Characterization of *Arc1* in Age-Dependent Changes in Sweet Taste Preference

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Abstract:

Deficits in chemosensory processing are associated with healthy aging, as well as numerous neurodegenerative disorders, including Alzheimer's Disease (AD). The fruit fly, *Drosophila melanogaster*, is a powerful model for studying chemosensation, aging, and neurodegeneration, yet the effects of aging and neurodegeneration on chemosensation remain largely unexplored. Previous work in the lab has revealed that taste perception to sugars (not fats) is reduced with age, which also coincides with changes in neural activity and presynaptic structure in sweet taste neurons. Functional genomics of *Drosophila's* taste parts recognized aging-genes, such as Activity-regulated cytoskeleton protein 1 (*Arc1*). *Arc1* is located in the extracellular vesicles and is known for its mRNA binding activity. Overall, this research will characterize the candidate gene, *Arc1* in regulating age-dependent declines in taste preference to sugars and sets the stage for investigating the mechanisms by which sweet taste neurons change during aging.

Background:

Figure 1. Animals, from flies to humans, can recognize a wide range tastants, however the valence of these tanstants changes across the lifespan.

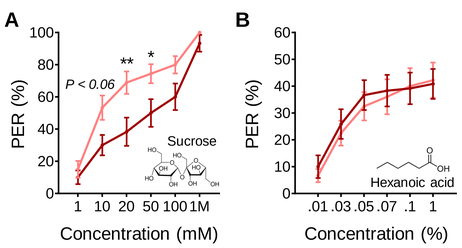


Figure 2. Taste response to sugar **(A)**, but not fatty acids **(B)**, is reduced at intermediate concentrations in aging flies. N = 20-30. *P < 0.05; ** P < 0.01.

10 days 40 days

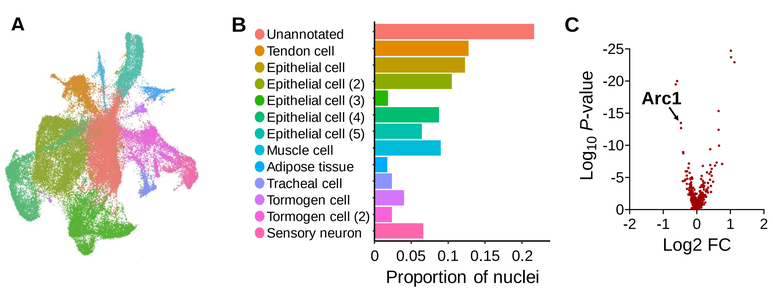


Figure 3. snRNA-sequencing of the labellum in young and aged flies. **(A)** UMAP visualization representing unique clusters. Each color and dot on the plot represent a unique cluster and nucleus, respectively. **(B)** The proportion of nuclei for each broad cell cluster. **(C)** Volcano plot depicting differentially expressed genes within the sensory cluster between 10- and 40-day-old flies.

Hypothesis:

Here, we investigate the role of *Arc1* in *Drosophila* age-dependent decline in specifically taste preference and synaptic function. We hypothesize that if the A*rc1 gene* is required for taste preference to sugars in our fly species, then silencing expression of the *Arc1* gene will reduce behavioral responses to sugar.

Methodology:

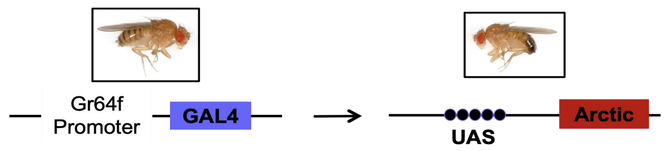
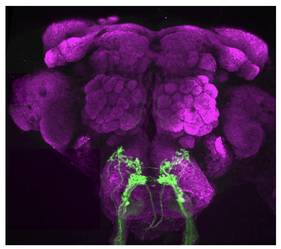


Figure 4. Targeted over-expression of Arc1, using the GAL4-UAS system. Flies expressing the GAL4 protein under the control of the Gr64f promoter are crossed with flies carrying the transgene of interest, in this case Arc1, flanked by the Upstream Activation Sequence (UAS). The resulting progeny expresses Arc1 in cells that also express Gr64f.

Figure 5. Expression of GFP in sweet taste neurons labeled by Gr64f-GAL4. These neurons have axon terminals in the sub-esophagael zone (SEZ), the taste center of the brain, and are responsive to both sucrose and hexanoic acid.



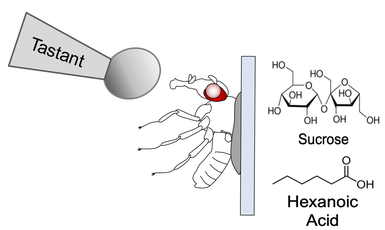


Figure 6. Proboscis extension response (PER). PER was measured in females flies after a 24 hr starvation period. Flies were first satiated with water, then a Kimwipe saturated with either sucrose or hexanoic acid was applied to the fly's labellum for a maximum of three seconds and then removed to observe proboscis reflex.

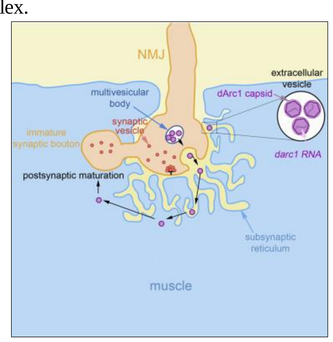


Figure 7. *Drosophila Arc1* mRNA is located inside extracellular vesicles that are trafficked from neuromuscular junction (NMJ) synapses to the muscle to affect synaptic plasticity.

Results:

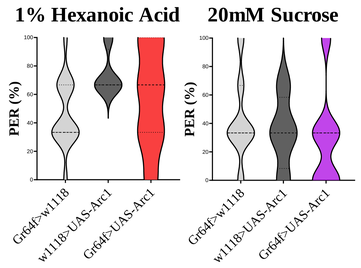


Figure 8. Arc1 overexpression in sweet-taste neurons has no effect on taste preference. N = 4-15.

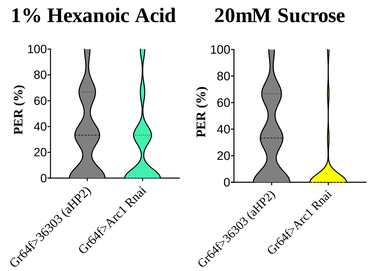


Figure 9. Silencing expression of Arc1 in sweet-taste neurons significantly decreases response to both 1% Hexanoic Acid and 20mM Sucrose. N = 28-30.

Figure 10. Deactivation of all Arc1 neurons has modality specific effects on taste. N = 40-49.

Conclusion:

- The decline in taste response is modality-specific.
- Functional genomics identiified many genes associated with this decline in taste response, including Arc1.
- Follow-up experiments will characterize and functionally validate the effect of A*rc1* on sugar taste perception during aging.

References:

- Brown, E. B., Lloyd, E., Martin-Peña, A., McFarlane, S., Dahanukar, A., & Keene, A. C. (2024).
- Aging Is Associated With A Modality-Specific Decline In Taste. *BioRxiv*. https://doi.org/10.1101/2024.02.01.578408

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