Support for the Amyloid Cascade Hypothesis in Guiding Further Avenues of Treatment in Alzheimer's Disease

Brendan Kortjohn and Marc Nahmani
Division of Sciences & Mathematics, University of Washington, Tacoma | Tacoma, WA 98402

ABSTRACT

Alzheimer's disease currently affects 50 million individuals and is expected to increase to 150 million by 2050. Despite this, the neurodegenerative disease still has minimal treatments, and there is only one FDA approved drug that has shown any slowing in cognitive decline. This drug, Aduhelm, attacks the amyloid-beta plaques that form in Alzheimer's, evidence supporting the predominant theory in Alzheimer's pathogenesis, the Amyloid Cascade Hypothesis (ACH). However, there are conflicting reports about whether evidence supporting Aduhelm warranted FDA approval. Some scientists suggest that the underlying pathology of Alzheimer's is via tau, which involves the accumulation of neurofibrillary tau tangles that progress to the disease's diagnostic lesions. To determine if degrading amyloid plaques is the most beneficial path of treatment, I conducted a comprehensive literature review of current Alzheimer's research and understanding of how the disease is treated. This review found that the ACH should remain the prevailing theory based on Alzheimer's progression, indicating that amyloid plaques are necessary to induce the phosphorylation crucial to the development of tau tangles. This data suggests that Alzheimer's disease develops via an amyloid induced tau-pathology. In addition, a multitude of other treatments have been shown to reduce these plaques as well along with Aduhelm, which renews promise in using the ACH to develop treatments. Using the ACH as a guide and implementing the treatments listed in this paper, new drugs like Aduhelm target the perpetrator of Alzheimer's and may stop or reverse progression to more severe presentations of the disease.

WHAT IS ALZHEIMER'S DISEASE (AD)?

- Alzheimer's Disease (AD) is the most common form of dementia
- Neurodegenerative, attacks and degrades neurons leading to cognitive decline
- Currently around 50 million people affected, expected to rise to 150 million by 2050
- Deaths attributed to AD rose by 89% from 2000-2014, whereas deaths related to heart disease and pulmonary disease decreased in that same timeframe

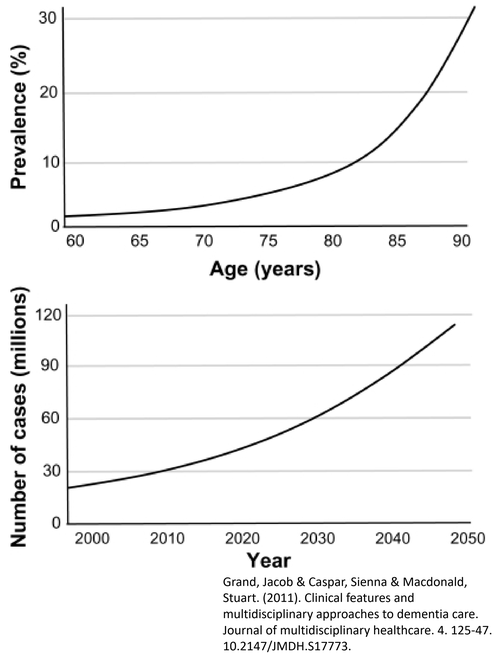
MOTIVATION

- I have always viewed the brain as a puzzle, and the amount of understanding that we have of it compared to other organs in the body is fascinating to me
- There is a genetic factor to AD, and I know that I am at increased risk due to the disease running in my family, so I was interested to see how the disease functioned

METHODOLOGY

- Completed a comprehensive literature review going over the current understanding and treatment of AD
- Reviewed articles from neuroscience, biology, and PubMed and compiled them into a paper to form conclusions

ALZHEIMER'S PREVALENCE AND SEVERITY



Grand, Jacob & Caspar, Sienna & Macdonald, Stuart. (2011). Clinical features and multidisciplinary approaches to dementia care. Journal of multidisciplinary healthcare. 4. 125-47. 10.2147/JMDH.S17773.

Figure 1 – Worldwide data showing the trend of Alzheimer's prevalence in the general population as a function of age, and the total number of cases of the disease by year.

HOW DOES AD WORK?

- Characterized by tau neurofibrillary tangles and amyloid-beta (Aβ) plaques
- Mechanism historically viewed via "Amyloid Cascade Hypothesis"
- Dysregulation of protein causes harmful species of Aβ to form
- Tau protein normally promotes stability, becomes unbound

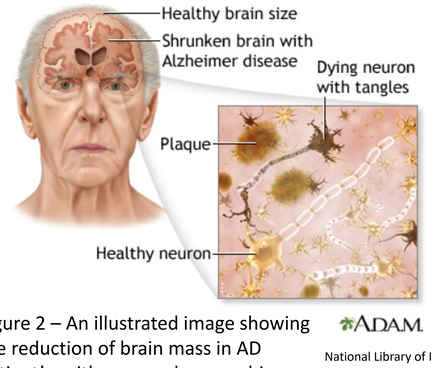


Figure 2 – An illustrated image showing the reduction of brain mass in AD patient's, with a secondary graphic showing the anatomy of Aβ plaques and tau tangles.

National Library of Medicine, 2023, https://medlineplus.gov/ency/article/000760.htm

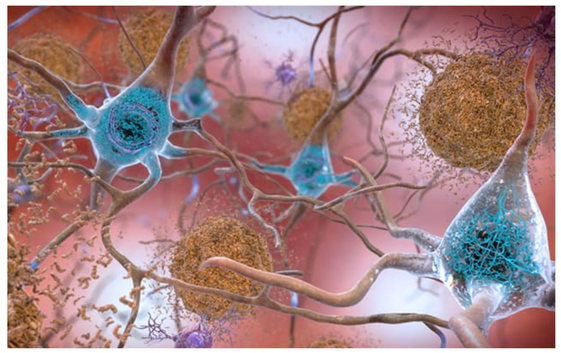


Figure 3 – Artist interpretation of neuronal soma (blue) with aggregates of Aβ (yellow/brown) accumulating on the neurons resulting in degradation.

National Institute on Aging, NIH, 2017

CRITICISMS: β-AMYLOID VS TAU TANGLES

- Some scientists became frustrated with slow clinical progress via treating Aβ plaques, suggested pivoting to tau pathologies
- Until very recently, treatments only alleviated symptoms, but none showed any reversing or slowing effects
- Aduhelm was created, which is currently the only drug approved that shows any slowing of cognitive decline

FINDINGS

- AD was reexamined is now thought to function via a **"amyloid-mediated tau pathology"**
- Multiple factors have been shown to reduce Aβ plaques, such as:
  - Hormone treatments (testosterone/estrogen)
  - Butyrylcholinesterase inhibition
  - Oxidative stress
- These treatments are a combination of preemptive and corrective
- Aduhelm, the only drug shown to have slowed effects of cognitive decline, operates on Aβ plaques

NEXT STEPS

Next steps based on this paper include:

- Observing the interactions between the management techniques of Aβ listed earlier in this paper
- Due to the poor progression from mouse-based trials to human-based trials in Alzheimer's research, clinical trials should be prioritized as further attempts to treat the disease via Aβ are pursued

ADUHELM

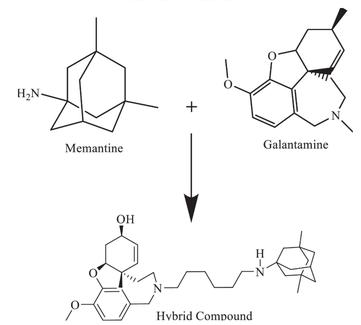


Figure 4 – One of the chemical reactions that contributes to the synthesis of Aduhelm, with memantine and galantamine reacted together to form a hybrid compound.

Rouchan Ali, Ghanshyam Das Gupta, Pooja A. Chawla, Aducanumab: A new hope in Alzheimer's disease, Health Sciences Review, Volume 4, 2022, 100039, ISSN 2772-6320, https://doi.org/10.1016/j.hsr.2022.100039.

CONCLUSIONS

- The Amyloid Cascade Hypothesis has been shown to have curative effects (i.e., the restoration of neurological function) via the novel drug Aduhelm
- Findings heavily debated on whether they warranted FDA approval, however this mechanism has produced results
  - Due to less then significant findings
- Comparative to other avenues such as tau treatments, which have not shown any slowing effects
- This progress shows that the Amyloid Cascade Hypothesis should continue to guide treatments
- Other factors should be taken into account, as they help to reduce Aβ plaque aggregation
- Importance should still be placed on clinical trials

REFERENCES

FLOWCODE PRIVACY.FLOWCODE.COM