Review Article **IJOAR (2022) 5:94**

International Journal of Aging Research (ISSN:2637-3742)

NEW APPROACHER IN THE DEVELOPMENT OF ALZHEIMER'S DISEASE MODIFYING DRUGS

Pedro César de Souza

Mauricio de Nassau University Center. Recife, PE, Brasil

ABSTRACT

Introduction: Alzheimer's disease is a more common neurodegenerative disease, affecting 25 million people worldwide, or accounting for about 60 to 70% of all dementia cases. There is currently no exact mechanism to explain the pathophysiology of Alzheimer's disease, however, cascading metabolic amyloid and post-translational review of tau protein are used as major hypotheses. **Objective:** To demonstrate in the literature new approaches in the development of Alzheimer's disease modifiers. Methodology: This is a literature review study with a 5-year time frame, developed from the research of scientific articles published in international journals, through online databases such as "PubMed" and "Science Direct". **Results:** Alzheimer's disease-modifying drugs are not yet available, but many patients may, however, develop phase III clinical trials and are intended to modify as pathological stages leading to the disease. As disease-modifying therapies under study, these changes also affect Aβ and tau protein and also cause inflammation and oxidative damage. The results obtained in the clinical trials performed were positive and promising and are still under study. The results show that there is still a long way to go in the development of Alzheimer's disease modifying drugs. **Conclusion:** The results demonstrated that there is still a long way to go in the development of Alzheimer's disease modifying drugs, but nevertheless levels at the research level should be continued in order to improve the pathophysiology of the disease and find an effective treatment for this disease the same.

Keywords: Alzheimer's disease, β-amyloid, Tau hyperphosphorylation, Neurodegeneration

***Correspondence to Author:**
Pedro César de Souza
Mauricio de Nassau University Center. Recife, PE, Brasil

How to cite this article:
Pedro César de Souza. NEW APPROACHER IN THE DEVELOPMENT OF ALZHEIMER'S DISEASE MODIFYING DRUGS. International Journal of Aging Research, 2022, 5:94.

eSciPub LLC, Houston, TX USA.
Website: https://escipub.com/

INTRODUCTION

Neurodegenerative diseases are diseases that affect the central nervous system (CNS) causing progressive degeneration and neuronal death in certain regions of the brain[1]. There are several neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease, Multiple Sclerosis, Lewy body disease, among others[2]. AD is the most common neurodegenerative disease affecting about 25 million people worldwide, which accounts for about 60-70% of all dementia cases. These figures are expected to triple by 20503.4. The main neuropathological changes in AD are brain atrophy, the presence of senile cerebral plaques containing extracellular deposits of β-amyloid (Aβ) peptide, intraneuronal neurofibrillary tangles (ENF) containing hyperphosphorylated tau protein, and loss of neuronal cells. These neuropathological alterations manifest themselves with the progressive loss of memory and cognitive functions (difficulty in reasoning, disorientation and difficulties in expressing oneself[5,6]. Currently, there is no exact mechanism that explains the pathophysiology of AD, however the metabolic cascade amyloid and post-translational modification of tau protein, the protein responsible for stabilizing microtubules, are considered the most important hypotheses.Other mechanisms have been considered such as neurotransmitter dysfunction, mitochondrial dysfunction, oxidative stress, genetic and environmental factors[7. Current treatments available for AD do not alter the progression of the disease, they are limited to the alleviation of cognitive, behavioral and psychological symptoms. The two classes of drugs approved for the treatment of AD are: acetylcholinesterase inhibitors (IAChE) and the receptor antagonist of N-methyl-D-aspartate (NMDA) glutamate. as first-line treatment for AD and are donepezil, rivastigmine and galantamine. In a more advanced stage of the disease, memantine is used, which is the only non-competitive NMDA receptor antagonist approved for the treatment of AD. In order to treat the behavioral symptoms of the disease, antipsychotics, antidepressants and benzodiazepines are also used simultaneously[3]. Several studies are under development in phase III clinical trials and are intended to modify the pathological stages that lead to the disease[8]. The disease-modifying therapies under study have as main targets Aβ and tau protein and also inflammation[7].

METHODOLOGY

In order to carry out this study, a bibliographical survey was carried out in the scientific literature on the proposed topic. Selection for this review was based on journals in the following databases: PUBMED (National Library of Medicine and The National Institute of Health) and ScienceDirect. To search for scientific articles, the following keywords will be used: Alzheimer's disease, β-amyloid, Tau hyperphosphorylation, Neurodegeneration, with a time frame of 5 years.

RESULTS

Currently, drugs that are under development for AD are intended to modify the pathological stages that lead to the disease, thus acting in the evolution of the disease and thus called disease-modifying drugs[8]. During the last decades, several hypotheses have been proposed for the pathogenesis of AD, and the theory of the β-amyloid (Aβ) cascade and the hyperphosphorylation of tau are the theories that have been more widely accepted. Thus, the disease-modifying therapies under study have as main targets Aβ and tau protein and also inflammation[8,5]. There are three types of therapeutic approaches under development, which are: secretase inhibitors (β and γ), α-secretase activators, and Aβ aggregation inhibitors[4,5,8]. The β-secretase enzyme BACE1 is a promising therapeutic target, therefore, a good BACE1 inhibitor must be metabolically stable, orally bioavailable, have a low molecular weight, reduced susceptibility to P-glycoprotein or other transporters in order to achieve an effective penetration of the BBB.

Furthermore, they must also be highly selective so as not to interfere with other aspartic acid proteases (such as BACE2, cathepsin D) that have a high homology with the active site of BACE[5,2]. β-secretase inhibitors of non-peptide origin are in clinical trials in animal models with the prospect of promising results[9]. CTS-21166 is a β-secretase inhibitor that entered a phase I clinical trial in healthy young people to assess the safety and preliminary response of Aβ. It was found with this assay that this inhibitor has been shown to inhibit plasma Aβ. The next step will be to develop inhibitors with better pharmaceutical properties and carry out clinical trials to assess their efficacy in patients with AD[10,11]. The development of γ-secretase inhibitors is a promising target for AD modification. γ-secretase is a complex enzyme composed of four individual proteins that are presenilin, nicastrin, APH-1 (formerly pharynx-defective 1) and PSEN2 and has multiple cleavage sites and essential biological substrates. PPA is the best known substrate for γ-secretase, whose cleavage produces Aβ.

A group of non-steroidal anti-inflammatory drugs (NSAIDs) has been discovered to reduce Aβ42 levels by modeling the γ-secretase pathway[12]. Tarenflurbil (Flurizan®), which is an R-enantiomer of the NSAID lurbiprofen, was the first drug to modulate γ-secretase activity and acts by binding to a site other than the active center of the enzyme, changing the conformation of γ- secretase and thus interfering with PPA cleavage, producing smaller, non-toxic Aβ fragments without in any way altering other essential substrates for the enzyme. In studies carried out in transgenic mice, tarenflurbil has been shown to reduce the accumulation of amyloid plaques, improve memory and behavioral performance[12]. Subsequently, clinical trials were carried out with individuals with mild to moderate AD, in which, in the phase I study, the drug was well tolerated, without evidence of gastrointestinal toxicity, however, it did not produce a significant reduction in Aβ42 in CSF and plasma. In phase II and phase III trials, they showed positive effects on performing daily and global tasks, but did not reveal benefits on cognitive performance. These results called into question the benefits of γ-secretase modeling, as well as the amyloid cascade hypothesis. A possible justification for the failure of this study is the weak potency of tarenflurbil as a γ-secretase modulator and a poor distribution of this compound at the level of the CNS[12]. Recently, second-generation γ-secretase modelers such as avagacestat (BMS-708), begacestat (GSI-953) and E2012 (highly selective inhibitor of Notch sparing γ-secretase), begacestat (GSI-953) and E201213. Avagacestat is a highly selective inhibitor of γ-secretase, which has already been tested in a phase I clinical trial and observed a decrease in Aβ in the CSF. It is currently in a phase II clinical trial[14].

Another possible therapeutic approach is the stimulation of the α-secretase enzyme because since the α-secretase and β-secretase enzymes compete for the same PPA substrate, if there is a greater activation of α-secretase, there will be a decrease in the sPPAβ substrate available for the amyloidogenic pathway and thus a decrease in Aβ production. Consequently, there is an increased formation of the soluble sPPAα fragment that has neuroprotective properties and is a stimulant of synaptogenesis. Thus, the activation of α-secretase has a great therapeutic potential for AD[15]. Currently, there are not many compounds that stimulate this α-secretase pathway that have reached a stage of animal studies and later clinical trials with AD patients, as is the case with etazolate[16]. Ethazolate is an activator of the neurotrophic α-secretase pathway that promotes symptomatic relief and modifies AD progression. This compound has been shown in a phase II clinical trial conducted in 159 subjects with mild to moderate AD to be safe and well tolerated. These positive results supported the development of etazolate in order to assess its clinical efficacy and confirm its tolerability in a larger sample of people and for a long period of time[17]. Another therapeutic under

development for the treatment of AD is the prevention of Aβ aggregation since this prevents the formation of oligomers, fibrils and protofibrils and finally the amyloid plaques which ultimately leads to the neurodegeneration characteristic of AD. Currently, several anti-aggregating compounds are in clinical trials, such as tramiprosate, colostrinin, clioquinol, PBT2 and scyllo-inositol. The mechanisms of action of these compounds are variable, but they are not yet completely known, however it is thought that they can prevent the formation of fibrils and facilitate the elimination of soluble Aβ[18]. Substances such as tramiprosate, colostrinin and coliquinol have been tested in transgenic mice, class I and class II clinical trials where they have shown to decrease na. Ark of familiar plaques and a decrease in CSF ab levels. Current studies of tau protein modifying drugs have been directed to develop anti-inflammatory compounds and compounds that inhibit tau aggregation[19]. Tau protein is a protein that provides stability to microtubules and that in AD is found to be abnormally hyperphosphorylated and consequently aggregates, leading to the formation of ENF that accumulate in neurons. The distribution and burden of tau is better correlated with disease severity than the amyloid burden. Therefore, considering the importance of this protein for AD, therapies based on the modification of tau are under investigation, as an alternative target to therapies based on the Aβ protein.

There is evidence from studies that tau aggregation can be stopped through low molecular weight compounds such as methylthionine chloride (CMT) [18]. CMT, better known as methylene blue, is a promising compound as it has antioxidant properties, reduces Aβ oligomerization and interferes with tau aggregation by binding to the domain responsible for the self-aggregation of truncated tau fragments. A placebo-controlled phase II clinical trial was performed in 321 individuals with mild or moderate AD using doses of 30 mg, 60 mg or 100 mg of CMT for 24 weeks[18]. This study showed an 80% decrease in the AD progression rate in individuals who received CMT compared to the placebo group. Despite the promising results observed, further studies are needed to demonstrate the efficacy and safety of CMT, and a phase III clinical trial is pending approval[19]. Epothilone D (BMS-241027) is a microtubule stabilizing agent that acts by inhibiting the disintegration of microtubules to maintain the axon transport function, and on the other hand, prevents the formation of tau aggregates. Studies were carried out in animal models with epothilone D where there was a decrease in cognitive and behavioral deficits. Epothilone D is able to penetrate the BBB and exert better efficacy at low concentration and a phase I clinical trial in individuals with AD is currently ongoing[19]. Nicotinamide is a precursor compound of the coenzyme NAD+ that has been shown in animal model studies to reduce tau phosphorylation and protect microtubule stabilization.

This compound has been subjected to clinical trials with patients with mild to moderate AD and has been shown to be safe and well-tolerated, so a phase II clinical trial is currently underway[19]. Inflammatory phenomena occur in the periphery of amyloid plaques, through the accumulation of microglial cells around the plaques, cytokine reactions and activation of the complement cascade. Epidemiological evidence suggests that the prolonged use of NSAIDs protects against the development of AD, with this protective effect being dependent on the duration of treatment[15,16]. However, several prospective studies with rofecoxib, naproxen, diclofenac, celecoxib, dapsone, hydroxy-chloroquine and nimesulin showed that these drugs failed to slow the progression of cognitive decline in patients with mild to moderate AD. However, the same group of patients was used in a study with indomethacin, in which a delay in cognitive decline was observed, but due to the great gastrointestinal toxicity of indomethacin they limited its use[20].

CONCLUSION

The drugs currently approved for AD are IAChE and the glutamate receptor antagonist NMDA, however these do not alter the progression of the disease, they only reduce the severity of its symptoms. Therefore, it is necessary to invest in scientific research in order to develop drugs that modify AD, halting its progression. Currently, there are no AD-modifying drugs available, although several drugs have already been tested in phase III clinical trials, however, none have yet been approved. Drugs such as tarenflurbil, tramiprosate and semagacestat were ineffective in the final clinical stages of the trials and other drugs such as avagacestat, etazolate, CAD-106, solanezumab, IVIg, methylthionine chloride and lithium are still being tested in advanced clinical trials. In conclusion, it is of great importance to continue the investigation in order to broaden and deepen the understanding of AD pathophysiology, realizing a better relationship between Aβ protein, tau protein and other factors that trigger the disease. Combination therapies of drugs with different targets or modifying factors (eg, Aβ, tau, and apoE4) are a hypothesis to consider. Further studies should be carried out in order to develop better biomarkers of the disease that will be useful both for diagnosis and for conducting clinical trials.

REFERENCES

[1]. EU Joint Programme – Neurodegenerative Disease. What is neurodegenerative disease?. JPND. 2017

[2]. Taipa R, Pinho J, Melo-Pires M. Clinico-pathological correlations of the most common neurodegenerative dementias. Front Neurol. 2017 Jan;3: 68.

[3]. Dalvi A. Alzheimer's Disease. Dis Mon. 2018 Dec;58(12):666–77.

[4]. Castellani RJ, Rolston RK, Smith MA. Alzheimer Disease. Dis Mon. 2018 Sep;56(9):484–546.

[5]. Xiaoting S, Jin L, Ling P. Review of drugs for Alzheimer's disease. Drug Discov Ther. 2017;6(6):285–90.

[6]. Mu Y, Gage FH. Adult hippocampal neurogenesis and its role in Alzheimer's disease. Mol Neurodegener. 2019 Jan;6: 85.

[7]. Dong S, Duan Y, Hu Y, Zhao Z. Advances in the pathogenesis of Alzheimer's disease: a re-evaluation of amyloid cascade hypothesis. Transl Neurodegener. BioMed Central Ltd; 2018 Jan 21;1(1):18.

[8]. Galimberti D, Scarpini E. Disease-modifying treatments for Alzheimer's disease. Ther Adv Neurol Disord. 2018;4(4):203–16.

[9]. Chu LW. Alzheimer's disease: early diagnosis and treatment. Hong Kong Med J. 2018;18(3):228–37.

[10]. Alzheimer's Disease International. Relatório sobre a Doença de Alzheimer no Mundo. 2018.

[11]. Sosa-Ortiz AL, Acosta-Castillo I, Prince MJ. Epidemiology of Dementias and Alzheimer's Disease. Arch Med Res. Elsevier Inc; 2017;43(8):600–8.

[12]. Chen JH, Lin KP, Chen YC. Risk Factors for Dementia. J Formos Med Assoc. Formosan Medical Association & Elsevier; 2017;108(10):754–64.

[13]. World Health Organization. Dementia: a public health priority. World Health Organization. Reino Unido; 2017. Novas abordagens no desenvolvimento de fármacos modificadores da Doença de Alzheimer 64

[14]. Associação Alzheimer Portugal. Plano Nacional de Intervenção Alzheimer. 2019.

[15]. Fiţa IG, Enciu A-M, Stănoiu BP. New insights on Alzheimer's disease diagnostic. Rom J Morphol Embryol. 2020 Jan;52(3 Suppl):975–9.

[16]. Anderson SH. Alzheimer Disease. Medscape. 2019.

[17]. Morris JK, Honea RA, Vidoni ED, Swerdlow RH, Burns JM. Is Alzheimer's disease a systemic disease? Biochim Biophys Acta. 2020 Sep;1842(9):1340–9.

[18]. Lemere CA. Immunotherapy for Alzheimer's disease: hoops and hurdles. Mol Neurodegener. Molecular Neurodegeneration; 2020;8(1):36.

[19]. Perl DP. Neuropathology of Alzheimer's Disease. Mt Sinai J Med. 2019;77(1):32– 42.

[20]. Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological Alterations in Alzheimer Disease. Cold Spring Harb Perspect Med. 2021;1(1):1– 24.