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REVIEW

Feeling Hot and Cold: Thermal Sensation in *Drosophila*

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Abstract Sensing environmental temperature is crucial for animal life. The model animal, *Drosophila melanogaster*, can be investigated with a large number of genetic tools, which have greatly facilitated studies of the cellular and molecular mechanisms of thermal sensing. At the molecular level, a group of proteins, including Transient Receptor Potential channels and ionotropic receptors, have been characterized as potential thermal sensors in both larval and adult *Drosophila*. At the cellular and circuit levels, peripheral and central thermosensory neurons have been identified. More interestingly, thermal information has been found to be specifically encoded by specific central neurons. In this short review, we mainly survey the progress in understanding the molecular mechanisms of thermosensation and the neuronal mechanisms of thermal information processing in the brain of *Drosophila*. Other recent temperature-related findings such as its impact on neurosecretion and thermotactic behavior in *Drosophila* are also introduced.

Keywords *Drosophila* · Temperature · Thermal sensation

Introduction

Sensing environmental temperature and making proper responses are crucial for animal survival. Temperature has a profound impact on body weight [1–6], longevity [7], behaviors such as those governed by circadian rhythms [8], and the ability to sense itch [9] and pain [10]. How do animals sense environmental temperature? Although a number of thermosensory proteins have been identified at the molecular level [11–19], factors that sense specific temperatures over different ranges have not been well characterized. Moreover, neurons that function downstream from the primary thermosensory neurons remain to be discovered.

In *Drosophila melanogaster*, the molecular and cellular bases of temperature sensation have been well studied and significant progress has been made in the past few years [20–22]. Here, we review these studies, focusing mainly on the cellular and molecular basis of thermal sensation and thermal information processing in the fruit fly.

Techniques for Studying Thermosensation in *Drosophila*

Upon encountering a temperature that may be harmful, animals try to escape and find a more comfortable place. A convenient way to measure fly responses to temperature is thermotaxis. Two behavioral paradigms are commonly used: the thermal gradient test and the two-temperature choice plate [22–25]. In the thermal gradient test, flies are allowed to redistribute on a plate in which the temperature continuously and evenly changes from one end to the other. Flies primarily stay within their favorite temperature range. If thermosensation is disrupted, the distribution range of their favorite temperature shifts either to the cooler or warmer side. In the two-temperature choice assay, flies must choose between two temperatures, one being warm and the other cool. Even if neither temperature is ideal, the flies have to choose the more favorable one. Recently, a paradigm for

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finer tracking and analysis of thermotactic behavior at higher temporal resolution has been developed [26, 27]. But so far, it has not been widely used for screening temperature sensation-related neurons and molecules.

The thermotaxis assay is fast and convenient. However, to study thermosensation at higher temporal resolution and at the cellular level, Ca^{2+} imaging is commonly used [25, 27–30]. When temperature or temperature-change excites certain neurons, the intracellular Ca^{2+} concentration increases, causing brightening of the fluorescence of ectopically-expressed genetically-encoded Ca^{2+} indicators such as GCaMP or RCaMP. Ca^{2+} imaging can easily be used to screen for temperature-sensitive neurons or molecules with a standard fluorescence or confocal microscope.

Electrophysiological recording is also commonly used in studying thermosensory neurons. The sensitivity and temporal resolution of such recording are much higher than those of Ca^{2+} imaging (milliseconds *versus* seconds). Thus, when a temperature change is too rapid or too small to be detectable by Ca^{2+} imaging, electrophysiological recording is necessary [30–32].

Electrophysiological and Ca^{2+}-imaging techniques can be used to measure fast responses to temperature. However, if we want to know the neuronal responses to chronic exposure to cold or heat, a longer monitoring time is required. Although this is practically challenging for electrophysiological and Ca^{2+}-imaging methods, Ca-LexA (Ca^{2+}-dependent nuclear import of LexA) provides a perfect solution [33]. In Ca-LexA, excitation of neurons induces higher intracellular Ca^{2+} concentrations, which in turn leads to the translocation into the nucleus of NFAT (Nuclear Factor of Activated T cells) fused with LexA. This activates LexAop-driven expression of green fluorescent protein (GFP). Because the accumulation of the GFP signal is a relatively chronic process, relatively long temperature exposure times that extend from hours to days are generally required [34].

Neuronal Basis of Thermosensation in *Drosophila*

Temperature-Sensing Neurons

Primary thermosensory neurons in the peripheral nervous system express temperature-sensitive proteins. Temperature is sensed by both external and internal sensors. In adult flies, sensory neurons that respond to rising (hot) or falling (cold) temperatures are found in the antennae. Cold-sensing neurons expressing *brv1*, a gene encoding a cold-sensitive TRPP (transient receptor potential polycystic) channel, are located both at the base of aristae and in the sacculus region of the 3rd antennal segment [25]. Interestingly, in addition to the three cold-sensing neurons that express *brv1*, three heat-sensing neurons that express gustatory receptor GR28B(D), a heat-sensitive protein, are located at the base of each arista [32]. Together, these six neurons make an ideal thermal sensation space. Importantly, the cold-sensing neurons are inhibited by heat, while the heat-sensing neurons are inhibited by cold. This means that removal of a hot (or cold) stimulus can have an anti-inhibitory effect, thus producing a cold (or hot) sensation. These temperature-sensing neurons project to a central region called the proximal antennal protocerebrum (PAP) to form synapses with downstream projection neurons for further information processing. Notably, the targets of cold- and heat-sensing neurons are discrete in the PAP, indicating that cold and heat information are processed separately [25].

Aside from these peripheral neurons on the body surface, other internal neurons can also sense temperature. *Drosophila* transient receptor potential A1 (dTRPA1) is expressed in warmth-sensitive AC (anterior cell) neurons located in the anterior part of the brain [30]. AC neurons project toward several other brain regions, including the antennal lobes where their neurites arborize in the two glomeruli VL2a and VL2p. Like the peripheral heat-sensing neurons described above, the neurons expressing dTRPA1 also project to the PAP. These joint projections likely form a heat-receptive center in the brain, although further downstream circuits remain to be characterized.

Temperature sensors have also been identified in fly larvae. Similar to the position of antennae in the adult body, larval thermosensors are found in the anterior tip of the larval head. The cell bodies of larval thermosensors are located in two ganglia: the dorsal organ ganglion (DOG) and the terminal organ ganglion (TOG) [27, 29, 35, 36]. The dendrites of these neurons extend to two structures just beneath the skin called terminal organs and dorsal organs [22], which may collect external temperature information. At least for sensing cold, both TOG and DOG neurons respond to temperature drops below 25 °C. As detailed below, DOG neurons express the cool-responsive ionotropic receptors IR21a and IR25a [35]; these neurons respond quickly to temperature drops, even when the basal temperature is set as low as 17 °C, and their activity is inhibited when temperature rises. While silencing DOG thermosensing neurons abolishes larval avoidance of cold temperature, blocking TOG thermosensing neurons does not have the same effect. The TOG/DOG thermosensing neurons project to the antennal lobes to form synapses with secondary neurons, similar to olfactory neurons in the adult and larval antennal lobes [37]. In addition to the TOG and DOG neurons in the larval head, neurons of the lateral body wall also respond to temperature changes within the 10–40 °C range (basal level at 18 °C), with multidendritic neurons showing the strongest responses. Most of these neurons appear to be activated by rising temperatures and inhibited by dropping temperatures [29]. Nevertheless,

because reproducing observations in individual neurons is difficult, further investigation is required to address the details of the thermal sensitivity conferred by these body-wall neurons.

Internal Representation of Temperature

Frank *et al*. [38] identified secondary neurons that receive input from the heat and cold cells located at the base of the aristae and named them "thermal projection neurons"(tPNs). tPNs project to brain regions such as the lateral protocerebrum, the mushroom bodies, and the lateral horn. The most impressive finding was that these tPNs display feature-representation properties. Some tPNs are broadly-tuned, responding to both rising and falling temperatures, with peak responses correlating well with stimulus intensity. These broadly-tuned tPNs are the largest group and project to all the target regions noted above. This suggests that these neurons provide significant drive to higher-order thermosensory regions during any temperature transient. Other tPNs are narrowly tuned and less numerous. They come in two types: fast-adapting and slow-adapting. Fast-adapting tPNs respond to the onset or offset of a temperature rise or fall, with peak responses that do not faithfully scale with stimulus intensity. Thus, fast-adapting tPNs may be able to track rapidly-evolving temperature transients. Slow-adapting tPNs respond to cold or heat with peak responses that scale with the magnitude of the stimulus. In these cells, the response persists as heating or cooling continues. Accordingly, responses begin to decay only after the temperature stops changing.

Interestingly, a group of cold-activated "OFF response" fast-adapting tPNs only respond to cooling preceded by a heating phase. The response is evident only when temperature drops to the baseline level. This suggests that inhibitory interactions exist between circuits that process heat and cold. Indeed, as reported in a paper published back-to-back [39], "heat projection" neurons not only receive excitatory input from heat-sensing neurons, they also receive indirect excitatory input from cold-sensing neurons. This is achieved through disinhibition, when cold-sensing neurons reduce the activity of inhibitory intermediate connections onto heat projection neurons [39, 40]. The properties of these neurons provide new insights into how thermal information is processed.

Deeper in the brain, Tomchik [41] reported that a distinct subset of PPL1 dopaminergic (DA) neurons projecting to the vertical lobes of the mushroom bodies are responsive to cooling, while protocerebral anterior medial-type DA neurons projecting to the horizontal lobes of the mushroom bodies are not. These PPL1 neurons exhibit primary phasic responses to cooling, biased toward the initial decrease in temperature. Although no direct evidence has shown that these neurons receive inputs from the thermal sensory neurons or thermal projection neurons described above, ablating the antennae reduces the response of PPL1-DA neurons in the MV1 region of the mushroom bodies when temperatures drop. If the antennae and maxillary palps are removed, the responses of DA neurons in both the MP1 and MV1 regions of the mushroom bodies are reduced. These observations suggest that the cold-responsive DA neurons receive input from thermal sensory neurons in the antennae and that thermal sensors may also exist in the maxillary palps. Nevertheless, more evidence is needed to elaborate on this proposal.

Impact of Temperature on Neurosecretory Neurons

Thermal information is received by some neurosecretory cells, which in turn have physiological effects by releasing neuropeptides. In *Drosophila* larvae, cold stimulates insulin-producing cells (IPCs) through DOG neurons [34]. Cold not only stimulates IPCs, but also enhances the expression of insulin-like peptide coding genes (*dilps*) and the secretion of insulin-like peptides. Elevated levels of insulin-like peptides in the hemolymph in turn affect larval development and growth. In addition to DILPs, our unpublished observations indicate that cold also stimulates DH44 neurons and induces higher expression levels of diuretic hormone-44, a neuropeptide thought to mediate stress responses. Some other secretory neurons that project to the ring gland are also activated by cold. These findings suggest that temperature, at least cold, affects a wide range of neurosecretory cells and the expression and function of neuropeptides, as well as having profound effects on internal physiology, behaviors, and development.

Molecular Basis of Thermosensation in *Drosophila*

Transient Receptor Potential (TRP) Channels

In mammals, members of the TRP family are known to confer thermal sensitivity [12, 18, 19, 25]. TRPA1 and TRPM8 are cold sensors, while TRPV1-4 sense heat [25]. Among these, TRPA1, TRPV1, and TRPV2 function within the noxious (i.e., painful) temperature range, while the others function within the innocuous range (i.e., coolness and warmth). In addition, TRPM3 is a nociceptive heat sensor [17]. More recently, TRPM2 has been reported to be a warmth sensor in mice [42, 43].

TRP channels are also known to confer thermal sensitivity in the fruit fly, although the mechanisms differ from those in mammals. dTRPA1, unlike its mammalian cold-sensing homologue, has been identified as a warmth sensor [23, 30, 44]. Compared with wild-type fly larvae, those

carrying a TRPA1 loss-of-function mutation distribute themselves in warmer temperature zones, ranging from 27 °C to 41 °C [22]. dTRPA1 mutant adult flies also show reduced avoidance of warm temperatures ranging from 28–32 °C [30]. The isoform dTRPA1(B), but not dTRPA1(A), confers thermosensitivity on neurons, although the latter can make cells more thermally sensitive [31, 45]. Ca^{2+} imaging and electrophysiological recordings from TRPA1-expressing neurons in the fly brain have shown that they are activated specifically when the temperature rises above 24.9 °C. Loss of dTRPA1 function completely abolishes this response. Interestingly, Kwon *et al*. reported that dTRPA1 is also required for larvae to slightly prefer 18 °C over higher temperatures such as 19 °C. In this case, dTRPA1 may function downstream of the Gq protein-signaling pathway as an indirect influence on thermosensitive neurons, rather than as a direct thermosensor [23]. In addition to sensing innocuous thermal stimulation, dTRPA1 is also involved in avoiding noxious heat [46].

An important implication of dTRPA1 studies is the generation of flies in which dTRPA1 is ectopically expressed in cells, which can then be excited by temperatures >27 °C. Because thermal stimulation is convenient and non-invasive, this technique has been quickly adopted and is widely used in behavioral neuroscience [30, 47].

Another TRPA family member named *painless* senses temperatures >42 °C [48], but is generally considered to function primarily in nociception induced by high temperature (temperatures >42 °C are usually considered painful to flies).

Work from the Charles Zuker lab has revealed another group of TRP channels as candidate cold sensors [25]. The genes *brv1*, *brv2*, and *brv3* all code for channels homologous to mammalian TRPP channels, and are expressed in cold-sensing neurons (temperature drop to as low as 11 °C), but not in warmth-sensing neurons (temperatures >25 °C). These genes are co-expressed in the same sensory neurons and may work jointly to facilitate the ability to sense cold. Ca^{2+}-imaging assays show that ablating *brv1* or *brv2* eliminates the response to temperature drops in these neurons, suggesting that they are required for sensing cold. In addition, the *brv1/2/3* genes are also required for avoiding cold in a two-temperature thermotaxis paradigm in which flies are forced to choose between 25 °C and a lower temperature.

Non-TRP Proteins

Aside from TRP channels, studies have also found other receptor proteins that confer thermal sensitivity. A gustatory receptor GR28B(D) confers sensitivity to high temperature in adult *Drosophila* [32]. In fact, GR28B(D) and dTRPA1(B) are mutually replaceable for sensing high temperature, although they are differentially expressed and mediate different types of thermotactic behavior. GR28B(D) is expressed in peripheral hot cells in the base of the aristae in antennae, while dTRPA1 is expressed in AC cells of the anterior brain. GR28B(D) is required for rapid negative thermotaxis while dTPRA1 is required for slow thermotaxis on a shallow and broad thermal gradient.

Members of another large protein family, the ionotropic receptors IR21a and IR25a also function in thermosensation. Generally considered to be involved in detecting tastes and smells, they have also been found to be required for cold sensing and cold-avoidance behavior in larvae [35]. These receptors are expressed in larval DOG neurons that sense cold. Ectopic expression of IR21a confers coolness sensitivity in an IR25a-dependent manner, suggesting that these two receptors work together in sensing cold.

Other Molecules and Neurons Involved in *Drosophila* Thermotaxis

Besides the thermally-responsive molecules and neurons described above, other proteins and neurons have been shown to be involved in fly thermotaxis. The TRPC family members TRP and TRPL proteins required for fly vision are indispensable for avoiding coolness in larvae [44]. IAV (inactive), a TRPV family member previously known to be required for hearing in adult flies [49], is also required for larval thermotaxis [50]. IAV function in the chordotonal organs of flies is necessary for larval preference of 17.5 °C over slightly lower temperatures of 14–16 °C [50]. Strikingly, rhodopsins Rh1 (encoded by the *ninaE* gene), Rh5, and Rh6, which are photoreceptors in the adult retina, are also required for larval thermotaxis between 18 °C and a slightly higher temperature ranging between 19 °C and 24 °C [51, 52]. However, it remains unclear whether these proteins are direct thermosensors, or simply play a role downstream of thermosensory neurons like dTRPA1 in thermotaxis between 18 °C and slightly higher temperatures [24]. According to a recent report, labellum mechanosensation mediated by the TRPV family member *nan*—a close homologue of *iav*—represses gustatory responses to sugar in adult flies [53]. Thus, at least in the case of *iav*-dependent thermotaxis, larval thermosensation may be regulated by *iav*-mediated mechanosensation. Undoubtedly, more evidence is needed to test this hypothesis.

Summary and Prospects

To date, studies on *Drosophila* thermosensation have largely been restricted to the primary sensory neurons and related molecules required for thermosensation. A few

studies have begun to investigate deeper into the brain for higher-level thermal information-processing. Several questions remain to be explored:

1. What are the cellular and molecular bases of cutaneous thermosensation? Because sensing temperature is distributed throughout the skin in mammals, as well as in the larval body wall, we would expect to find thermosensory neurons in the surface and limbs of the adult fly. However, no such report has been published.
2. What are the effects of chronic temperature exposure? Although Gr2bB and dTRPA1 are involved in rapid and relatively slow thermal avoidance, respectively, sensory molecules or neurons that respond to chronic temperature changes have not been identified. Since chronic thermal experience greatly affects animal physiology, this aspect deserves more investigation.
3. How does *Drosophila* sense internal temperature? Most studies have investigated how flies sense changes in environmental temperature. However, sensing internal temperature is also an important aspect of thermosensation in warm-blooded animals. Although fruit flies are cold-blooded, they might also have internal temperature-sensing mechanisms that differ from those in warm-blooded animals only in terms of how body temperature is regulated.
4. How is thermal information processed in the brain? Finding thermal representations in tPNs is just a first glimpse of the mechanisms by which thermal information is internally processed, and the bulk of neuronal circuits downstream from these primary and secondary neurons are still uncharacterized. So far, few studies have investigated higher-level thermal information-processing by neurons deeper in the brain.

With the help of genetic tools and rapid building of the connectome for the *Drosophila* brain, we believe that solving these problems is foreseeable in the near future.

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References

1. Schreider E. Geographical distribution of the body-weight/body-surface ratio. Nature 1950, 165: 286.
2. Ruff CB. Morphological adaptation to climate in modern and fossil hominids.Yearb Phys Anthropol 1994, 37: 65–107.
3. Bergmann C. "Über die Verhältnisse der Wärmeökonomie der ThierezuihrerGrösse". Göttinger Studien 1847, 3: 595–708.
4. Neel JV. The interrelations of temperature, body size, and character expression in *Drosophila melanogaster*. Genetics 1940, 25: 225–250.
5. Nunney L, Cheung W. The effect of temperature on body size and fecundityin female *Drosophila melanogaster*: evidence for adaptive plasticity. Evolution 1997, 51: 1529–1535.
6. Angilletta MJ, Steury TD, Sears MW. Temperature, growth rate and body size in ectotherms: fitting pieces of a life-history puzzle. Integr Comp Biol 2004, 44: 498–509.
7. Xiao R, Liu J, Xu XZ. Thermosensation and longevity. J Comp Physiol A Neuroethol Sens Neural Behav Physiol 2015, 201: 857–867.
8. Kidd PB, Young MW, Siggia ED. Temperature compensation and temperature sensation in the circadian clock. Proc Natl Acad Sci U S A 2015, 112: E6284–6292.
9. Snyder LM, Ross SE. Itch and its inhibition by counter stimuli. Handb Exp Pharmacol 2015, 226: 191–206.
10. Julius D. TRP channels and pain. Annu Rev Cell Dev Biol 2013, 29: 355–384.
11. Viswanath V, Story GM, Peier AM, Petrus MJ, Lee VM, Hwang SW, *et al*. Opposite thermosensor in fruitfly and mouse. Nature 2003, 423: 822–823.
12. Feng Q. Temperature sensing by thermal TRP channels: thermodynamic basis and molecular insights. Curr Top Membr 2014, 74: 19–50.
13. Palkar R, Lippoldt EK, McKemy DD. The molecular and cellular basis of thermosensation in mammals.Curr Opin Neurobiol 2015, 34: 14–19.
14. Aoki I, Mori I. Molecular biology of thermosensory transduction in *C. elegans*. Curr Opin Neurobiol 2015, 34: 117–124.
15. Zhang X. Molecular sensors and modulators of thermoreception. Channels (Austin) 2015, 9: 73–81.
16. Vriens J, Nilius B, Voets T. Peripheral thermosensation in mammals. Nat Rev Neurosci 2014, 15: 573–589.
17. Vriens J, Owsianik G, Hofmann T, Philipp SE, Stab J, Chen X, *et al*. TRPM3 is a nociceptor channel involved in the detection of noxious heat. Neuron 2011, 70: 482–494.
18. Patapoutian A, Peier AM, Story GM, Viswanath V. ThermoTRP channels and beyond: mechanisms of temperature sensation. Nat Rev Neurosci 2003, 4: 529–539.
19. Dhaka A, Viswanath V, Patapoutian A. Trp ion channels and temperature sensation. Annu Rev Neurosci 2006, 29: 135–161.
20. Barbagallo B, Garrity PA. Temperature sensation in *Drosophila*. Curr Opin Neurobiol 2015, 34: 8–13.
21. Sengupta P, Garrity P. Sensing temperature. Curr Biol 2013, 23: R304–307.
22. Dillon ME, Wang G, Garrity PA, Huey RB. Review: Thermal preference in *Drosophila*. J Therm Biol 2009, 34: 109–119.
23. Rosenzweig M, Brennan KM, Tayler TD, Phelps PO, Patapoutian A, Garrity PA. The *Drosophila* ortholog of vertebrate TRPA1 regulates thermotaxis. Genes Dev 2005, 19: 419–424.
24. Kwon Y, Shim HS, Wang X, Montell C. Control of thermotactic behavior via coupling of a TRP channel to a phospholipase C signaling cascade. Nat Neurosci 2008, 11: 871–873.
25. Gallio M, Ofstad TA, Macpherson LJ, Wang JW, Zuker CS. The coding of temperature in the *Drosophila* brain. Cell 2011, 144: 614–624.
26. Lahiri S, Shen K, Klein M, Tang A, Kane E, Gershow M, *et al*. Two alternating motor programs drive navigation in *Drosophila* larva. PLoS One 2011, 6:e23180.
27. Klein M, Afonso B, Vonner AJ, Hernandez-Nunez L, Berck M, Tabone CJ, *et al*. Sensory determinants of behavioral dynamics in *Drosophila* thermotaxis. Proc Natl Acad Sci U S A 2015, 112: E220–229.

28. Tian L, Hires SA, Mao T, Huber D, Chiappe ME, Chalasani SH, *et al*. Imaging neural activity in worms, flies and mice with improved GCaMP calcium indicators. Nat Methods 2009, 6: 875–881.
29. Liu L, Yermolaieva O, Johnson WA, Abboud FM, Welsh MJ. Identification and function ofthermosensory neurons in *Drosophila* larvae. Nat Neurosci 2003, 6: 267–273.
30. Hamada FN, Rosenzweig M, Kang K, Pulver SR, Ghezzi A, Jegla TJ, *et al*. An internal thermal sensor controlling temperature preference in *Drosophila*. Nature 2008, 454: 217–220.
31. Kang K, Panzano VC, Chang EC, Ni L, Dainis AM, Jenkins AM, *et al*. Modulation of TRPA1 thermal sensitivity enables sensory discrimination in *Drosophila*. Nature 2011, 481: 76–80.
32. Ni L, Bronk P, Chang EC, Lowell AM, Flam JO, Panzano VC, *et al*. A gustatory receptor paralogue controls rapid warmth avoidance in *Drosophila*. Nature 2013, 500: 580–584.
33. Masuyama K, Zhang Y, Rao Y, Wang JW. Mapping neural circuits with activity-dependent nuclear import of a transcription factor. J Neurogenet 2012, 26: 89–102.
34. Li Q, Gong Z. Cold-sensing regulates *Drosophila* growth through insulin-producing cells. Nat Commun 2015, 6: 10083.
35. Ni L, Klein M, Svec KV, Budelli G, Chang EC, Ferrer AJ, *et al*. the ionotropic receptors IR21a and IR25a mediate cool sensing in *Drosophila*. Elife 2016, 5: e13254.
36. Kwon JY, Dahanukar A, Weiss LA, Carlson JR. Molecular and cellularorganization of the taste system in the *Drosophila* larva. J Neurosci 2011, 31: 15300–15309.
37. Asahina K, Louis M, Piccinotti S, Vosshall LB, A circuit supporting concentration-invariant odor perception in *Drosophila*. J Biol 2009, 8: 9.
38. Frank DD, Jouandet GC, Kearney PJ, Macpherson LJ, Gallio M. Temperature representation in the *Drosophila* brain. Nature 2015, 519: 358–361.
39. Liu WW, Mazor O, Wilson RI. Thermosensory processing in the *Drosophila* brain. Nature 2015, 519: 353–357.
40. Florence TJ, Reiser MB. Neuroscience: hot on the trail of temperature processing. Nature 2015, 519: 296–297.
41. Tomchik SM. Dopaminergic neurons encode a distributed, asymmetric representation of temperature in *Drosophila*. J Neurosci 2013, 33: 2166–2176.
42. Tan CH, McNaughton PA. The TRPM2 ion channel is required for sensitivity to warmth. Nature 2016, 6: 460–463.
43. Song K, Wang H, Kamm GB, Pohle J, Reis FC, Heppenstall P, *et al*. The TRPM2 channel is a hypothalamic heat sensor that limits fever and can drive hypothermia. Science 2016, 353: 1393–1398.
44. Rosenzweig M, Kang K, Garrity PA. Distinct TRP channels are required for warm and cool avoidance in *Drosophila melanogaster*. Proc Natl Acad Sci U S A 2008, 105: 14668–14673.
45. Zhong L, Bellemer A, Yan H, Honjo K, Robertson J, Hwang RY, *et al*. Thermosensory and nonthermosensory isoforms of *Drosophila melanogaster* TRPA1 reveal heat-sensor domains of a thermoTRP channel. Cell Rep 2012, 1: 43–55.
46. Neely GG, Keene AC, Duchek P, Chang EC, Wang QP, Aksoy YA, *et al*. TrpA1 regulates thermal nociception in *Drosophila*. PLoS One 2011, 6: e24343.
47. von PhilipsbornAC, Liu T, Yu JY, Masser C, Bidaye SS, Dickson BJ. Neuronal control of *Drosophila* courtship song. Neuron 2011, 69: 509–522.
48. Tracey WD Jr, Wilson RI, Laurent G, Benzer S. painless, a *Drosophila* gene essential for nociception. Cell 2003, 113: 261–273.
49. Gong Z, Son W, Chung YD, Kim J, Shin DW, McClung CA, *et al*. Two interdependent TRPV channel subunits, inactive and Nanchung, mediate hearing in *Drosophila*. J Neurosci 2004, 24: 9059–9066.
50. Kwon Y, Shen WL, Shim HS, Montell C. Fine thermotactic discrimination between the optimal and slightly cooler temperatures via a TRPV channel in chordotonal neurons. J Neurosci 2010, 30: 10465–10471.
51. Shen WL, Kwon Y, Adegbola AA, Luo J, Chess A, Montell C. Function of rhodopsin in temperature discrimination in *Drosophila*. Science 2011, 331: 1333–1336.
52. Sokabe T, Chen HC, Luo J, Montell C. A switch in thermal preference in *Drosophila* larvae depends on multiple rhodopsins. Cell Rep 2016, 17: 336–344.
53. Jeong YT, Oh SM, Shim J, Seo JT, Kwon JY, Moon SJ. Mechanosensory neurons control sweet sensing in *Drosophila*. Nat Commun 2016, 7: 12872.