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Are Tau Therapies a Treatment Possibility in Alzheimer's?

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Abstract

Introduction:

Currently, Alzheimer's disease has two main hallmarks, amyloid plaque formation which proceeds the presence of neurofibrillary tau tangles. Amyloid is the main therapeutic target in clinical trials to improve cognition in Alzheimer's disease. Despite promising outcomes in animal models amyloid targeting therapies failed to reduce cognitive impairment in humans. Why exactly this is remains unclear although there are fundamental problems with the amyloid cascade hypothesis, the trial designs, particularly primary outcome measures and how animal models relate to human disease. It is possible that tau is a bigger driver of toxicity than previously believed, with several trials in tau targeting therapies now underway hoping to bring positive results. For this to be successful these trials must overcome the shortcomings of amyloid targeting trials to create appropriate targets with meaningful outcomes for patients. This article explores the notion that tau-targeting therapies could hit the same barriers as the amyloid hypothesis.

1 Introduction

Alzheimer's disease (AD) is a global health crisis with an increasing incidence arising from the ageing population. Symptomatic therapies exist however the prognosis remains unchanged despite ongoing research. The continued development of future disease modifying therapies is based on the two main features of AD; histopathological accumulation of amyloid plaques and hyperphosphorylated neurofibrillary tangles (NFTs) eventually leading to neuronal death and brain atrophy.

It was widely accepted that amyloid plaque formation is the driving force of AD, which precipitates NFT formation and toxicity later in the disease although the exact interactions between amyloid and tau are unknown. This was supported by familial variants of AD in which proteins involved in the amyloid processing cascade contain mutations, with the APOE4 allele being the single biggest risk factor for AD. Reasonably, there have been many attempts to reduce or 'detoxify' amyloid plaque as a therapeutic target. Despite promising outcomes in mice models and phase 1 testing, amyloid targeting therapies including Bapinezumab and Solanezumab monoclonal antibodies have failed to reduce cognitive impairment in humans (Huang, Chao, & Hu, 2020; van Dyck, 2018).

To understand why the trials have failed one must ask several questions:

1) Is amyloid truly the correct target? Indeed, amyloid is present in normal ageing demonstrating a disconnect between load and clinical symptoms and is greatly conserved over an

evolutionary timescale suggesting an unknown function.

2) Is the intervention too late? Trials recruit patients already displaying signs of mild cognitive impairment (MCI) and a patient presenting in clinic has already laid down all of the plaque they are going to produce and are now experiencing atrophy.

3) Are the primary outcomes in clinical trials appropriate? If the patient has cerebral atrophy, is it reasonable to expect cognition to improve after therapeutic administration, or is cessation/slowing of decline more appropriate? (Whitehouse, 2014).

2 Tau

Tau is a microtubule-associated protein implicated in microtubule stability and dynamic regulation of the axonal transport apparatus (Medina, Hernández, & Avila, 2016). Tau has been proposed to mediate AD pathology via intracellular and extracellular mechanisms. Intracellular mechanisms include the aggregation of tau by hyperphosphorylation, producing NFTs detected on histology at autopsy in AD as well as other tauopathies such as progressive supranuclear palsy (PSP). Secondly, three repeat (3R) and four repeat (4R) tau isoforms are balanced physiologically. The switch to an excess of 4R tau has been implicated in disease. Extracellular tau oligomers may escape the cell independently of cell death which is associated with synaptic decline in AD and tau spread throughout the brain (Sebastián-Serrano, Diego-García, & Díaz-Hernández, 2018).

Given the lack of success with amyloid targeting therapies there is now a discussion on whether tau is a bigger driver of toxicity, with trials in tau targeting therapies such as Tideglusib, Methylene blue and Davunetide now underway (Congdon & Sigurdsson, 2018). Will research in tau-targeting therapies hit the same barriers as amyloid-targeting ones? This is analysed by addressing the implication of tau in AD at the level of: topographical distribution; relationship with atrophy; tau in normal ageing and cognitive decline and the outcomes of tau therapies.

3 Methods

Articles cited have been obtained from PubMed using syntax: Alzheimer's disease, therapy, tau, amyloid-beta. Inclusion criteria included: peer reviewed; clinical diagnosis of AD or MCI in human studies; primary research data and reviews. Exclusion criteria included dissertations, abstracts, editorials and unpublished comments. 26 papers were chosen in an initial search with 16 fitting this criteria.

4 Results and discussion: Tau as a therapeutic target

4.1 Tau in AD, MCI and normal ageing

Tau in the cerebrospinal fluid (CSF) may not be more predictive of AD progression than amyloid, with increased correlations with cognitive impairment (Brier et al., 2016; Kandimalla et al., 2013). A drawback from the amyloid hypothesis is its presence in normal ageing. A study by Lowe et al., (2018), studied widespread association in tau with ageing, MCI and AD using positron emission tomography (PET)(Lowe et al., 2018). Similarly, to amyloid, the authors found tau globally present in cognitively unimpaired individuals as part of a normal ageing process, however there was elevated tau in patients with MCI and AD in comparison to cognitively unimpaired individuals. Other studies support this, finding globally elevated tau with MCI and AD, with a higher load in AD (Sabbagh et al., 2010). Although presence of tau in normal ageing demonstrates it is unlikely tau infers toxicity alone, these studies suggests a potential NFT burden accumulating prior to clinical symptoms. Indeed, in the Lowe et al., (2018) study cognitively impaired individuals had a higher load of NFTs at a younger age further supporting this notion (Lowe et al., 2018). Tau is therefore a logical target at this stage as it accumulates before MCI and is more predictive than amyloid for progression.

4.2 Topographical distribution and atrophy

Learning and memory are the most affected aspects of cognition in AD which is performed by medial temporal lobe structures such as the hippocampal cortex and the entorhinal cortex. These are most affected by atrophy in AD. Therefore, it would be reasonable to expect pathological mechanisms to be taking place here. There is also global damage for example in occipitotemporal regions (reduced ability to read and write) and in frontal lobes (social behaviour and decision making) (Fitzgerald M.J.T, Gregory Gruener, 2012).

Although tau is found globally in normal ageing, differing distribution may be a driver in disease and be more closely linked to clinical symptoms than amyloid. Indeed amyloid deposition appears to develop in the isocortex, with lower effects on subcortical structures (Lane, Hardy, & Schott, 2018). The topographical distribution of tau throughout the brain can be classified into Braak staging (Braak & Braak, 1991; Braak, Alafuzoff, Arzberger, Kretzschmar, & Tredici, 2006).

Table 1.

Stage	Brain regions involved
Stage I and II: Transentorhinal Clinically silent	Entorhinal and transentorhinal cortex, moving towards the hippocampus
Stage III and IV: Limbic MCI	Severe involvement of the entorhinal cortex. Extension to neocortex. Insular cortex becomes affected in stage IV. Some temporal lobe involvement.
Stage V and VI: Isocortical AD	Large neocortical involvement across temporal, occipital and frontal lobes.

Braak staging of tau in AD. Moving through the stages shows a spread from the entorhinal region later affecting many areas of the cortex which give rise to memory loss followed by sensory, motor and higher function debilitation in later disease. Figure adjusted from H. Braak Braak, (1991) (Braak & Braak, 1991)

These stages describe a sequentially 'predictable' pattern of NFT spread from the entorhinal cortex and hippocampus towards the limbic and isocortical regions throughout AD progression. However, there is now mounting evidence that tau does not always accumulate and spread in this manner.

Interestingly, Sabbagh et al., (2010) found tangle accumulation had a stronger correlation with cognitive impairment in the neocortex than with the hippocampus and entorhinal cortex (Sabbagh et al., 2010). This correlation with the neocortex was more positive in patients with AD over MCI. Comparing this with amyloid, correlations were stronger with NFTs than amyloid plaques in entorhinal and hippocampal regions in the AD patient group. Other studies have found tau accumulation predominantly in the frontal regions with atrophy only in later stages (Harrison et al., 2019). Moreover, Lowe et al., (2018), have found higher Braak staging present in cognitively unimpaired individuals (Lowe et al., 2018). An explanation for this is the hippocampus and entorhinal cortex are more susceptible to toxic effects of tau accumulation and therefore succumbs to neurodegeneration at a lower threshold than the frontal regions of the brain, or, that tau is under-represented as atrophy has already occurred. A 2 year study by Harrison et al., (2019), compared tau-PET signalling with atrophy later in the disease course and found that atrophy followed the pattern of tau deposition and new tau seeded between scans (Harrison et al., 2019). Longitudinal studies tracking tau accumulation and neurodegeneration can show whether tau directly antecedes atrophy, although timescales in current studies remain too low and record data once a diagnosis has already been established. Measuring the degenerating brain is not wholly appropriate as if the neuron is gone, so are the pathological proteins that were present.

Tau may be a more appropriate target than amyloid as it is better correlated to clinical symptoms, has a higher presence in the hippocampus and entorhinal cortex and is also present before onset of symptoms. However, both are present in normal ageing and are not always correlated with atrophy hence the clinical picture is unlikely attributable to tau and amyloid alone. The next question is whether there has been success with tau therapies in AD.

4.3 Tau therapies

Therapies target multiple ways in which tau could propagate toxicity such as post translational modifications, aggregation, proteolytic cleavage, truncation and turnover. Specific therapies with either terminated or ongoing trials are discussed here.

4.4 LMTX

LMTX is a more stable form of methylene blue which prevents aggregation in vitro and improves cognitive function in mild and moderate AD patients after fifty weeks of treatment. Despite rescued learning impairment in two mouse models of AD, LMTX failed to rescue cognitive impairment in humans. The authors suggest a dosing issue and another trial with altered dose will finish in 2020. Indeed, lower concentrations of methylene blue were more beneficial than the higher dose tested in the initial trial (Huang et al., 2020; Congdon & Sigurdsson, 2018). As previously discussed, aggregates or oligomers could incur toxicity. By inhibiting aggregation, tau will remain in oligomeric form, although this has the capacity to be more toxic as both aggregates and oligomers have been linked to pathogenesis. The fact that mice models showed promise is not necessarily reliable as oligomers may not have a negative effect on cognition in mice as AD does not occur naturally in these animals.

4.5 Davunetide

Davunetide is an inhibitor of activity dependent neuroprotective protein (ADNP) which has an interesting although incomplete link with tauopathies, with a deficiency in mouse models causing disease. It has been postulated that davunetide is neuroprotective by microtubule stabilisation and reducing tau-hyperphosphorylation. Although the drug is safe and well tolerated in a phase II study there has been no improvement in cognition in a trial in PSP and there are no further trials planned for the drug (Huang et al., 2020; Bakota & Brandt, 2016).

4.6 Tideglusib

Tideglusib is an irreversible inhibitor of GSK3 which phosphorylates tau. In animal models tideglusib reduces tau phosphorylation, amyloid burden and improves cognition in AD patients in a pilot study. In a larger cohort benefit was seen in patients with mild AD in isolation but there was no significant improvement when the entire cohort was taken together (Congdon & Sigurdsson, 2018). This could demonstrate the need for stage targeting of AD. Separating patients into mild, moderate and severe groups might be beneficial to find a drug that targets mild symptoms and therefore delays progression.

4.7 C2N-8E12 (AbbV-8E12)

Immunotherapies are in very early stages of development predominantly going through safety trials with minimal data on outcomes around cognition. One example is passive immunisation with C2N-8E12 antibody which has been shown to prevent NFT aggregation, hyperphosphorylation and improved cognition in mice. In a phase I trial humans were given three doses over twelve weeks, with twenty-nine of thirty participants producing IgGs, however some adverse effects such as microhaemorrhage and infection were reported, a larger study is now underway to evaluate safety (Huang et al., 2020).

5 Conclusion

The trials for tau targeting therapies have not yielded positive results so far, with many trials failing to meet primary outcomes. So is the field heading in the same direction as amyloid?

Is tau the correct target? From the evidence given here, tau could be a reasonable target but has many pitfalls. The presence of tau in normal ageing is concerning particularly if higher Braak stages are present in cognitively unimpaired individuals. This is complicated further by the fact that most of the drugs in current trials are not primarily tau targeting (instead targeting a tau kinase or stabilise microtubules) and so cannot give a true correlation between presence of tau and decline in cognition. Moreover, microtubule instability may be a 'loss of function' mechanism in AD, but attention should also be given to gain of toxic functions of tau. Lastly, tau does not always correlate with atrophy which gives rise to clinical symptoms hence there may be a limit to what a successful tau targeting therapy could achieve.

Are interventions timely with appropriate outcome measures? As in amyloid, tau therapies are tested in patients with existing disease. With the field in such early stages, it is necessary to do this before looking at prophylaxis, however the outcome measures continue to be unreasonable, looking at improvement in cognitive function despite established atrophy and subsequent presence of clinical symptoms. Some therapies have shown promise in patients with MCI and studies presented here demonstrate atrophy occurring after accumulation of tau (Harrison et al., 2019). Therefore, using cessation of decline as oppose to improvement may be beneficial.

There are many similarities between tau and amyloid therapeutic trials. Research must address the pitfalls of the amyloid hypothesis in order to produce meaningful trials and results providing patients with acceptable treatments. Changing outcome measures, smarter targets and longitudinal trials will be necessary to do this.

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No conflicts of interest have been declared by any authors.

Authorship statement

All authors fulfill ICMJE authorship criteria, which can be accessed at `http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html`.

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Ethics statement

Authors declare that no ethical approval was required for this article.

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References

Bakota, L., & Brandt, R. (2016). Tau Biology and Tau-Directed Therapies for Alzheimer's Disease. *Drugs*. doi: 10.1007/s40265-015-0529-0

Braak, H., Alafuzoff, I., Arzberger, T., Kretzschmar, H., & Tredici, K. (2006). Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta Neuropathologica*. doi: 10.1007/s00401-006-0127-z

Braak, H., & Braak, E. (1991). *Neuropathological stageing of Alzheimer-related changes.* doi: 10.1007/BF00308809

Brier, M. R., Gordon, B., Friedrichsen, K., McCarthy, J., Stern, A., Christensen, J., ... Ances, B. M. (2016). Tau and Ab imaging, CSF measures, and cognition in Alzheimer's disease. *Science Translational Medicine*. doi: 10.1126/scitranslmed.aaf2362

Congdon, E. E., & Sigurdsson, E. M. (2018). *Tau-targeting therapies for Alzheimer disease.* doi: 10.1038/s41582-018-0013-z

Fitzgerald M.J.T, Gregory Gruener, E. M. (2012). *Clincal Neuroanatomy and Neuorscience*. doi: 10.1016/b978-0-7506-1447-4.50014-1

Harrison, T. M., La Joie, R., Maass, A., Baker, S. L., Swinnerton, K., Fenton, L., ... Jagust, W. J. (2019). Longitudinal tau accumulation and atrophy in aging and alzheimer disease. *Annals of Neurology*. doi: 10.1002/ana.25406

Huang, L. K., Chao, S. P., & Hu, C. J. (2020). *Clinical trials of new drugs for Alzheimer disease.* doi: 10.1186/s12929-019-0609-7

Kandimalla, R. J., Prabhakar, S., Wani, W. Y., Kaushal, A., Gupta, N., Sharma, D. R., ... Gill, K. D. (2013). CSF p-Tau levels in the prediction of Alzheimer's disease. *Biology Open*. doi: 10.1242/bio.20135447

Lane, C. A., Hardy, J., & Schott, J. M. (2018). *Alzheimer's disease.* doi: 10.1111/ene.13439

Lowe, V. J., Wiste, H. J., Senjem, M. L., Weigand, S. D., Therneau, T. M., Boeve, B. F., ... Jack, C. R. (2018).

Widespread brain tau and its association with ageing, Braak stage and Alzheimer's dementia. *Brain*. doi: 10.1093/brain/awx320

Medina, M., Hernández, F., & Avila, J. (2016). *New features about tau function and dysfunction.* doi: 10.3390/biom6020021

Sabbagh, M., Cooper, K., DeLange, J., Stoehr, J., Thind, K., Lahti, T., ... Beach, T. (2010). Functional, Global and Cognitive Decline Correlates to Accumulation of Alzheimers Pathology in MCI and AD. *Current Alzheimer Research*. doi: 10.2174/156720510791162340

Sebastián-Serrano, Á., Diego-García, L. D., & Díaz-Hernández, M. (2018). *The neurotoxic role of extracellular tau protein.* doi: 10.3390/ijms19040998

van Dyck, C. H. (2018). *Anti-Amyloid-β Monoclonal Antibodies for Alzheimer's Disease: Pitfalls and Promise.* doi: 10.1016/j.biopsych.2017.08.010

Whitehouse, P. J. (2014). *The end of Alzheimer's disease - From biochemical pharmacology to ecopsychosociology: A personal perspective.* doi: 10.1016/j.bcp.2013.11.017