Role of calcium signaling in \[A\beta42\]-mediated neurodegeneration in a Drosophila model of Alzheimer’s disease

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Alzheimer’s disease (AD) is a neurodegenerative disease that affects more than 5.7 million Americans and is the sixth leading cause of death in the United States alone, where it is the sixth leading cause of death. While there is currently no cure for the disease, it is a highly investigated topic of research. The Drosophila melanogaster eye model is an excellent system to study AD, due to the highly conserved genetic machinery shared between flies and humans. We have developed a transgenic fly model of AD in which we use the GAL4-UAS system to misexpress high levels of human Aβ42 peptides in the photoreceptor neurons in the fly eye. We use this system to determine whether modulating the function of the calcium signaling pathway can modify Aβ42-mediated neurodegeneration. We used RNAi to knock down six components of the calcium signaling pathway: atmRNAi, secrrRNAi, ora5RNAi, inx2RNAi, ip3rRNAi, and plc 21cRNAi in an Aβ42 background in the eye and observed the effects in both eye antenna imaginal discs and adult eyes. Our results showed evidence that knocking down components of the calcium signaling pathway may ameliorate the neurodegeneration mediated by Aβ42. Aberrant calcium signaling has also been implicated in cancer and other neurological diseases besides AD. Our research further implicates intracellular calcium signaling in neurodegenerative disorders such as AD. Further research will determine the molecular mechanisms linking calcium signaling with Aβ42-mediated neurodegeneration.

## Abstract

### Alzheimer’s Disease

- Alzheimer’s disease (AD) is the sixth leading cause of death in the United States and has no known cure.
- More than 5.7 million Americans have AD.
- Throughout the brain normal deposits of proteins form amyloid plaques and tau tangles.
- This leads to neuronal cell death.

### Why use Drosophila?

- Many genes are conserved between flies and humans.
- Flies have less genetic redundancy:
  - Basic cell biological pathways are nearly identical in flies and humans (eye and brain)
  - Flies have less genetic redundancy.
- Ideal human disease model for genome wide genetic screens.

### Experimental design

**Approach:** Use RNAi to knock down components of the calcium signaling pathway in flies expressing Aβ42 in retinal neurons and determine the effects on the eye-antennal imaginal disc and adult eye.

### Results

- Calcium is an important component for cellular signaling. Multiple pathways control calcium concentration within the given areas.
- Alzheimer’s associated peptide amyloid beta disrupts many pathways involved in calcium signaling leading to higher calcium concentration in the cytoplasm.
- The higher cytosolic calcium concentration potentially leads to mitochondrial dysfunction and apoptosis.
- This contributes to the development and progression of Alzheimer’s disease.

### Future directions

- Downregulating the levels of expression of the six components (atmRNAi, secrrRNAi, ora5RNAi, inx2RNAi, ip3rRNAi, and plc 21cRNAi) of the calcium signaling pathway demonstrated evidence of rescue of the Aβ42 phenotype in fly eye (animals reared at 29°C).
- Our results suggest that inactivation of calcium signaling pathway may block Aβ42-mediated neurodegeneration.
- This has relevance for design of treatments for AD.
- **Significance:** Our studies show a role for calcium signaling pathway in neurodegeneration disorders such as Alzheimer’s.

### Conclusions

- Misexpress proteins involved in calcium signaling in flies expressing Aβ42 and determine the effect on adult eyes and eye discs.
- Determine the mechanism of action by which the intracellular calcium signaling pathway is involved in the progression of Alzheimer’s disease.

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