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Modifying the Effects of Aβ40 and Aβ42 Proteins in patients with Alzheimer's Disease

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BIOL 488 – Senior Capstone
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Background Information/ Introduction

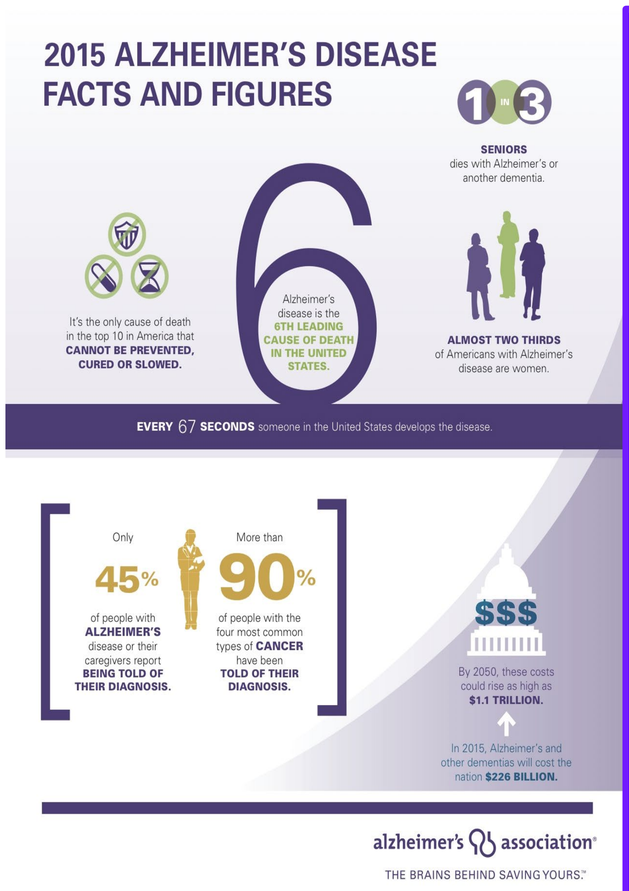

Figure 1. Alzheimer's Disease Facts
Alzheimer's Disease affects 1 in 3 seniors, and is the 6th leading cause of death in the United States.

- Alzheimer Disease is the most common cause of Dementia, which slowly deteriorates the brain.
- Tangles and Plaques are two major components in the process of Alzheimer's.
- Plaques and Tangles interfere with neuron signaling in the brain, which can lead to memory impairment.
- There are two specific groups of AD. Familial, which is early onset and Sporadic, which is late onset.
- Amyloid-Beta 40 (Aβ40) and Amyloid-Beta 42 (Aβ42) are responsible for neurodegeneration and age-dependent learning defects.

Specific Aim: My specific aim is to modify Amyloid-Beta 40 (Aβ40) and Amyloid-Beta 42 (Aβ42). This is so the proteins will not interfere with neuronal signaling. This modification should act as a therapy for patients.

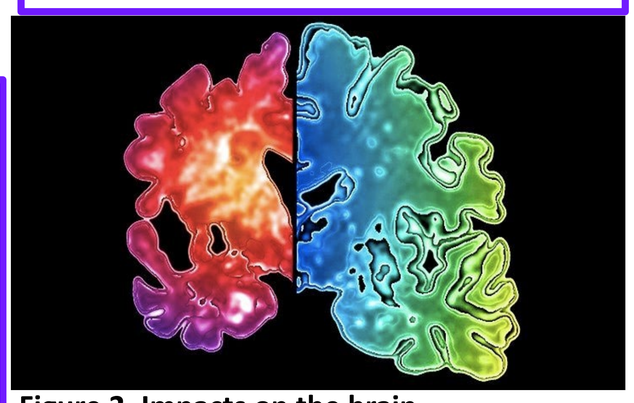

Figure 2. Impacts on the brain
On the left side, this figure displays the atrophic affects of Alzheimer's Disease. The right side displays a healthy brain.

Experimental Results

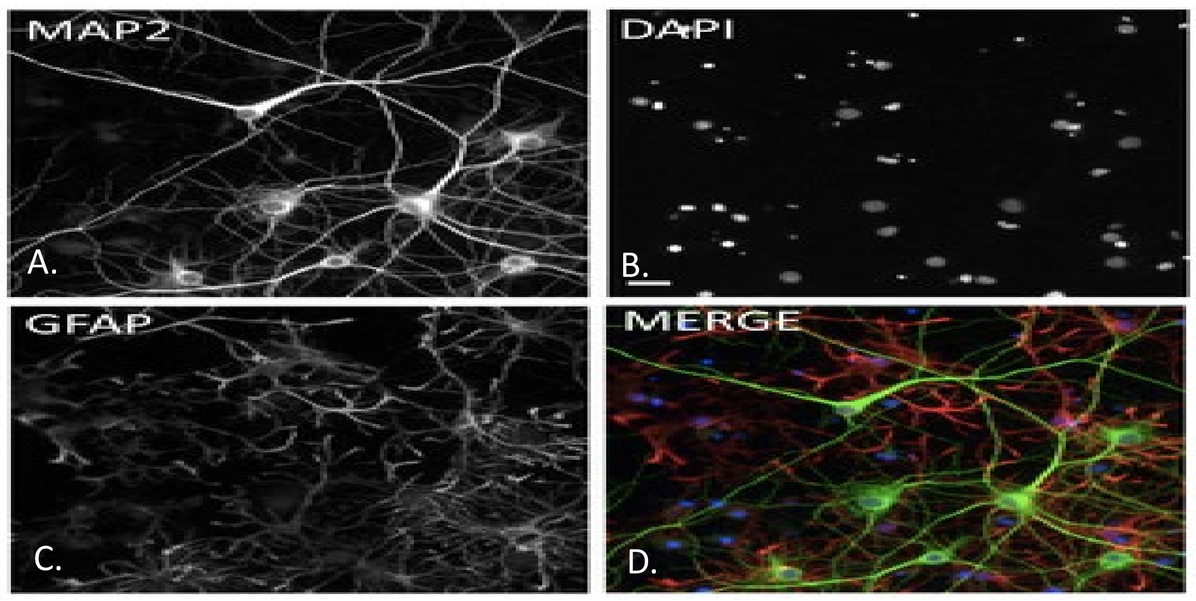

Figure 3. Hippocampal/cortical cultures immunofluorescent labeling.
A. Labeled MAP2 neurons. **B**. Labeled DAPI nuclei. **C**. Labeled GFAP glia and Nuclei. **D**. This image displays the merging parts of all three images. The percentage of neurons was 26.0 ± 1.1% in the cultures. This was based on the untreated control wells. (Izzo 2014) The primary rat neurons can replicate the electrophysiological state-dependent signaling.

A.. **B.**

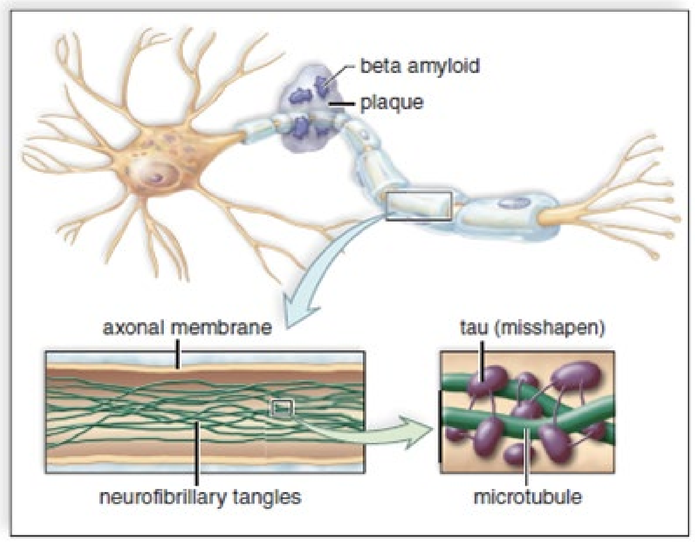

Figure 4. Plaques and Tangles
These illustrations display the process of how plaques and tangles function in the brain. **A.** The top picture shows where plaques are located on the nueron. The bottom picture shows how tau are attached to the microtubules. **B.** This illustration shows the atrophic affects of the brain from plaques and tangles.

Proposed Methodology

Neuronal Cultures
- Collect rat embryos and extract their Hippocampus and Cortical tissue. Add 2.5% Trypsin to dissociate the cells. Place cells in 384-poly D-Lysine coated plates with Neurobasal Media, Glutamax, and antibiotics

Trafficking Assay
- With the compounds and Abeta40 & Abeta42 oligomer preparations, treat the neurons. Incubate at 37 Celsius in 5% of CO2 for 24 hours. Add Tetrazolium salts to the final concentration of 0.75 mm. Incubate the solution for 60 minutes.

Preparations for Amyloid Oligomers
- Evaporate the 1,1,1,3,3,3,hexafluoro-2-propanol from a solution of 0.253 mg Abeta 40/42 to prepare Abeta monomer film. Dissolve film in DMSO and dilute to 100 mM with cold Basal Media Eagle media. Incubate at 4 degrees Celsius to make oligomers.

Abeta Binding Assay
- For Synthetic Abeta 40/42 oligomer preparation, add oligomers an hour prior to the compounds. For 15 minutes, fix the cells with 0.5% of Triton X-1003, .75% formaldehyde and block with 5% goat serum. Incubate with the primary antibodies for Synaptophysin-1, glial fibrillary acidic protein and Abeta, MAP-2.

Synapse Counting Assay
- Before adding 6 mM of synthetic Abeta 40/42 oligomers, treat cultures with compounds. Then, incubate for 24 hours. Use the ThermoFisher/Cellomics Neuronal Profiling bio application to count the synaptophysin-immunopositive puncta .

Statistical Assay
- The well averages will be looked at with the KS distance test. The Abeta 40/42 oligomers will be observed with the Western Blot Analysis. The treatment differences will be looked at with One-way ANOVA.

Discussion/ Conclusions

Potential Pitfalls:
- Creating a therapy could cause issues with patients.
- There could possibly be failure to provide therapeutic benefits for patients with Alzheimer's Disease.
- There could also be a failure in therapy if the patient has undergone too much neuronal loss.

Potential Conclusions:
- The symptoms of neurodegeneration could decrease with modifications done to the Amyloid Beta-40 and 42 proteins.
- This could serve as a therapy for AD patients and save people from losing their memory entirely.
- A cure still hasn't been found for Alzheimer's, so it's important to continue researching this insufferable disease.

Literature Cited

Izzo NJ, Staniszewski A, To L, Fa M, Teich AF, Saeed F, et al. (2014) Alzheimer's Therapeutics Targeting Amyloid Beta 1–42 Oligomers I: Abeta 42 Oligomer Binding to Specific Neuronal Receptors Is Displaced by Drug Candidates That Improve Cognitive Deficits. PLoS ONE (11):1-19.
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