How The Amino Acid L-Serine Provides Neuroprotection Against L-BMAA Induced Alzheimer's Disease

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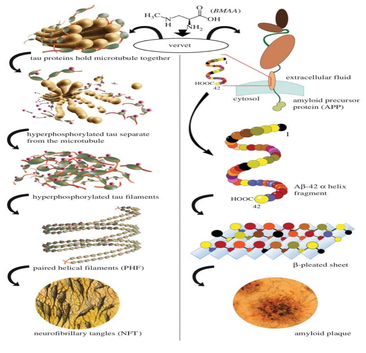
Abstract

More than 6 million people in America are living with Alzheimer's Disease (AD) and there are no cures or treatments. It is time to move on from the β-amyloid hypothesis and broaden AD research. New research is suggesting that dietary exposure to a cyanobacterial toxin known as L-BMAA is causing neurodegenerative diseases such as AD, ALS, and Parkinson's Disease. L-BMAA is misincorporated during protein folding, in place of the proper amino acid, L-Serine. It has been shown that the naturally occurring amino acid, L-Serine, can provide neuroprotection against L-BMAA, but the mechanism by which L-Serine infers this protection is unclear. This thesis will examine how the amino acid L-Serine can be used as a preventative measure against L-BMAA-induced Alzheimer's Disease. Both articles by Dunlop et al., 2018 have shown that L-Serine provides neuroprotection by diluting the cell and decreasing the probability that L-BMAA is misincorporated, and also by increasing the unfolded protein response. In both studies, QPCR and Western Blotting were used to study what genes and cellular pathways both L-Serine and L-BMAA activated. As more researchers begin to move away from the β-amyloid hypothesis, it is important that we broaden our research horizons and work with other disciplines within the scientific community. By studying AD from different angles, a better understanding of AD will be gained, potentially offering other therapeutic approaches to treating AD.

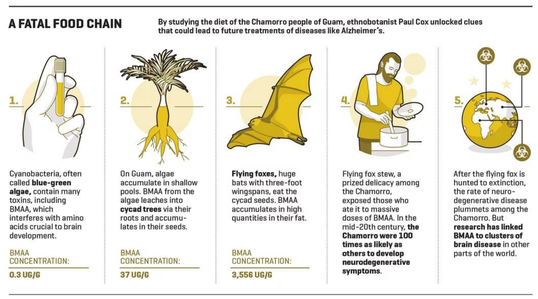
Introduction

- Alzheimer's Disease (AD) was discovered over 100 years ago, but we have yet to develop a cure or effective treatment (Goedert & Spillantini, 2006).
- 30 years ago the β-amyloid hypothesis was proposed as a mechanism to understand AD, but it has become a dead end (Goedert et al., 2006).
- New research has shown that the cyanobacterial toxin, L-BMAA, causes neurodegenerative diseases such as AD, ALS, and Parkinson's Disease (Cox et al., 2016).
- It has been shown that the amino acid L-Serine provides neuroprotection against L-BMAA thus protection against AD (Metcalf et al., 2018).
- The mechansim by which L-BMAA causes neurodegeneration is understood, but less is known about how L-Serine provides protection (Dunlop et al., 2018).
- New research suggests that L-Serine provides neuroprotection by elevating the UPR response within cells (Dunlop et al., 2018).



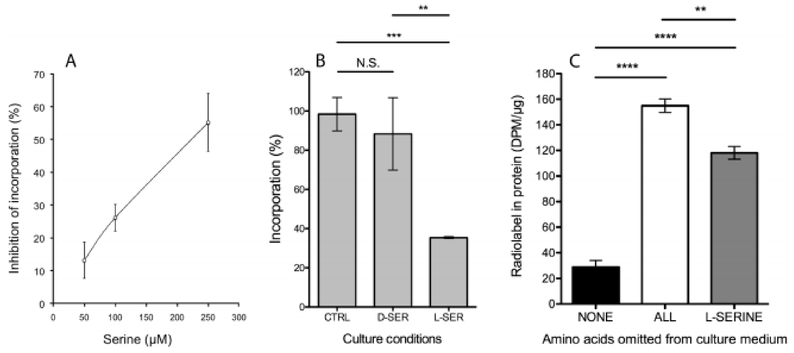
The diagram to the left displays the process of NFT and β-amyloid plaque formation (Cox et al., 2016).

Stepwise Process of the Consumption of L-BMAA by the Chamorro People of Guam



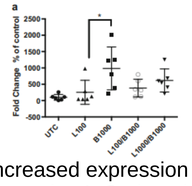
L-BMAA concentration increases as the toxin is transferred from cyanobacteria, to cycad seeds, to flying foxes.

L-Serine Mediated Inhibition of L-BMAA Incorporation



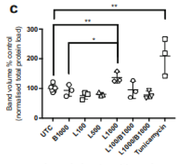
L-Serine significantly inhibited the incorporation of L-BMAA when compared to other treatments.

ATF4 Expression in SY5Y Neuroblastoma Cells After Being Treated With Combinations of L-Serine and L-BMAA



L-BMAA increased expression of ATF4 when compared to L-Serine, thus suggesting L-BMAA activated the PERK pathway.

PDI Levels in SY5Y Neuroblastoma Cells After Being Treated With Combinations of L-Serine and L-BMAA



Cells treated with L-Serine had significantly higher levels of PDI protein when compared to controls and L-BMAA.

Conclusions

- L-Serine and L-BMAA modulated numerous amounts of the same genes and they follow similar cellular pathways (Dunlop et al., 2018).
- L-Serine increases translation of the ER chaperone PDI, which plays an important role in the UPR.
- PDI helps break down misfolded proteins through endoplasmic reticulum-associated degradation (ERAD).
- By activating ER stress and triggering the UPR, L-Serine could be priming cells to respond to neurotoxic stress pre-emptively.
- L-Serine could be conferring this protection by acting as a proteostasis regulator (PR).
- As a PR, L-Serine helps cells quickly respond to oxidative stress thus favoring a quick return to homeostasis.
- By upregulating the UPR, heat shock genes, and transcription factors, L-Serine primes cells to respond rapidly when exposed to a neurotoxin.

Future Directions

A phase II clinical trial is already underway to approve L-Serine as a treatment for Alzheimer's Disease. The next step would be getting L-Serine approved for a phase III clinical trial. In addition to AD, L-Serine has been show to be neuroprotective against other NDs such as ALS, and Parkinson's Disease. If it could be shown that L-Serine can be used as a neuroprotectant against all of these diseases, we would then have a cheap and natural way to fight ND.

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