A Critical Review on the Conventional and Modern Molecular Target For Alzheimer's Disease

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Abstract
Alzheimer's disease is a progressive brain disease that is becoming a major health problem in today's world due to the aging population. Despite it being widely known that diet has a significant impact on the prevention and progression of Alzheimer's disease, the literature data are still scarce and controversial. The application of the principles of rational nutrition for the elderly is suggested for Alzheimer's disease. This study has been design to focus the correlation between the conventional molecular target to modern target, two major pathological lesions in the brain, amyloid plaques and neurofibrillary tangles (NFTs) composed mainly of amyloid-β (Aβ) peptides and hyperphosphorylated tau, respectively. Although accumulation of toxic Aβ species in the brain has been proposed as one of the important early events in AD, continued lack of success of clinical trials based on Aβ-targeting drugs has triggered the field to seek out alternative disease mechanisms and related therapeutic strategies. Human induced pluripotent stem cell (iPSC) technologies have changed the face of preclinical research and iPSC-derived cell types are being utilized to study an array of human conditions, including neurodegenerative disease. All major brain cell types can now be differentiated from iPSCs, while increasingly complex co-culture systems are being developed to facilitate neuroscience research. Many cellular functions perturbed in Alzheimer's disease can be recapitulated using iPSC-derived cells in vitro, and co-culture platforms are beginning to yield insights into the complex interactions that occur between brain cell types during neurodegeneration. Further, iPSC-based systems and genome editing tools will be critical in understanding the roles of the numerous new genes and mutations found to modify Alzheimer's disease risk in the past decade. While still in their relative infancy, these developing iPSC-based technologies hold considerable promise to push forward efforts to combat Alzheimer's disease and other neurodegenerative disorders. One of the new approaches is to uncover novel roles of pathological tau and Human induced pluripotent stem cell (iPSC) technologies with during disease progression.

Keywords: Alzheimer's disease, Neurofibrillary tangles, Human induced pluripotent stem cell (iPSC) technologies, Amyloid-β (Aβ), Tau protein.

Introduction

Alzheimer's Disease is a progressive neurodegenerative disorder primarily affecting the elderly population. It is characterized by the accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein in the brain, leading to neuronal death and cognitive impairment. The molecular mechanisms underlying AD have been a subject of extensive research, resulting in the identification of various therapeutic targets. While conventional targets like Aβ and tau have dominated the therapeutic landscape, modern approaches focus on a broader range of molecular targets, including neuroinflammation, oxidative stress, and synaptic dysfunction.

2. Conventional Molecular Targets:

2.1 Amyloid-Beta (Aβ): The amyloid cascade hypothesis has been central to AD research for decades, positing that the accumulation of Aβ peptides in the brain is the primary event leading to AD pathology. Aβ is derived from the amyloid precursor protein (APP) through the action of β-secretase and γ-secretase enzymes. The aggregation of Aβ into plaques disrupts cell function, leading to synaptic loss and neurodegeneration. Therapeutic strategies targeting Aβ include inhibitors of β-secretase and γ-secretase, as well as monoclonal antibodies designed to clear Aβ plaques from the brain. However, clinical trials targeting Aβ have largely been disappointing, with many failing to demonstrate significant clinical benefit (Karran et al., 2011).

2.2 Tau Protein: Another conventional target in AD is the tau protein, which forms NFTs within neurons. In its hyperphosphorylated state, tau loses its ability to stabilize microtubules, leading to cytoskeletal disruption and neuronal death. Therapeutic strategies targeting tau include kinase inhibitors, which prevent tau phosphorylation, and tau aggregation inhibitors, which prevent NFT formation. Despite promising preclinical data, tau-targeted therapies have also faced challenges in clinical trials, with limited efficacy observed in AD patients (Congdon & Sigurdsson, 2018).

3. Modern Molecular Targets:

3.1 Neuroinflammation: Neuroinflammation is increasingly recognized as a critical component of AD pathology. Microglia, the brain's resident immune cells, become activated in response to Aβ accumulation, leading to chronic

inflammation and neurotoxicity. Modern therapeutic approaches aim to modulate microglial activation and reduce pro-inflammatory cytokine production. Agents such as non-steroidal anti-inflammatory drugs (NSAIDs) and specific inhibitors of pro-inflammatory signaling pathways, like the NLRP3 inflammasome, are being explored as potential treatments for AD (Heneka et al., 2015).

3.2 Oxidative Stress: Oxidative stress plays a significant role in AD progression, contributing to neuronal damage and death. The brain is particularly vulnerable to oxidative damage due to its high metabolic activity and lipid-rich environment. Modern therapeutic strategies focus on enhancing the brain's antioxidant defenses, either through direct administration of antioxidants or by upregulating endogenous antioxidant pathways. Compounds like resveratrol and N-acetylcysteine have shown potential in reducing oxidative stress in preclinical studies, although their clinical efficacy remains to be fully established (Butterfield & Halliwell, 2019).

3.3 Synaptic Dysfunction: Synaptic loss is a hallmark of AD and is closely correlated with cognitive decline. Modern therapeutic strategies aim to preserve synaptic function by targeting key proteins involved in synaptic transmission and plasticity, such as synaptophysin and PSD-95. Additionally, modulation of neurotransmitter systems, particularly the glutamatergic and cholinergic systems, is being explored to enhance synaptic function and improve cognitive outcomes in AD patients (Frere & Slutsky, 2018). The landscape of AD therapy has evolved significantly, moving from a focus on conventional targets like Aβ and tau to a broader approach encompassing neuroinflammation, oxidative stress, and synaptic dysfunction. While conventional therapies have faced numerous challenges, particularly in clinical trials, modern approaches offer new hope for effective treatment. However, the complexity of AD pathology suggests that a multi-targeted approach, possibly combining conventional and modern therapies, may be necessary to achieve meaningful clinical outcomes.

Animal Model used for Alzheimer

Animal models are indispensable tools in Alzheimer's Disease (AD) research, allowing scientists to study disease mechanisms and test potential therapies in a controlled environment. These models range from rodents to larger mammals, each offering unique insights into the pathology of AD. Below is a detailed overview of the commonly used animal models in AD research.

4.1. Rodent Models:

4.1.1. Transgenic Mice: Transgenic mice are the most widely used animal models for AD research. These mice are genetically engineered to express human genes associated with AD, such as the amyloid precursor protein (APP), presenilin-1 (PS1), and tau. APP/PS1 Mice: These mice express human APP and PS1 mutations that are known to cause familial AD. They develop amyloid plaques similar to those observed in human AD patients, making them valuable for studying amyloid pathology and testing anti-amyloid therapies (Jankowsky et al., 2004). 3xTg-AD Mice: These mice carry three mutations: APP, PS1, and tau. They develop both amyloid plaques and neurofibrillary tangles, providing a more comprehensive model of AD pathology (Oddo et al., 2003).

4.1.2. Non-transgenic Rodent Models: In addition to transgenic models, non-transgenic rodents are also used, particularly in studies focusing on environmental or pharmacological induction of AD-like symptoms. Scopolamine-Induced Amnesia: This model uses scopolamine, a muscarinic receptor antagonist, to induce memory impairment in rodents, mimicking the cognitive deficits seen in AD. It is commonly used to screen potential cognitive enhancers (Bartus et al., 1982). Streptozotocin (STZ)-Induced Models: Intracerebral or intracerebroventricular injection of STZ, a compound that induces insulin resistance, is used to mimic sporadic AD, particularly focusing on the metabolic aspects of the disease (Salkovic-Petrisic et al., 2006).

4.2. Non-Rodent Models:

4.2.1 Non-Human Primates: Non-human primates, such as rhesus monkeys and marmosets, are used in AD research due to their closer genetic and physiological similarities to humans. While they do not naturally develop AD, aged primates can exhibit amyloid plaque formation and cognitive decline, making them valuable for studying disease progression and testing therapies in a model more similar to humans (Lemere et al., 2004).

4.2.2 Canine Models: Aged dogs, particularly beagles, can naturally develop amyloid plaques and cognitive deficits akin to those seen in human AD. Canine models are useful for studying the natural progression of the disease and testing therapeutic interventions (Cummings et al., 1996).

4.2.3. Zebrafish: Zebrafish are emerging as a model for AD due to their genetic manipulability, rapid development, and the simplicity of imaging their transparent embryos. Transgenic zebrafish expressing human APP or tau genes are used to study the early stages of amyloid and tau pathology (Newman et al., 2010).

4.3. Limitations of Animal Models: Despite their utility, animal models have limitations. For instance, the overexpression of APP or tau in transgenic mice does not perfectly replicate human AD, particularly the sporadic form of the disease,

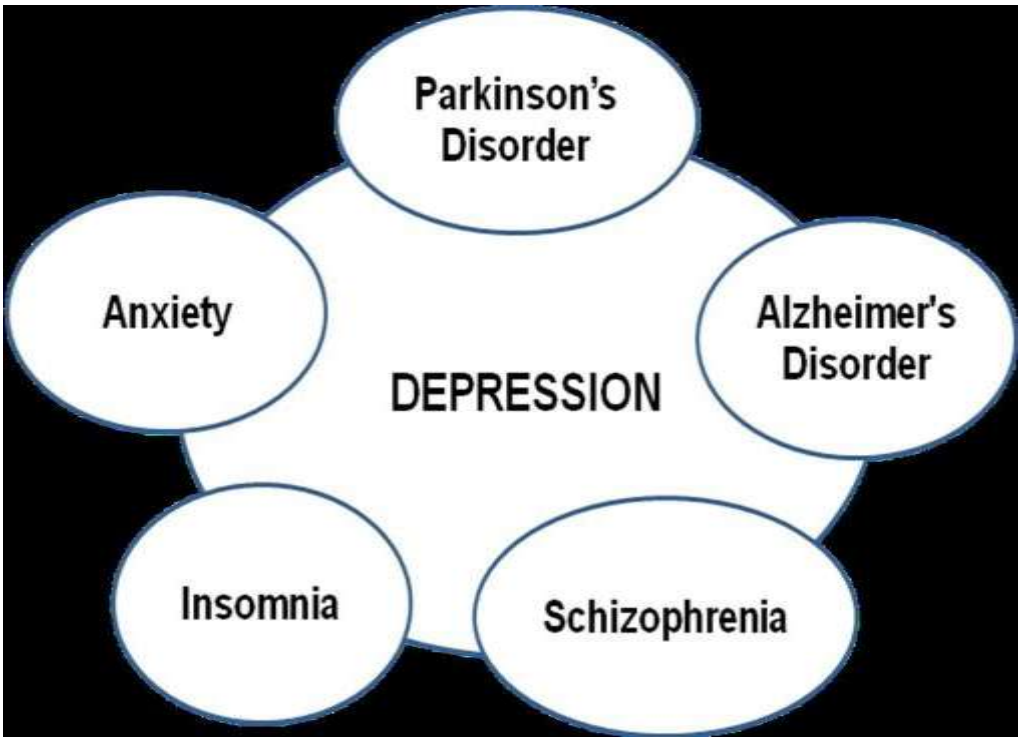
which accounts for the majority of AD cases. Moreover, the failure of many therapies that were effective in animal models to translate into human trials highlights the differences in disease pathology between species (Aisen, et al., 2017)

Role of vascular Dementia in Alzheimer

Vascular dementia and Alzheimer's disease often coexist, particularly in older adults, and this overlap can exacerbate cognitive decline. Vascular dementia results from impaired blood flow to the brain, leading to cognitive deficits. When vascular damage occurs alongside the pathological changes of Alzheimer's disease, such as amyloid plaques and neurofibrillary tangles, the overall impact on cognition can be more severe (Atkinson, 2017).

Exacerbation of Cognitive Decline: Vascular changes can accelerate the cognitive decline associated with Alzheimer's disease by contributing to brain tissue damage and reducing the brain's ability to compensate for Alzheimer's pathology. Many individuals diagnosed with Alzheimer's disease actually have mixed dementia, a condition where both Alzheimer's disease and vascular dementia contribute to cognitive decline. This mixed pathology complicates diagnosis and treatment. Vascular contributions to Alzheimer's disease may lead to earlier onset of symptoms or more rapid progression of the disease. This is due to the cumulative impact of both vascular insufficiency and neurodegenerative changes (Brody, 2011).Understanding the role of vascular factors in Alzheimer's disease has important implications for treatment. Managing cardiovascular risk factors (e.g., hypertension, diabetes) can help reduce the vascular contributions to dementia and potentially slow the progression of Alzheimer's disease (Hardy & Davies, 1988).

Molecular targets in the context of vascular dementia and Alzheimer's disease are crucial for developing therapeutic strategies aimed at slowing or preventing cognitive decline. These targets include proteins, receptors, enzymes, and pathways involved in the pathophysiology of these diseases.



Key Molecular Targets in Vascular Dementia and Alzheimer's Disease:

Amyloid-β (Aβ) Peptide:

In Alzheimer's disease, the accumulation of amyloid-β plaques is a hallmark feature. These plaques contribute to neuroinflammation, synaptic dysfunction, and neuronal death. Strategies include inhibiting Aβ production, promoting its clearance, and preventing its aggregation. Drugs like *bapineuzumab* and *solanezumab* have targeted Aβ, though with limited success in clinical trials (Mangialasche, Solomon, Winblad, Mecocci, & Kivipelto, 2010).

Tau Protein:

In Alzheimer's disease, tau proteins become hyperphosphorylated, leading to the formation of neurofibrillary tangles, which disrupt neuronal function and contribute to cell death. Efforts to reduce tau phosphorylation or promote its clearance are ongoing. Tau-targeted therapies include *anti-tau antibodies* and *tau kinase inhibitors* (Serý, Povová, Míšek, Pešák, & Janout, 2013).

Neuroinflammation and Microglia:

Chronic inflammation and activation of microglia (the brain's immune cells) are common in both Alzheimer's and vascular dementia. This inflammation exacerbates neuronal damage and disease progression. Anti-inflammatory approaches, such as *nonsteroidal anti-inflammatory drugs (NSAIDs)* and specific inhibitors of microglial activation, are being investigated. *P2X7 receptor antagonists* and *NLRP3 inflammasome inhibitors* are examples of targets within this pathway (Zvěřová, 2019).

Vascular Endothelial Growth Factor (VEGF):
VEGF plays a critical role in angiogenesis (the formation of new blood vessels) and neuroprotection. However, dysregulation of VEGF can contribute to vascular damage and cognitive impairment. Modulating VEGF signaling to promote vascular repair and maintain blood-brain barrier integrity is a potential therapeutic approach. *Bevacizumab*, an anti-VEGF antibody, is an example, although its role in dementia treatment is still under investigation (Rossor, 1993).

RAGE (Receptor for Advanced Glycation End Products):
RAGE is involved in the inflammatory response and oxidative stress in both Alzheimer's disease and vascular dementia. It interacts with Aβ and promotes neuroinflammation and vascular damage. Inhibitors of RAGE signaling are being explored to reduce inflammation and oxidative stress. Small molecules like *azilsartan* and *FPS-ZM1* are examples (Powell, Ziso, & Larner, 2019).

BACE1 (Beta-secretase 1):
BACE1 is an enzyme involved in the production of amyloid-β from its precursor protein (APP). Inhibition of BACE1 reduces the formation of amyloid plaques. BACE1 inhibitors, such as *verubecestat* and *lanabecestat*, have been developed to reduce Aβ levels, though clinical outcomes have been mixed (Lane, Hardy, & Schott, 2018).

Angiotensin II Receptors:
Angiotensin II is involved in blood pressure regulation and vascular health. Its receptors, particularly AT1R, contribute to vascular dysfunction and cognitive decline in vascular dementia. Angiotensin receptor blockers (ARBs) like *losartan* and *telmisartan* have been investigated for their potential neuroprotective effects by improving cerebral blood flow and reducing oxidative stress (Qiu, Kivipelto, & von Strauss, 2009).

NMDA Receptors:
Overactivation of NMDA (N-methyl-D-aspartate) receptors leads to excitotoxicity, a process contributing to neuronal damage in both Alzheimer's and vascular dementia. *Memantine*, an NMDA receptor antagonist, is used in Alzheimer's treatment to reduce excitotoxicity and improve cognitive function (Knapskog, Engedal, Selbæk, & Øksengård, 2021).

Discussion
molecular targets in the context of vascular dementia and Alzheimer's disease highlights the complexity of these neurodegenerative conditions and the challenges in developing effective therapies. Understanding these molecular targets is crucial for devising strategies that could slow down or even halt disease progression. Amyloid-β (Aβ) and tau proteins have long been the central focus of Alzheimer's research, given their role in the formation of amyloid plaques and neurofibrillary tangles, respectively. These pathological hallmarks have been targeted in numerous therapeutic efforts (Bennett & Evans, 1992) The hypothesis that reducing Aβ levels could mitigate Alzheimer's symptoms led to the development of drugs aimed at inhibiting its production, enhancing its clearance, or preventing its aggregation. However, clinical trials with Aβ-targeting drugs, like bapineuzumab and solanezumab, have yielded disappointing results, with limited efficacy in improving cognitive outcomes. This has raised questions about the amyloid hypothesis, suggesting that Aβ might be more of a downstream effect rather than the root cause of Alzheimer's pathology. Targeting tau has also been a focus, particularly in efforts to prevent its hyperphosphorylation and subsequent tangle formation. Despite the potential of tau-targeted therapies, such as anti-tau antibodies and kinase inhibitors, translating these approaches into clinical success has been challenging. The failures in clinical trials underscore the complexity of tau pathology and the need for a deeper understanding of its role in neurodegeneration (Van Stavern, 2020). Recent years have seen a shift in focus toward neuroinflammation and the role of vascular contributions in dementia, recognizing that Alzheimer's and vascular dementia often coexist.

The interaction between vascular damage and neurodegenerative processes is an area of growing interest: The activation of microglia, the brain's immune cells, and the resulting chronic inflammation are increasingly recognized as critical factors in the progression of both Alzheimer's disease and vascular dementia. Targeting microglial activation and the associated inflammatory pathways presents a promising avenue for therapy (van Leeuwen, 2019). However, the dual role of microglia—both protective and destructive—complicates therapeutic strategies, as suppressing inflammation too much could impair essential immune functions. Vascular dysfunction is a significant contributor to cognitive decline, especially in vascular dementia. The interplay between vascular damage and Alzheimer's pathology suggests that improving vascular health could slow cognitive deterioration. Drugs that target vascular endothelial growth factor (VEGF) signaling, angiotensin II receptors, and other pathways involved in vascular integrity and blood flow are being investigated. For instance, angiotensin receptor blockers (ARBs) like losartan not only help manage blood pressure but may also offer

neuroprotective benefits by improving cerebral blood flow (2016). This receptor is involved in oxidative stress and inflammation, both of which contribute to neurodegeneration. Inhibiting RAGE signaling has the potential to reduce these harmful processes. However, given the receptor's involvement in various physiological processes, selective inhibition without unwanted side effects remains a significant challenge. Overactivation of NMDA receptors leads to excitotoxicity, a key factor in neuronal death. Memantine, an NMDA receptor antagonist, is one of the few drugs approved for Alzheimer's treatment. It helps reduce excitotoxicity and is moderately effective in managing symptoms, though it does not address the underlying causes of the disease (Mantzavinos & Alexiou, 2017).

Future Directions

The focus on these molecular targets reflects a broader understanding that Alzheimer's disease and vascular dementia are not the result of a single pathological process but rather a confluence of various factors, including amyloid pathology, tau dysfunction, neuroinflammation, and vascular damage. This multifactorial nature of these diseases necessitates a more integrated therapeutic approach, Given the limited success of monotherapies targeting single molecules, there is a growing interest in combination therapies that address multiple pathways simultaneously. For example, a therapy that combines anti-inflammatory drugs with agents that improve vascular health might offer more significant benefits than either approach alone. The heterogeneity of Alzheimer's and vascular dementia suggests that personalized medicine, tailored to the specific pathological features present in each patient, could be more effective than a one-size-fits-all approach. Biomarkers that reflect individual disease mechanisms could guide the selection of the most appropriate therapies. Addressing modifiable risk factors such as hypertension, diabetes, and lifestyle choices (e.g., diet, exercise) can play a crucial role in reducing the incidence of both Alzheimer's disease and vascular dementia. Early intervention in at-risk populations may help delay or prevent the onset of cognitive decline. In conclusion, while significant challenges remain in translating knowledge of molecular targets into effective treatments, the ongoing research is providing a more nuanced understanding of these complex diseases. As our understanding of the molecular underpinnings of Alzheimer's and vascular dementia evolves, so too will our ability to develop therapies that can meaningfully alter the course of these debilitating conditions.

Conclusion: Animal models remain essential in the study of Alzheimer’s Disease, providing critical insights into disease mechanisms and serving as platforms for the development and testing of new therapies. However, the limitations of these models must be acknowledged, and their results should be interpreted with caution when translating findings to human AD.

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