The Effect Of Therapeutic Drugs on Tau Proteins

ABSTRACT

Background
This research delves into the role of therapeutic agents' influence on tau protein levels in one's brain, ultimately exemplifying their ability to impact cognitive health.

Objective
Through a literature review, this research helps organize information presented in different research studies regarding therapeutic agents and their ability to affect tau protein levels.

Methods
Sources for this literature review were found through screening original research articles found through PubMed analyzing the effect of therapeutic agents on tau protein levels and human cognitive development.

Conclusion
Therapeutic agents have a paramount effect on tau levels in the brain, yet these effects vary depending on the agent being used. This research helped depict the potential of certain therapeutic agents in the neuroscience field and how impactful they could be when faced with neurodegenerative diseases such as Alzheimer's or Parkinson's disease.

INTRODUCTION

Neurodegenerative diseases are proven to be more prevalent in the elderly [1]. Most neurodegenerative diseases lead to dementia, which is estimated to affect 150 million people worldwide by 2050 and currently costs around $10 trillion to the healthcare system [1]. With that being said, our future relies on therapeutic agents to fight these neurodegenerative diseases, with the first therapeutic agents approved by the FDA in 2003 [2]. A key pathophysiological mechanism identified with neurodegenerative diseases is excess tau levels, leading to tangles as

well as amyloid plaques combining together to ultimately interfere with connectivity between neurons [3].

Some of the therapeutic agents that were identified throughout this literature review were posited to help participants with Alzheimer's disease in slowing the process in which tau proteins tangle and interfere with communication linkage. As therapeutic agents are still being developed, their refined strategies are proving to make a difference in the field of neurodegenerative diseases [1].

Therapeutic agents may also be found in everyday consumables such as seeds and vegetables like cauliflower and lettuce [4]. Not only do these help patients with symptoms of neurodegenerative disease, but they are also known to fight them, as it is proven that cauliflower and lettuce contain a type of therapeutic agent named sulforaphane, which ultimately helps break down tau protein tangles as well as plaque created by beta amyloid fragments, both of which play a huge role in dementia.

All in all, therapeutic agents are extremely essential in our war against neurodegenerative diseases; therefore, it is important to research in this area due to the amount of potential that it may bring to the field of neuroscience.

METHODS

The review used PubMed to identify studies for inclusion. Keywords included tau proteins, neurodegenerative diseases, and therapeutic agents, with a filter option to specifically look for clinical trials. Inclusion criteria for clinical trials included at least 100 participants, publication year after 2015, and quantitative result reporting.

RESULTS

In this review article, 5 articles were included that demonstrated the influence of therapeutic agents in targeting tau proteins [5-9]. Five drugs were reviewed in these articles collectively, with Suvorexant proving to have a paramount effect on tau protein deceleration while other agents such as MAPTRx were proven to reduce inflammation and neurogranin levels in patients with mild Alzheimer's disease [5,6]. Some drugs were found to also have other benefits, such as Donanemab, which reduces not only tau levels but also amyloid levels, presenting a unique finding in the field of neuroscience [7]. Although many of the drugs tested in the articles were proven to have some effect on Alzheimer's, others, such as somorinemab, were proven to not have an effect on Alzheimer's disease, as they had little to no influence on tau protein levels throughout the 73-week time period they were monitored [9].

Study	Focus	Information	Relevance

“Tau-targeting antisense oligonucleotide $MAPT_{Rx}$ in mild Alzheimer’s disease: a phase 1b, randomized, placebo-controlled trial” [5]	The differing effect of MAPTRx versus a placebo on tau proteins in Alzheimer's disease.	Inflammation decreased within those dosed with MAPTRx, whereas those dosed with placebo remained the same.	This clinical trial suggests that MAPTRx may play a role in reducing inflammation for patients with Alzheimer’s. Neurograining levels were reduced within those dosed with MAPTRx. Ultimately, MAPTRx helped alleviate symptoms for those diagnosed with Alzheimer's.
“Suvorexant Acutely Decreases Tau Phosphorylation and Aβ in the Human CNS” [6]	Therapeutic agents aimed at decelerating the progress of tau protein blockades.	The ratio of phosphorylated to unphosphorylated tau-threonine-181 was decreased 10%–15% in participants treated with suvorexant compared to placebo.	Given the role of tau protein blockades in the progression of Alzheimer’s disease, by decelerating this process, the drug poses a possibility to slow the progression of the disease.
“Association of Amyloid Reduction After Donanemab Treatment With Tau Pathology and Clinical Outcomes: The TRAILBLAZER-ALZ Randomized Clinical Trial” [7]	The influence of amyloid reduction on tau protein progression.	Donanemab slowed tau accumulation as well as reduced levels of amyloid, with greater results seen in participants with higher levels of baseline amyloid. Amyloid levels were also predicted to stay low for approximately another 3.9 years after stopping treatment. .	Donanemab offers a unique benefit of decreasing both tau accumulation and amyloid levels, both of which are implicated in Alzheimer’s disease
“Exploratory Tau Biomarker Results From a Multiple Ascending-Dose	Varying dosages of BIIB080 may differentially influence the reduction of tau	The treatment BIIB080 was analyzed to lower tau protein buildup. Higher doses were	The relevance of this research is established through the slowing of tau accumulation through

Study of BIIB080 in Alzheimer Disease: A Randomized Clinical Trial" [8]	protein levels within patients.	proven to have greater efficacy with decreasing tau levels.	BIIB080, with higher doses showing increased efficacy.
"Safety and Efficacy of Semorinemab in Individuals With Prodromal to Mild Alzheimer Disease: A Randomized Clinical Trial" [9]	Analyze the effect of somorinemab on tau proteins to see if it may stop the accumulation and slow mild Alzheimer's disease.	Semorinemab was deemed safe as well as observed to not have influenced tau protein levels; therefore, it didn't succeed in slowing the effect of Alzheimer's disease.	The relevance of this research is established through semorinemab being proven to not have an effect on the reduction of tau proteins; therefore, no effect on AD as well.

DISCUSSION

All in all, these articles exemplify the effect of therapeutic agents on tau protein levels, providing insights into Alzheimer's disease management. Most of these drugs influence the body through the reduction of tau proteins.

For example, suvorexant lowers phosphorylated tau threonine 181 levels [6]. Previously, suvorexant was used to treat patients with insomnia by selectively blocking the binding between receptors and neuropeptides [6]. This same clinical drug used for insomnia has helped block the bindings between tau proteins to prevent tangles that promote Alzheimer's disease. BIIB080 was also found to reduce Alzheimer's disease growth through the slowing of tau protein growth [8]. Different doses of BIIB080 reduced different amounts of CSF t-tau and p-tau181 [8]. It is likely that the reduction of CSF t-tau and p-tau181 may result in slowed disease progression in Alzheimer's disease. One of the more unique drugs being researched is donanemab; donanemab specializes in the reduction of tau levels as well as amyloid levels, and patients dosed with donanemab, who had complete plaque clearance within a 24-week time period, were proven to have a greater reduction in tau levels [7]. Interestingly, though MAPTRx has little to no effect on tau protein levels, its ability to alleviate symptoms for patients makes it all the more useful [5]. MAPTRx is able to execute this task through the reduction of inflammation, which can improve cognitive health [5]. MAPTRx also increases neurogranin levels, which, when reduced, play a role in cognitive decline [5]. Unfortunately, semorinemab has little to no influence on Alzheimer's disease, as the clinical trial showed zero improvement in cognitive health for patients with Alzheimer's disease [9]. Though semorinemab was proven to be safe for dosage, its lack of effectiveness in the context of Alzheimer's research suggests a need for further development [9].

The information stated above supports the hypothesis that various therapeutic agents may improve symptoms of neurodegenerative diseases such as Alzheimer's disease in the future. Future research should focus on continuing to develop, test, and implement therapeutic agents to improve patient care and quality of life.

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