TRPs, including TRPL and Inactive, are implicated in cool-responsive behavior, but none have been directly linked to the detection of cool temperatures[32, 33]. In contrast, a detailed understanding of larval responses to cooling is emerging at the behavioral and cellular levels[4, 6, 34]. At the behavioral level, larval thermotaxis involves the alternation between two behavioral states: forward movement (running) and head-sweeping (linked to turning)[6, 34]. Running is powered by peristaltic waves that propagate from tail to head, propelling the larva forward, while head-sweeping involves the asymmetric contraction of the animal's anterior segments, sweeping the larval anterior from side to side[34]. When navigating on a gradient of cooler than preferred temperatures, larva tend to move toward more favorable (warmer) temperatures by regulating run length and by modulating the direction of the turns they make between runs[6]. Run lengths tend to be shorter when moving toward unfavorable (cooler) temperatures and longer when moving toward favorable (warmer) temperature. In this way, the larva executes a biased random walk driving net movement in the favorable direction[6], similar to bacterial chemotaxis[35]. But unlike a bacterium, whose runs are punctuated by random reorientations, the larva also uses the head-sweeping program to execute biased turns that tend to reorient the animal in favorable run directions. These strategies also underlie larval avoidance of innocuously warmth[6], and they resemble strategies driving larval phototaxis and chemotaxis[36], suggesting multiple sensory pathways feed into similar neural pathways.

At the cellular level, initial studies suggested the cool receptors driving thermotaxis might reside in the terminal organ, a pair of sensory ganglia at the larval anterior[37]. However, the cell-specific promoter used to establish the terminal organ's importance, GH86-Gal4, also drives gene expression in sensory neurons of the nearby dorsal organs, clouding the picture[4]. Surprisingly, severing nerves from the terminal organs to the brain has no effect on innocuous cool avoidance, while severing the nerves from the dorsal organs completely eliminates the response, suggesting the dorsal organ houses the relevant thermoreceptors[4]. Indeed, each dorsal organ contains three highly cool-responsive neurons (Fig. 1). Cell-specific inhibition of these neurons eliminates cool avoidance behavior, while optogenetic activation of these neurons evokes the thermotactic behavioral program[4]. Thus, these thermoreceptors are critical for innocuous thermosensation.

The dorsal organ's cool receptors have two important physiological features. First, their thermosensitivity (they exhibit significant calcium responses upon ~0.005°C/sec fluctuations[4]) places them among the most sensitive biological thermoreceptors known, such as those of the rattlesnake pit organ[38]. In addition, while these neurons respond to cooling, they can operate at very warm temperatures[4]. When cooled from a starting temperature in

the mid-30s, two of the three cells begin responding near 32°C, warmer than the first instar larva's preferred range of 22-28°C. This places the cool receptors with many other thermoreceptors more sensitive to the direction and rate of temperature change than its absolute value[39]. Perhaps the name "cooling receptors" might be more apt.

High-temperature nociception: sensitive and sensitized to harm

The first thermoreceptors identified in *Drosophila* were the multiple dendritic (md) neurons (Fig. 1), a set of high-temperature nociceptors that tile the larval body wall and trigger a characteristic rolling escape response when activated by temperatures over ~39°C [7]. Two TRP channels, TRPA1 and Painless are critical for this response[7, 40]. Painless appears to function as a high-temperature-responsive thermoTRP exhibiting robust activity at temperatures above ~42°C in heterologous cells[41]. In contrast, TRPA1's role is enigmatic. The TRPA1 gene encodes not just one channel isoform, but rather multiple TRPA1 channel isoforms[42, 43]. These isoforms range from the highly warmth-responsive isoform present in the AC neurons to thermally insensitive isoforms present in TRPA1-dependent chemoreceptors[42, 43]. Interestingly, Zhong et al. found that a TRPA1 isoform with no detectable thermosensitivity could support high-temperature nociception when expressed in the md neurons, suggesting that TRPA1 is not acting as thermoreceptor in these neurons[43]. So while Painless appears to be a high-temperature receptor, TRPA1's role in high-temperature nociception remains mysterious. Painless and TRPA1 are also implicated in high-temperature nociception in adult flies[40, 44], but whether the mechanisms are similar to those in the larva is unknown.

From a biomedical perspective, nociceptor sensitization after tissue damage contributes to pain and inflammation in mammals[45]. Sensitization to noxious stimulation can be classified in terms of allodynia, a decrease in the stimulus threshold sensed as noxious, and hyperalgesia, an increase in the magnitude of the response to a normally noxious stimulus. The md nociceptors have been used as a potential model for investigating these processes. Fly larvae exhibit both types of sensitization to heat after UV-elicited tissue damage[46], and two evolutionarily conserved signaling pathways, the Tumour Necrosis Factor (TNF)[46] and Hedgehog (Hh)[47] pathways, are known to be involved in this sensitization. TNF signaling, also involved in mammalian nociceptor sensitization [48], was specifically implicated in larval allodynia. UV damage to epithelial cells elicited production of the *Drosophila* TNF Eiger, which sensitizes the md neurons via the TNF receptor Wengen[46]. Hedgehog signaling, on the other hand, promotes both allodynia and hyperalgesia[47]. Intriguingly, allodynia induction by both Hh and TNF signaling appear to specifically involve Painless, while Hh-induced hyperalgesia specifically involves TRPA1[47]. The complexities of the *Painless* and *TrpA1* genes, which each encode multiple channel isoforms[42, 43, 49], raise the possibility that gene regulatory mechanisms could contribute to these sensitization responses.

Looking ahead

The last few years have seen significant advances in identifying the molecules, cells, and behavioral strategies mediating thermosensation in *Drosophila*. Still, our understanding of thermosensation, in flies and in other animals, lags behind our knowledge of other senses

like vision, olfaction and gustation. In the fly, many of the key thermosensory neurons and thermoreceptor molecules remain unidentified, and for those that have been identified, we have little insight into how they perform their thermosensory functions. For example, whether the exceptional sensitivity of thermosensors found in the larval dorsal organ (or the rattlesnake pit organ) reflects specific signal amplification pathways, as in vertebrate phototransduction[50], is unknown, as are the mechanisms by which temperature activates molecular thermoreceptors[31]. Insights are needed on multiple levels, from molecular biology to sensory physiology to biophysics. At the circuit level, while some interneurons responsive to thermoreceptor activation have been characterized, the explosion of genetic tools for marking and manipulating identified neurons in the fly brain[51] promises to transform our understanding of how thermosensory information is processed and interfaces with other sensory inputs to modulate behavior. In an ecological context, an understanding of thermosensation *Drosophila melanogaster* provides an entry point for studying variation within and between the many species of *Drosophila*, from latitudinal clines of *Drosophila melanogaster*, to extremophiles like the desert-dwelling *Drosophila mojavensis*. Such work will increase our knowledge of how animal distributions emerge, and provide insights and tools to help monitor, understand and perhaps predict the impacts of climate change on other insects, from disease vectors to agricultural pests[52]. Although *Drosophila* has little thermal mass, the study of its thermosensory behavior permits experimental access to many weighty topics.

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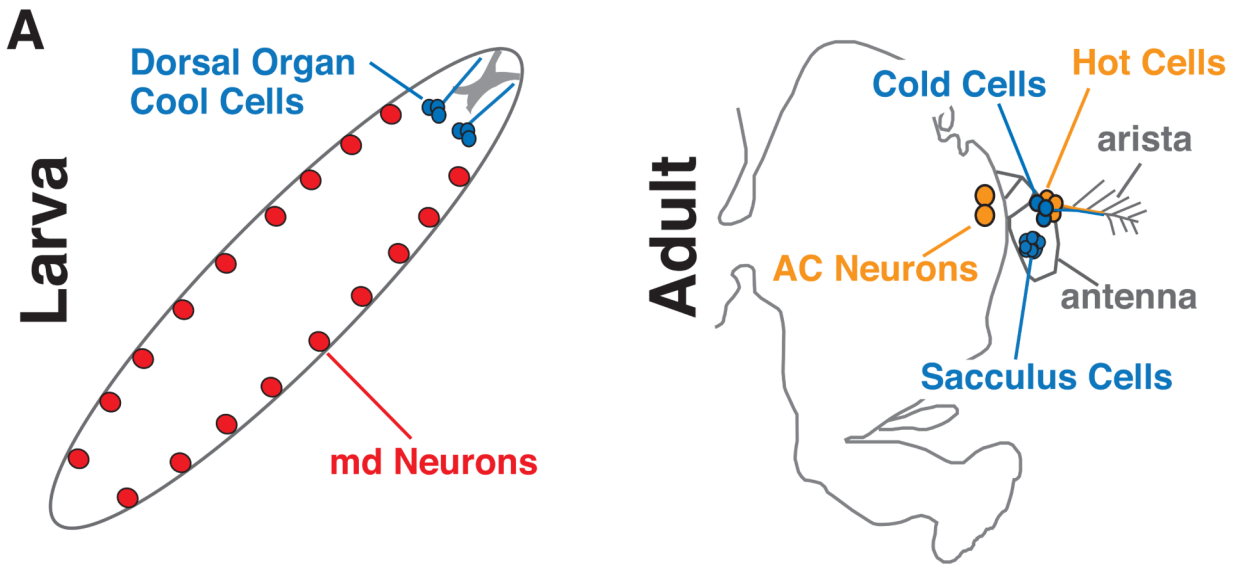

B

		Thermoreceptor Neurons	Molecular Thermoreceptors	Behavioral Responses
Noxious warmth	Larva	Multiple Dendritic (md) Neurons	Painless	Rolling escape
	Adult	?	Painless?	Jumping escape
Innocuous warmth	Larva	?	Rhodopsin pathway? TRPA1?	Thermotaxis
	Adult	Hot Cells (HCs)	GR28b(D)	Rapid thermotaxis
		Anterior Cells (ACs)	TRPA1	Long-term preference Temperature-odor memory
Innocuous cool	Larva	Dorsal Organ Cool Cells (DOCCs)	?	Thermotaxis
	Adult	Cold Cells (CCs) Sacculus Cells (SCs)	Brv1/Brv2/Brv3?	Rapid thermotaxis Long-term preference

Figure 1. *Drosophila* thermosensory systems

A. Thermosensory neurons of the larval (left) and adult (right) nervous systems. **B.** Molecular thermoreceptors and associated behavioral responses for each class of thermosensory neuron.