The Department of Biosciences and Nutrition

Feeding State Modulates Nociception in Caenorhabditis elegans

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An important function of the nervous system is to respond to changes in the environment. The nematode *C. elegans* chemotaxes towards attractants, and escapes noxious stimuli. Chemotaxis to salts like NaCl requires the two ASE neurons ASEL and ASER, and escape responses require the nociceptive ASH neurons. To study the molecular mechanisms underlying these behaviors, we adopted a combination of behavioral genetics and *in vivo* calcium imaging, which allows monitoring of neuronal activity in living animals.

Calcium imaging experiments revealed that ASEL and ASER are functionally asymmetric. ASEL is an ON-cell activated by increases in NaCl concentration, and ASER is an OFF-cell activated by decreases in NaCl. Activation of ASEL results in forward runs and activation of ASER results in turns. Signal transduction in the ASE neurons involve cGMP signaling, and activation of both neurons require the TAX-2/TAX-4 nucleotide gated channel and the EGL-4 cGMP-dependent kinase. Together ASEL and ASER function to regulate chemotaxis up a concentration gradient, a behavior that is essential for locating food sources.

Calcium imaging allows the monitoring of neuronal activity, but not the study of neurons in isolation from input to other sensory neurons. To enable such experiments, we developed a method called Functional Rescue in Single Sensory Cilia (FRISSC). In FRISSC, a null mutation in the RFX transcription factor DAF-19C, which is required for ciliogenesis, is rescued cell-specifically. This allows restoration of cilia and sensory function in individual neurons. We evaluated FRISSC and tested if the restored cilia are fully functional, by performing calcium imaging. Expression of DAF-19 in a *daf-19* mutant background in ASER, rescued cilia formation and sensory responses in ASER. This demonstrates that FRISSC generates fully functional cilia, and that the rescue is cell-specific and cell-autonomous. Thus, FRISSC is a useful method to study sensory neurons in isolation and to dissect neural circuits.

We used FRISSC in a study concerning modulation of nociception by nutritional status. We found that the nociceptive ASH neurons are enhanced by food through dopaminergic signaling. In a food-rich environment, escape responses to soluble repellents are increased, and the ASH neurons are sensitized. This effect requires sensory input to the dopaminergic neurons and the dopamine receptor DOP-4. Together these results indicate that dopamine functions as a direct signal of food to sensitize the ASH neurons and increase escape responses.

In addition, neuropeptide signaling inhibits nociception in the absence of food. Overexpression analysis revealed that in the absence of an external food source, the FMRFamide-related peptide FLP-8 inhibits responses to soluble repellents. This effect requires the neuropeptide receptor NPR-1, which acts on the nociceptive ASH neurons to increase adaptation to soluble repellents. Thus, FLP-8 and NPR-1 act in the same pathway to signal the absence of food and increase ASH adaptation, and have the opposite effect to dopamine. These results demonstrate that feeding state modulates nociception through a complex network of bioamine and neuropeptide signaling.

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