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Understanding the link between sugar diet and Alzheimer’s Disease using Drosophila eye model

Jordan Dubbs1, Ian Tobal1, Neha Gogia1, Ankita Sarkar1, Akanksha Raj1 and Amit Singh1,2,3,4

1) Department of Biology, University of Dayton, 300 College Park Drive, Dayton, OH; 2) Premedical Program, University of Dayton; 3) Center for Tissue Regeneration & Engineering (TREND), University of Dayton, 300 College Park Drive, Dayton, OH; 4) Center for Genomic Advocacy (TCGA), Indiana State University, Terre Haute, IN, USA.

Abstract

Alzheimer’s disease (AD), is a progressive neurodegenerative disorder and is the sixth leading cause of death in the United States (US), with no cure to date. It is caused by abnormal cleavage of amyloid precursor proteins (APP), generating amyloid-beta 42 (Aβ42) plaques that trigger neuronal cell death by unknown mechanism(s). Neuroinflammation (body’s response to repair, damage and defend against foreign agents) is another characteristic feature of this disease. According to US Department of Agriculture (2017), an average American consumes 94 g of sugar per day which is equivalent to amount of sugar in 2.4 cans of coke. The impact of this high amount of blood sugar can be very significant as breakdown of glucose in high-sugar diet damages the enzymes that regulate inflammation (in immune responses), resulting in mis-regulated neuroinflammation, strokes, and chemical imbalances, and thus may contribute towards AD. In our study, we want to elucidate the effect of both high and low sugar diet on Alzheimer’s. To test our hypothesis, we have used Drosophila melanogaster (a.k.a. fruit fly), (as genetic machinery is conserved from flies to humans) and developed a fly model of AD, where human Aβ42 peptides can be misexpressed in Drosophila eye using GAL4/UAS system. We placed flies expressing human Aβ42 in eyes as well as the central nervous system on regular, low, and high sugar diet. We examined the phenotypes in eye, imaginal discs and adult flies. We also performed a series of behavioral assays to understand the impact of these different diets. Our study shows, that a high-sugar diet displays a more aggressive progression of AD as compared to a normal diet or a low-sugar diet. This research has significant bearings in understanding the potential link between AD and diabetes, as both are very prominent diseases in today’s world.

Aim of Research

- The average American consumes more than three times the recommended sugar intake (USA 2017).
- It is known that high blood sugar negatively impact the brain.
- The precise relationship between Alzheimer’s Disease and Diabetes remains unknown.
- Finding the connection between these two diseases is crucial.

Alzheimer’s Disease and Diabetes

- AD
  - Progressive neurodegenerative disorder
  - Caused by mis-cleavage of the Amyloid Precursor Protein
  - No cure to date
  - Linked to insulin resistance and inflammation
- Diabetes
  - Impaired ability to produce or respond to insulin hormone
  - Irregular metabolism and higher levels of glucose in blood
  - May be linked to internal inflammation

Drosophila melanogaster

- Short life cycle
  - 10-14 days in 25ºC
  - 8-10 days in 29ºC
- Express Alzheimer’s Disease phenotype in eye
- Nearly 75% of fruit fly genetic machinery is conserved in humans

Experimental Plan

- Phenotypic Analysis
  - Normal Diet
  - High Sugar Diet
  - Low Sugar Diet

- Behavioral Assay: Climbing Test
  - Determine how many flies cross the bar in a given amount of time

The GMR>Aβ42 x Gal 4 Elav flies on the high sugar diet performed worse on this assay than the control flies and the low sugar diet flies.

Conclusions

- Our results show that the amount of sugar in a diet does impact the progression of Alzheimer’s Disease to a certain degree.
- High sugar diet seems to worsen the effects of AD more than the normal or low sugar diet.
- The 597 x pac-AM6 flies that were given the high sugar diet displayed higher levels of punctum 2 expression in the eye imaginal disc. Pac-AM6 is a factor involved in the c-Jun N-terminal kinase (JNK). This pathway is heavily implicated in apoptosis.
- This leads us to believe that when given a high sugar diet the flies with Alzheimer’s Disease experienced greater amounts of cell death.

Future Directions

- Collect ecdysone and life span data
- Confocal imaging
- 597 x pac-AM6, N1, H3 and Wnt
- Investigate up/down regulation of genes of interest
- Introduce new genes that may lead to eye rescue

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