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Update article

Molecular mechanism for trimetric G protein-coupled thermosensation and synaptic regulation in the temperature response circuit of *Caenorhabditis elegans*

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ABSTRACT

How the nervous system controls the sensation and memory of information from the environment is an essential question. The nematode *Caenorhabditis elegans* is a useful model for elucidating neural information processing that mediates sensation and memory. The entire nervous system of *C. elegans* consists of only 302 neurons, and their wiring diagram has been revealed by electron microscopy analysis. Here, we review the molecular and physiological mechanisms responsible for the neural circuit-mediated temperature-seeking behavior (thermotaxis) in *C. elegans*. Recent molecular biology studies and optogenetic analyses, such as the optical manipulation of neural activity, and neural imaging have revealed the novel concept of neural calculation. Most significantly, trimetric G proteincoupled thermosensation, single sensory neuron-based memory, and the orchestrated synaptic transmission system have been elucidated.

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1. Thermotaxis behavior of *C. elegans*

Animals can sense and process enormous amounts of environmental information *via* neural circuits. Currently, a major goal of neuroscience is understanding the fundamental molecular and physiological systems needed for neural information processing. The nematode *Caenorhabditis elegans* is a good model organism for studying neural systems because *C. elegans* consists of only 959 cells including 302 neurons (Fig. 1A) (Brenner, 1974; Sulston et al., 1983). A detailed understanding of stereotyped cell positions and the entire cell lineage from the oocyte to adult has facilitated *in vivo* analyses at cellular levels. Electron microscopy (EM) analysis revealed that the *C. elegans* connectome contains approximately 5000 chemical synapses and approximately 600 electrical gap junctions (White et al., 1986). This vast collection of extremely detailed morphological data is a tremendous advantage for studying neural circuits and how they perform calculations.

Although *C. elegans* has simple neural circuits consisting of only 302 neurons, it can sense many environmental stimuli including chemical compounds, mechanical stimuli, light, and temperature. In response to these stimuli, *C. elegans* exhibits a variety of complicated behaviors (Bargmann and Kaplan, 1998; de Bono and Maricq, 2005; Kimata et al., 2012; Sasakura and Mori, 2013). Thermotaxis is one such behavior in which the mechanisms of temperature sensation and learning and memory are essential (Fig. 1B) (Kimata et al., 2012; Mori et al., 2007). After cultivation at a given temperature in the presence of food, *C. elegans* will subsequently seek out and migrate to that cultivation temperature and will confine its migration to a narrow isothermic range on a temperature gradient (Fig. 1B) (Hedgecock and Russell, 1975; Mori and Ohshima, 1995). About thirty-five years ago, Hedgecock and Russell (1975) defined this behavioral phenotype as "thermotaxis". In this review, we discuss how molecular genetics, the optical imaging of neuronal activity and the optical manipulation of neural circuits have recently revealed the molecular mechanisms of thermosensation, memory formation and the dynamics of neural circuitry in the thermotaxis neural circuit.

2. Neural circuit of thermotaxis behavior

To understand the neural processing mechanisms from temperature sensation to behavioral output, it is important to first examine the underlying neural circuit of thermotaxis (Fig. 1C). Mori and Ohshima (1995) proposed a simple neural circuit model for thermotaxis using single neuron laser ablation. In this model, a pair of AFD head sensory neurons sense temperature, and their information is transmitted to three downstream interneurons, AIY, AIZ and RIA (Fig. 1C) (Mori and Ohshima, 1995). RIA is a key interneuron for controlling thermotactic behavioral output because it connects to SMD and RMD, which are motorneurons that regulate muscle expansion and contraction (White et al., 1986) (Fig. 1C). Recent calcium imaging analysis (using a genetically encoded calcium indicator) showed that the intracellular calcium concentrations of AFD, AIY

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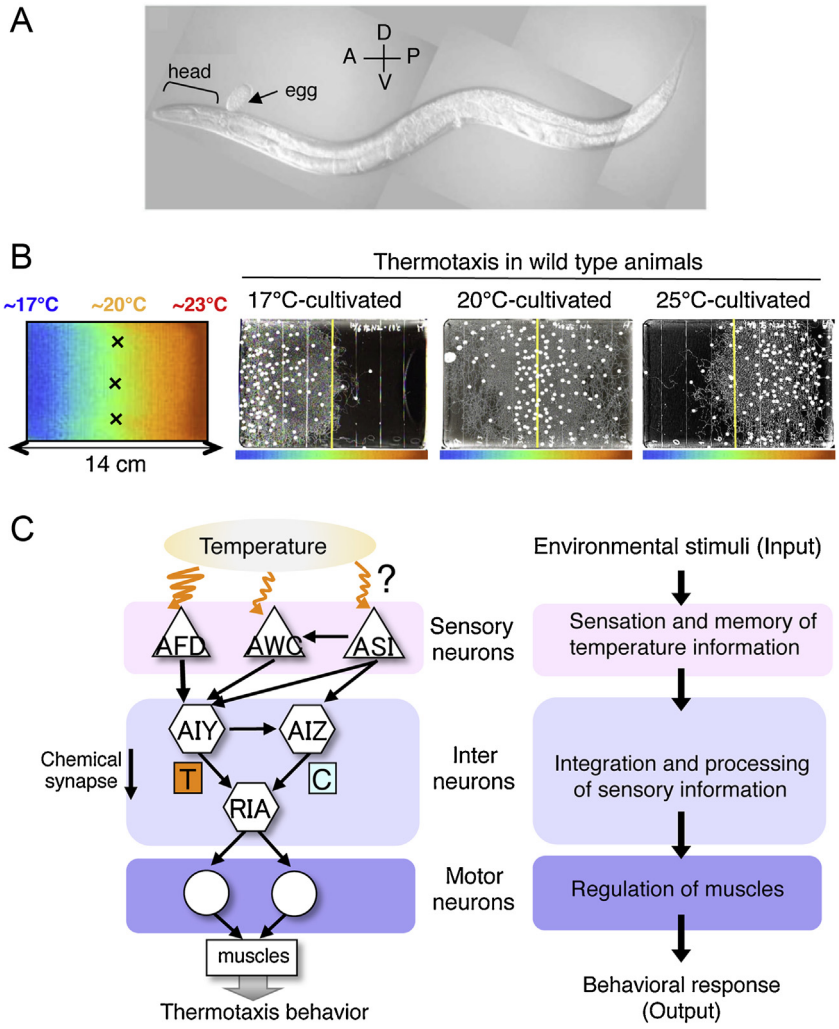

Fig. 1. Thermotaxis behavior in *C. elegans*. (A) Photograph of an adult *C. elegans*. The body length is almost 1 mm. A, P, D and H in the panel indicate anterior, posterior, dorsal and ventral, respectively. (B) Thermotaxis assay plate and its thermal gradient pattern. The left panel shows an assay plate, with a linear thermal gradient ranging from 17 to 23 °C without food. In this assay, worms started from the center of the plate (shown with ×). White dots on the three right panels indicate terminal points of individual worm movements after a 1 h thermotaxis assay. In *C. elegans*, most of the worms that were cultivated at a particular temperature with food migrate to their own cultivated temperature and stay in an area with a similar temperature. (C) A model of the thermotaxis neural circuit. Temperature stimuli are sensed by the AFD, AWC, and ASI thermosensory neurons. Thermal information is transmitted to the AIY and AIZ interneurons and is then integrated in the RIA interneuron. AIY interneurons mediate migration to higher temperature areas (thermophilic, T), and AIZ interneurons mediate migration to lower temperature (cryophilic, C) areas. This diagram is modified from previous reports (Kuhara et al., 2008; Mori and Ohshima, 1995).

and AIZ were elevated in response to temperature stimuli (Fig. 2A) (Biron et al., 2006; Clark et al., 2006; Kimura et al., 2004; Kuhara and Mori, 2006; Kuhara et al., 2008, 2011; Ohnishi et al., 2011). Significantly, temperature-dependent calcium concentration changes that occurred in the AIY were severely decreased in AFD-ablated animals, indicating that the temperature response of AIY is dependent on AFD activity (Biron et al., 2006; Clark et al., 2006).

Molecular genetics and calcium imaging analysis revealed that chemosensory neurons act as temperature-sensing neurons (Figs. 1C and 2B) (Biron et al., 2008; Kuhara et al., 2008). Mutant animals lacking the *eat-16* gene encoding the RGS (regulator of G protein signaling) protein show abnormal migration to a temperature that is colder than the previous cultivation temperature on a thermal gradient (Kuhara et al., 2008). The cryophilic abnormality of the *eat-16* mutant is rescued by expressing a wild-type *eat-16* gene in the AWC sensory neuron, which was originally identified as an olfactory neuron (Bargmann et al., 1993). Calcium imaging analysis showed that the calcium concentration in the AWC was increased by temperature stimuli (Fig. 2B) (Biron et al., 2008; Kuhara et al., 2008). These genetic and physiological results indicate that the AWC chemosensory neuron acts as a thermosensory neuron, and AWC senses two qualitatively different environmental stimuli, temperature and odorants. Recently, another chemosensory neuron (ASI) has been shown to be involved in AFD-dependent temperature processing (Beverly et al., 2011) (Fig. 2C).

3. Memory formation in single sensory neuron

How memory is stored in neural circuits is an important problem. Recent molecular physiology studies revealed that temperature-sensing neurons also act as memory storage neurons in the thermotaxis neural circuit (Kimura et al., 2004; Kuhara et al., 2008; Nishida et al., 2011). When the temperature is raised from 15 to 25 °C by 2 °C increments in a step-like manner, the AFD sensory neuron in wild-type nematodes originally cultivated at 20 °C responds to every increment above 19 °C in calcium imaging experiments (Fig. 2A) (Kimura et al., 2004). When animals were cultivated at 15 °C or 25 °C, the warming response of the AFD neurons exhibited a lower or higher threshold response, respectively, than the ones cultivated at 20 °C (Fig. 2A) (Kimura et al., 2004). A similar

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