Age-related dysregulation of cAMP signaling in taste circuits in a *Drosophila* model of Alzheimer's disease

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Abstract

Chemosensory dysfunction is an early and common symptom of neurodegenerative diseases, including Alzheimer's Disease (AD), often emerging before cognitive decline. Despite our extensive knowledge of the taste system in mammals and invertebrates, the processes underlying a decline in taste processing with age remain largely unexplored. Using *Drosophila melanogaster* as a genetic model, we examined how aging and AD alter responses to appetitive tastants. Both aging and AD selectively impaired sugar taste response while leaving fatty-acid taste intact, revealing modality-specific dysfunction in taste circuits during neurodegeneration. Sugars and fatty acids activate overlapping populations of taste neurons but utilize distinct second messenger signaling pathways. Sugars activate the cAMP signaling pathway, while fatty acids activate the PLC signaling pathway, suggesting that the age-related taste decline in sugar response may stem from dysregulation in cAMP signaling within these neurons. To test this hypothesis, performed ex vivo functional imaging of cAMP activity in sweet-taste neurons. We observed a dose-dependent decline in cAMP activity in response to Forskolin, a cAMP activator, in aged flies, suggesting reduced cAMP signaling in these neurons. To test whether this loss in taste response can be restored, we increased cAMP signaling in sweet-taste neurons through genetic activation. Chronic Gsalpha overactivation did not restore sugar taste in aged AD flies, indicating that neurodegeneration may disrupt downstream components of the cAMP pathway and damage sweet taste neurons in ways that cannot be rescued by enhancing cAMP alone. By establishing the *Drosophila* taste system as a model for investigating sensory decline in neurodegeneration, these findings provide a basis for mechanistic studies in vertebrate AD models that exhibit similar early chemosensory deficits. Overall, our results shed light on the molecular mechanisms that regulate taste response during aging and neurodegenerative disease.

Background

Proboscis Extension Response

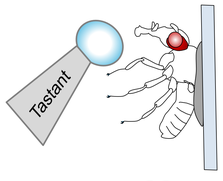

Figure 1. Proboscis extension response (PER) was measured in female flies after 24h of starvation. Tastant was applied to the fly's labellum for a maximum of 2s and then removed to observe the proboscis extension reflex.

Neuronal Expression of Taste Neurons

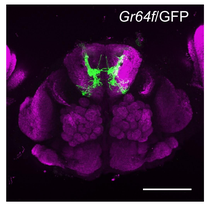

Figure 2. Expression pattern of *Gr64f* visualized with GFP. *Gr64f*-expressing neurons project to the subesophageal zone (SEZ), the taste center of the brain. Background staining is NC82 antibody (magenta). Scale bar = 100 µm.

cAMP Signaling Mediates Sensitivity to Sucrose

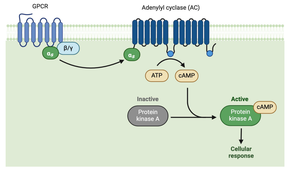

Figure 3. The cAMP pathways is responsible for detecting sugars (A). Diagrams adapted from BioRender.

Results

Sugar taste response declines during aging and AD

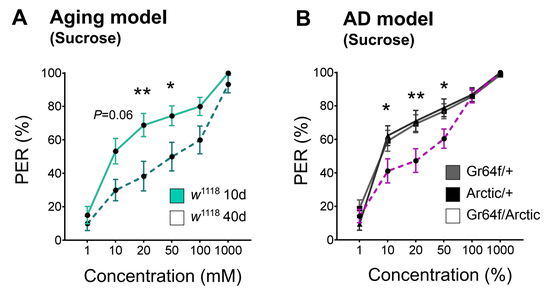

Figure 4. Taste response to sucrose during aging and in an AD fly model. Taste response to sucrose during **(A)** aging and **(B)** in a fly model of AD is reduced at intermediate concentrations.

Ex vivo activation of cAMP in Sweet Taste Neurons

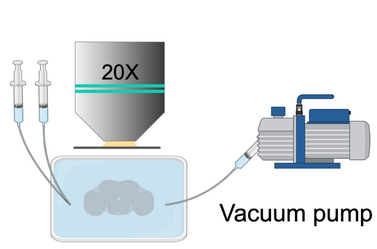

Figure 5. Schematic of ex vivo perfusion system.

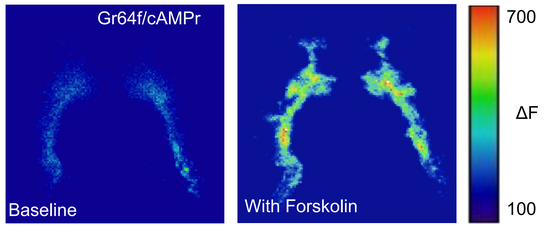

Figure 6. Ex vivo imaging of cAMP activity in sweet taste neurons. Representative images of change in fluorescence in *Gr64f* neurons of young flies in response to 100µM Forskolin

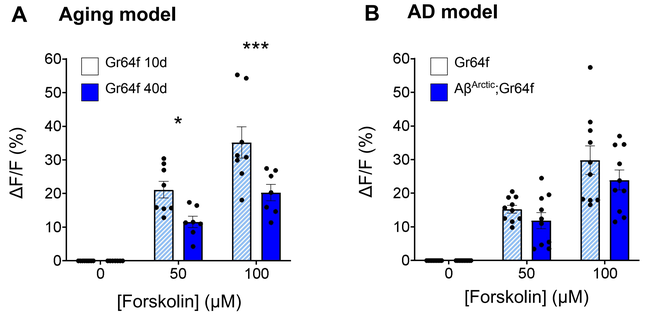

Figure 7. cAMP activity in sweet taste neurons is significantly reduced with during (A) aging, but not (B) in a fly model of AD. cAMP activity was measured in response to application of Forskolin, a cAMP activator.

Results (continued)

Transgenic activation of cAMP during aging

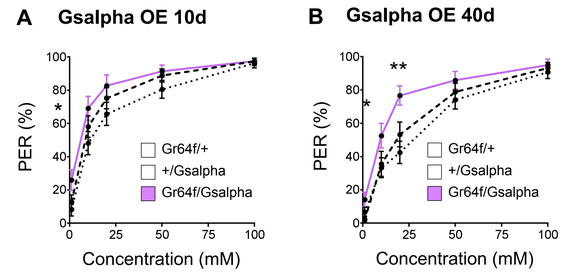

Figure 8. Transgenic overexpression of Gsalpha in sweet taste neurons increases taste response to sucrose in aged flies. Taste response to sugar was measured in **(A)** young and **(B)** aged flies.

Transgenic activation of cAMP during AD

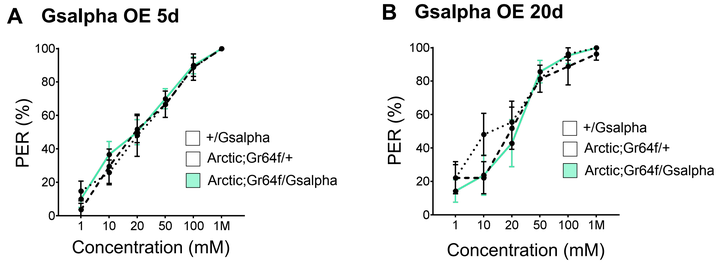

Figure 9. Transgenic overexpression of Gsalpha in sweet taste neurons in an AD model. Taste response to sugar was measured in **(A)** young and **(B)** aged Aβ^{Arctic}-expressing flies.

Conclusions

- Sugar taste response declines during aging and in a fly model of AD.
- Activity of cAMP in sweet taste neurons is significantly reduced during aging, but not in a fly model of AD.
- Transgenic manipulation of cAMP activity via Gsalpha expression increases sugar taste response during aging and AD.
- Overall, these results suggest different mechanisms underlie deficits in sugar taste response during aging and AD.

Acknowledgements

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References

Brown EB, Lloyd E, Riley R, Panahidizjikan Z, Martin-Peña A, McFarlane S, Dahanukar A, Keene AC. Aging is associated with a modality-specific decline in taste. iScience. 2024 Sep 10;27(10):110919.