Molecular Physiology

Pharyngeal Mechanosensory Neurons Control Food Swallow in *Drosophila melanogaster*

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Abstract

Swallowing, an early step in food ingestion, is under rigorous sensorimotor control. While the sensory perception of food viscosity by peripheral sensory organs in *Drosophila* and other animals has been previously studied [1], the role of internal sensory neurons in regulating swallowing remains unclear. This study addresses the molecular mechanisms by which internal sensory neurons monitor food viscosity to regulate swallowing. The authors identified a group of multi-dendritic mechanosensory neurons in the cibarium of *Drosophila*, termed md-C neurons, which express three distinct mechanotransduction channel genes: *nompC*, *Tmc*, and *piezo*. Inhibiting md-C neurons causes difficulty in emptying food from the cibarium, while their activation results in difficulty in cibarium filling. This research provides new insights into the sensory regulation of swallowing.

Text

In *Drosophila*, swallowing is driven by food pumping, which involves the suction and compression of the cibarium, followed by the true ingestion to the foregut [1]. This process consists of two steps: filling, where food is sucked into the cibarium, and emptying, where food is expelled into the foregut [1]. Previous research has shown that 1) pump frequency is largely regulated by food viscosity, rather than sucrose concentration or feeding state [2]; 2) silencing downstream motor neurons affects the rhythm of pumping and ingestion [2]. The authors advanced this knowledge by uncovering the molecular mechanism underlying the sensation of food viscosity and the activation of motor neurons. They identified a group of multi-dendritic mechanosensory neurons in the fly's cibarium, termed md-C neurons, which are essential for swallow control.

Zhang et al. (2024) began by testing the swallowing behavior of mutant homozygotes for three mechanotransduction channel genes (*nompC*, *piezo*, *Tmc*). They found that these flies exhibited a lower pumping frequency than wild-type flies, suggesting that the mechanical force is essential for maintaining the swallowing rhythm. Specifically, mechanosensation regulates the emptying phase of swallowing as the filling/emptying time ratios of the mutants are reduced.

The authors also tested the swallowing behaviors of mutants in response to different food viscosity. Interestingly, when flies were fed food with high concentrations (>1% methylcellulose), flies with mutated *Tmc* or *Piezo* genes exhibited incomplete emptying, while only about 20% of *nompC* mutants and wild-type flies occasionally exhibited

incomplete filling. The divergent phenotypes among different mutants prompted the authors to test double mutants. They found that only *nompC*/*nompC*; *Tmc* mutants showed more severe emptying difficulties compared to single mutants. This finding implies that the *nompC* and *Tmc* genes play non-redundant roles in the swallowing process, deserving further investigation.

Due to the crucial roles of all three mechanosensory channels, the authors focused on the neurons co-expressing these three genes. Using drivers Tmc-GAL4 and nompC-QF, they identified two groups of neurons: md-L neurons located in the labellum (fly tongue) and md-C neurons located in the cibarium. Loss-of-function experiment demonstrates that ablating md-C neurons, instead of the md-L neurons, affects disrupt pump frequency. Additionally, optogenetically activating md-C neurons induced difficulty in cibarium filling, and inhibiting md-C neurons via Kir2.1 caused difficulty in swallowing.
By staining the nuclei, the authors found the somata of md-C neurons are located in the cibarium instead of the brain, suggesting that their dendrites are located in the cibarium to sense food texture, and their axons projects to the subesophageal zone in the brain. To verify the function of md-C neurons, the authors conducted $Ca2^{+}$ and observed increase in fluorescence intensity during swallowing. Additionally, they demonstrated that activating the md-C neurons triggered the activation of the motor neurons MN12/11, indicating that the md-C neurons are upstream of the previously studied motor neurons.

In summary, md-C neurons, which co-express the mechanotransduction channel genes *nompC*, *Tmc*, and *piezo*, are crucial for coordinating the filling and emptying of the cibarium. These neurons receive signals related to food viscosity and transmit them to downstream motor neurons (MN12/11). Inhibition of md-C neurons causes difficulty in food emptying from the cibarium, while their activation leads to difficulty in cibarium filling.

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