



Investigating the Effectiveness of Disease Models for Modelling of Alzheimer's in the Brain

Medhavi Bhangale

Abstract

This research highlights Alzheimer's disease (AD) and its issue on the global population. It examines the causes of AD through environmental factors, such as age and the molecular level, including improper protein folding, production and protein aggregation, through which analysis of different forms of disease modeling for AD arises. Various forms of disease models that were examined included mouse models, 2D models, organoid models, computational models and Brain on Chip models. The research examined and emphasized each model's benefits and disadvantages, and concluded that the Brain on Chip was more efficient in modeling AD. This is because it incorporates more variables, such as the blood-brain barrier, and several cellular mechanisms undermining the potential factor of initiating AD, such as the development of A β plaques and their impact on blood blood-brain barrier, and overall synaptic connections. Therefore, this results in the deterioration of the neural connection. This paper promotes the need for further studies and research on better modeling of AD.

Keywords

Alzheimer's disease (AD); Dementia; Neurodegenerative disease; Amyloid-beta plaques proteins; Nerve Cells, Tangles; Neuron, Central nervous system (CNS); Protein aggregation; Amyloid precursor protein (APP); APP protein processing; Tau protein; Hyperphosphorylation; Post-translational modification (PTM) Amyloid β (A β); Glial Contributions; Amyloid precursor protein (APP); Precursor protein (PSEN); Presenilin-1 (PS1); Astrocytes; Oligodendrocytes; Microglial cells; Neurofibrillary tangles (NFT);

Longterm potentiation (LTP); Long-term depression (LTD); N-methyl-D-aspartate (NMDA); Glutamate (GLU); Microglia; Blood-brain barrier (BBB)

1. Introduction

1.1. Alzheimer's Disease: Causes, Symptoms and Treatment

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with multiple causes, including environmental factors. The environmental factors related to neurons include age, genetics, and cellular mechanisms. Aging plays the most significant role in the development of AD due to changes, such as the shrinking of certain brain regions, inflammation, blood vessel damage, the production of unstable molecules known as free radicals, and decreased energy production within cells (Ayodeji et al., 2024). AD causes the progressive impairment of behavioral and cognitive functions. The mental functions include memory, comprehension, language, attention, reasoning and judgment. Despite the detrimental symptoms of AD, there is no standardized cure or disease-modifying therapy (Kumar et al., 2024).

1.2. The Impact of Alzheimer's Disease on the Global Population

AD is a prevalent type of dementia, and it accounts for about 70% of dementia cases, affecting 20 million people worldwide (Abijoet al., 2024). Every 3 seconds, people develop Alzheimer's disease. 6.9 million Americans age 65 and older are living with Alzheimer's dementia at the current time. This number could grow to 13.8 million by 2060 (National Library of Medicine, 2024). In 2022, the global population of patients with AD dementia, prodromal AD and preclinical AD was estimated at 32 million, 69 million and 315 million, respectively. Altogether, they represent 416 million across the AD, or 22% of all people aged 50 and above (Gustavsson 2022).

People who are 65 years and older are vulnerable to being diagnosed with Alzheimer's disease. There are fewer than 10% of cases of people being diagnosed with Alzheimer's before that age range. In saying that, the lifetime risk for Alzheimer's at age 45 is 1 in 5 for women and 1 in 10 for men. Furthermore, about 1 in 9 people between the ages of 65 and 84, and 1 in 3 people aged 85 years and older, live with Alzheimer's (National Library of Medicine, 2024). The statistics show that AD is a major concern and continues to increase, affecting millions globally rapidly.

1.3. The Economic Burden of Alzheimer's Disease

As millions are diagnosed with AD, the disease impacts the economy negatively, as it imposes a substantial and growing economic burden worldwide. Research conducted by Lyn Xuan Tay and his team indicated that the cost of care has risen non-linearly with disease severity. Indirect caregiving costs have been identified as the primary contributor to societal and economic costs in community-dwelling patients. Formal caregiving accommodation has caused an increase in direct costs up to 67.3% of the overall economic burden of Alzheimer's disease (Tay et al., 2023). When special caregiving accommodations were implemented in daily care, it resulted in a shift in costs from indirect to direct non-medical expenses.

1.3.1 Information about Non-Medical Costs

More than 11 million family members and other unpaid caregivers provided an estimated 18.4 billion hours of care to people with Alzheimer's in 2023. These figures reflect a decline in the number of caregivers compared to a decade earlier, and an increase in the amount of care provided by each remaining caregiver. Unpaid caregiving for patients with Alzheimer's disease was valued at \$346.6 billion in 2023. Furthermore, the costs extended to unpaid caregivers' increased risk for emotional distress, negative mental and physical health outcomes. Members of the paid health care and broader community-based workforce are involved in diagnosing, treating and caring for people with AD (National Library of Medicine, 2024).

The systematic review by Tay et al. (2024) reported that the annual per capita cost of AD in the United States in 2024 ranges from \$468.28 for mild cases to \$171,283.80 for severe cases. Indirect caregiving costs represent the primary contributor to societal burden in community-dwelling patients. However, when formal caregiving services are utilized, there is a marked shift from indirect to direct non-medical costs. This includes formal caregiving, accounting for up to 67.3% of the total economic burden (National Library of Medicine, 2024).

For example, the annual global cost of AD exceeds US \$1.3 trillion and is projected to rise to US \$2.8 trillion by 2030 (Dementia Statistics, n.d.). These expenses encompass both direct medical and nonmedical costs, as well as indirect costs such as informal caregiving and productivity losses.

The distribution of this economic burden is uneven across populations. Currently, 60% of individuals with AD live in low-and middle-income countries, such as Bangladesh, where healthcare infrastructure is less

equipped to meet growing demands. High-income countries with aging populations, such as Japan, South Korea, Singapore, Australia and New Zealand, face disproportionately high prevalence rates of AD. Consequently, the burden of AD is experienced by the patients, their families, caregivers, and wider health and social care systems (Dementia Statistics, n.d.).

Health and long-term expenses are the leading cause of economic expenses, as the treatment and care are expensive. In 2024, health and long-term costs for people living with Alzheimer's disease were projected to reach \$384 billion (Youngtimers, 2024). The expenses for treatments and care for the patients play a large emotional and financial toll on the family members of the patients. Furthermore, the annual global cost of AD exceeds US \$1.3 trillion, and it is expected to rise to US \$2.8 trillion by 2030 (Dementia Statistics, n.d.).

2. Aims of the Study

Alzheimer's disease is a significant issue as it affects millions of people every year, and takes a toll on families, as the treatment and care facilities are expensive. However, in terms of the increasing prevalence and socioeconomic impact of Alzheimer's disease, the development and critical evaluation of robust disease models remain essential for elucidating its cellular mechanisms and informing therapeutic innovation.

The paper will analyze the main cellular mechanisms underlying Alzheimer's disease (AD) and evaluate the different disease models that are used to model AD. The models include mouse models, 2D disease models, 3D disease models/3D-printed microfluidic disease models/Brain-on-chip models, Organoid models, and Computational models of AD.

3. Hypothesis/Claim of the Research Paper

Out of all the methods of modeling, the Brain-On-Chip models, along with Organoid models, are hypothesized to be proven effective in disease models compared to other models, despite some of their drawbacks.

4. Literature Review

There is no clear or accurate understanding of the cellular mechanism underlying AD. However, it is widely supported that the products of amyloid β ($A\beta$), hyperphosphorylation of Tau proteins, and glial

contributions play a central role in triggering AD pathogenesis (Guo et al., 2020). According to Yale Medicine (2020), Alzheimer's disease occurs when several cellular processes break down. These cellular processes include the accumulation of amyloid-beta plaque proteins around nerve cells. As a result, this can decrease the cells' ability to communicate with each other and effectively relay messages within the brain. Thus, disrupting their ability to transport nutrients due to the formation of disease structures known as tangles (Yale School of Medicine, 2020).

The cellular mechanism begins in neurons that are located in the Central Nervous System (CNS). The Alzheimer's disease pathway is triggered by environmental factors, such as age and the molecular level, which includes improper protein folding and protein aggregation.

4.1. The Link Between Amyloid Protein Processing (APP) and AD

The amyloid- β ($A\beta$) and the amyloid precursor protein (APP) are transmembrane proteins that undergo proteolytic cleavage into defined fragments, and have been implicated in transport in the axon terminal (Muresan et al., 2009). Additionally, it is the principal component of AD-associated amyloid plaques.

Mutations in Presenilin-1 are characteristic of FAD. They can potentially promote $A\beta$ with an irregular protein fold accumulation through increased $A\beta$ production and impairment of autophagy functions. Autophagy is the process by which cells self-digest and protect neurons. In saying that, aged brains have a reduced capacity for autophagy, which results in senescence of microglia. Microglial cells are smaller cells that are derived from stem cells. However, some may be derived directly from neural stem cells. An increase in the $A\beta$ production can act as a barricade for cellular processes, as it prevents the cell from digesting the unwanted cell parts (Zhang et al., 2024).

The Amyloid Precursor Protein (APP) processing refers to the large amounts of APP that are continuously metabolized to $A\beta$ in the brain (O'Brien & Wong, 2011). It is dependent on three proteolytic secretase enzymes: α -, β -, and γ -secretase. Although the function of APP is unknown, its proposed role is a vesicle receptor for the microtubule motor kinesin-1 (Guo et al., 2020). APP processing plays a role in the pathogenesis of Alzheimer's disease. This is primarily because a delayed transport may result in premature cleavage of APP into fragments. The transportation is followed by the release of kinesin-1 from the vesicle and the early termination of transport, which favours the aggregation of $A\beta$ within the neurites.

The aggregation of A β results in detrimental consequences for neuronal function and survival. Thus, potentially resulting in Alzheimer's disease (Muresan et al., n.d.). Therefore, abnormal A β accumulation may initiate the inflammatory cascade in AD (Guo et al., 2020). Amyloid plaques, also known as the pathological hallmarks of AD, are clumps of misfolded proteins that accumulate in the brain, disrupting and killing neurons. The abnormal accumulation of the amyloid plaques results in the progressive cognitive impairment that is characteristic of the widespread Alzheimer's disease (LaFee, 2021).

In AD, factors such as genetic mutations, impaired clearance mechanisms, and interactions with other proteins can influence the accumulation of A β . Accumulation results in the accumulation of plaques through abnormal APP processing. The accumulation of plaques between neurons disrupts the external communication from a cell and triggers inflammatory responses, leading to neuronal damage and cognitive decline. Additionally, these plaques interfere with synaptic function. This function refers to interfering with the communication with other neural cells and contributes to the neurodegenerative processes that can result in AD (Abcam, 2025).

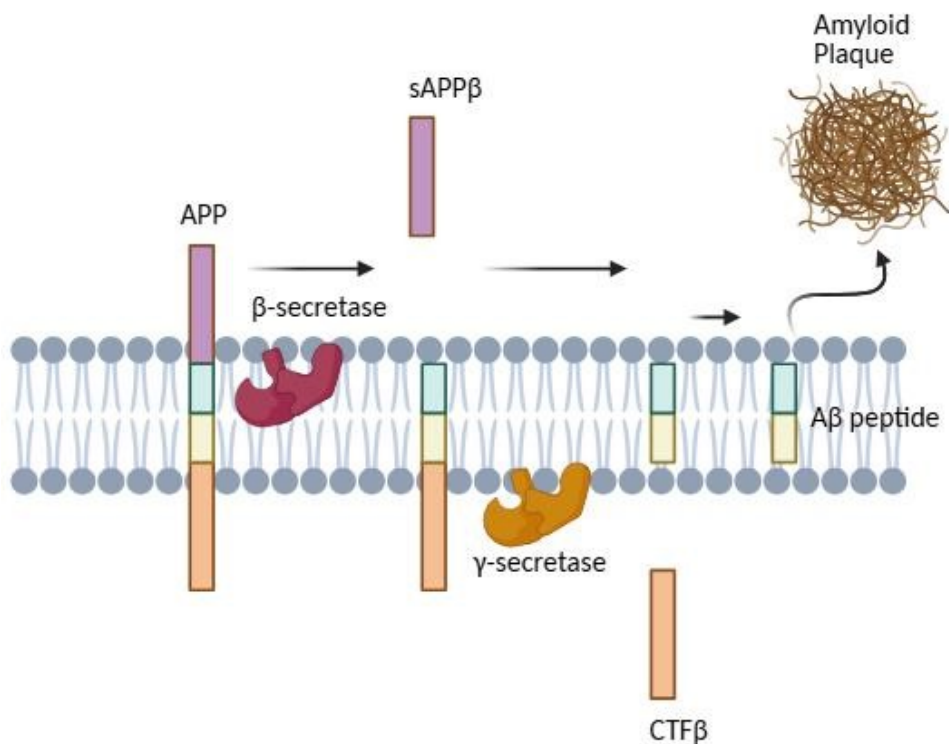


Figure 1: The Amyloidogenic pathway of Alzheimer's Disease (AD)

APP results in the formation of amyloid plaques. B-secretase cuts the soluble APP β protein fragment (sAPP β) from the APP protein. The γ -secretase cleaves the C-terminal fragment β (Generated from the

cleavage of β -secretase). These two cleavage events leave the A β peptide, which aggregates into the amyloid plaques. *Taken from Zhou et al., 2018, and adapted using Biorender.*

4.2. The Link Between Tau Hypophosphorylation and AD

Tau plays a role in the initiation of cell mechanisms and processes for AD. Tau refers to the microtubule-associated protein that forms insoluble filaments, which accumulate as neurofibrillary tangles (NFT) in AD and related tauopathies. The accumulation of abnormal Tau proteins results in the formation of sticky, thread-like structures known as neurofibrillary tangles. This buildup prevents Tau from carrying out its role, and it damages the neuron's inner skeleton, impairing communication between cells (Findely et al.,

2024). Under physiological conditions, Tau regulates the assembly and maintenance of the structural stability of microtubules. In the healthy brain, 2 to 3 residues on tau are phosphorylated. During phosphorylation, Tau has phosphates attached to it. However, in AD, the phosphorylation level of Tau is significantly higher, approximately nine phosphates per molecule (Medeiros et al., 2010).

Tau undergoes post-translational modifications to form Tau Oligomers. Post-translational modification occurs in a protein after translation or after completing its folding. The primary role of PTM is to alter a protein, including tau, to a functional diversity to maintain (Rawat et al., 2022). Tau oligomers are the aftermath of Tau hyperphosphorylation in the route of NFT formation. As hyper-phosphorylated tau dissociates from microtubules, its affinity for other tau monomers leads individual tau to bind to each other. Thus, forming a detergent-soluble molecule and oligomeric tau. The tau oligomers potentiate neuronal damage - specifically, loss of synaptic communication. This leads to neurodegeneration and traumatic brain injury (Shafiei et al., 2017).

Additionally, Tau and beta-amyloid interact in a way that causes each other's pathological effects. Betaamyloid plaques can promote tau hyperphosphorylation. On the other hand, tau tangles can enhance betaamyloid toxicity, creating a vicious cycle that accelerates neurodegeneration. The combined presence of tau tangles and beta-amyloid plaques severely disrupts neural communication and brain function. This interaction leads to widespread synaptic loss, neuronal death, and significant cognitive impairment (Abcam, 2025). Therefore, Tau proteins and Beta Amyloid can affect one another in a positive feedback loop, and in the case of mutations, can result in triggering AD pathways.

Several mechanisms, such as increased activity of tau kinases, chronic inflammation and cellular signaling imbalances can speed up the abnormal accumulation of Tau proteins, and cause tau to misfold and aggregate. Thus, forming tangles that impair neuronal function and communication (Abcam, 2025).

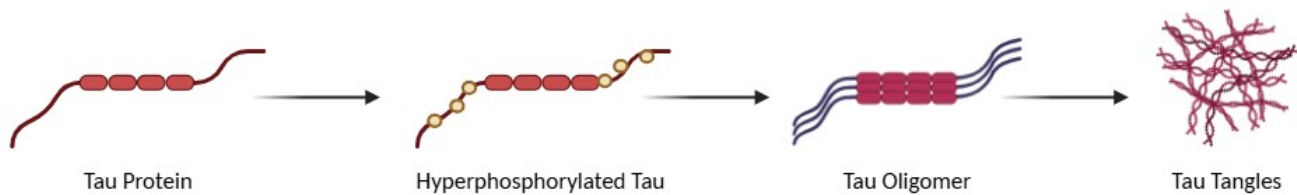


Figure 2: The figure is taken from Zheng & Wang, 2025, and adapted using Biorender.

Figure 2: Hyperphosphorylation of the Tau protein leads to Alzheimer's Disease: Tau protein and the formation of neurofibrillary tangles in the case of Alzheimer's Disease. The Tau protein undergoes post-translational modification (PTM) and gains more phosphates than usual, becoming hyperphosphorylated. The PTM initiates the accumulation of the hyperphosphorylated Tau, which leads to Tau oligomers. This results in Tau Tangle or neurofibrillary tangles.

4.3. Link between Glial Contributions and AD

Unlike neurons, glial cells are cells that do not participate directly in synaptic interactions and electrical signaling. However, their functions help define synaptic contacts and maintain the signaling abilities of neurons. Glia cells have three categories: astrocytes, oligodendrocytes and microglial cells. Astrocytes can mature in the nervous system. They are restricted to the brain and spinal cord. Astrocytes have elaborate local processes that give these cells a star-like appearance. They can maintain an appropriate chemical environment, which is used for neuronal signaling.

Oligodendrocytes are restricted to the central nervous system, and they lay down a laminated, lipid-rich wrapping called myelin around some, but not all, axons. Oligodendrocytes contribute to pathological factors, such as amyloid deposition, tau hyperphosphorylation and microglia activation. These factors are the main components of causing AD (Zhang et al., 2024). Myelin plays a role in the axons of neurons as they speed the action potential. An action potential is a brief, electrical signal that is generated and travels along the membrane of a neuron or muscle cell. It enables communication between cells. In AD, the action potential becomes desynchronized and increases the firing rate. Myelin shares many properties with tissue

macrophages, and is primarily a scavenger cell that removes cellular debris from sites of injury or normal cell turnover (Purves et al., 2001).

Glutamate is the most abundant excitatory neurotransmitter that is released by nerve cells in the brain. It is essential for the establishment of new neural networks, forming memory and learning through a process known as long-term potentiation (LTP) or long-term depression (LTD) of synaptic strength. LTP is the persistent strengthening of synapses between neurons, leading to increased efficiency and responsiveness for a sustained period. LTD is the process that weakens the synaptic strength. The two processes occur upon activation of N-methyl-D-aspartate (NMDA) receptors. NMDA is significant for Glutamate Recycling and maintaining Glutamate Homeostasis (Campos-Peña & Meraz-Ríos, 2014).

Glutamate is recycled and made by glial cells in our brain. Glial cells convert 'used' glutamate to glutamine, which is converted back into glutamate when it is delivered to the terminal area of nerve cells. For the brain to function properly, glutamate needs to be present in the right concentration, in the right places, and at the right time. A significant amount of glutamate can result in Alzheimer's disease (Cleveland Clinic, 2022). Additionally, Glutamate acts on both metabotropic and ionotropic receptors. It is situated at the intersection of several metabolic pathways and is crucial for memory and learning processes (Puranik & Song, 2024).

In normal conditions, Gli1 ion transporters are localized in both nerve endings and surrounding glial cells. The transporters regulate the low concentration of glutamate in the extracellular space. The transport system prevents cell damage, which is generated by excessive activation of glutamate receptors. When a neuron is depolarised, glutamate is released into the synaptic cleft, where it binds to glutamate receptors on pre- and post-synaptic neurons (Campos-Peña & Meraz-Ríos, 2014).

Glutamate is extensively recycled between neurons and astrocytes in a process known as the glutamate-glutamine cycle. The recycling of glutamate has a close relation to brain energy metabolism and is of high importance to sustain glutamatergic neurotransmission. However, a considerable amount of glutamate is also metabolized and serves as a metabolic hub, connecting glucose and amino acid metabolism in both neurons and astrocytes. Disruptions in glutamate clearance, leading to neuronal overstimulation and excitotoxicity, have been implicated in several neurodegenerative diseases.

Furthermore, the link between brain energy homeostasis and glutamate metabolism is gaining attention in several neurological conditions (Andersen et al., 2021).

The loss of synapses and neuronal death in AD impairs glutamatergic neuron activity, which can affect memory, cognition, behavior, and cortical and hippocampal processing. All of these are important for memory. Glutamate (GLU) signaling dysregulation is a major contributor to excitotoxicity and neurotoxicity in AD. Due to the excitotoxicity, it will result in dysregulation of the GLU, which is connected to neurodegenerative diseases, such as AD, and plays a significant role in Neurotoxicity. This is the effect of substances on the Nervous system, which results in dysfunction (Puranik & Song, 2024).

The overactivation of NMDA can result in excessive influx of Neural Calcium (Ca^{2+}) ions into neurons, which is caused by one of the primary processes known as the chronic overactivation of NMDA receptors. Several cellular activities, such as synaptic plasticity and neurotransmitter release, rely on Ca^{2+} under typical circumstances. Synaptic plasticity is the ability of the synapse to change and adapt as a response to activity. However, dangerous quantities of intracellular calcium build up when NMDA receptors are continually engaged. This excess sets off a cascade of detrimental intracellular processes. This includes several calcium-dependent enzymes, including calpains, protein kinases, and phospholipases, which would be activated by the high calcium concentration (Puranik & Song, 2024).

The enzymes set in motion processes that lead to the production of reactive oxygen species (ROS). An imbalance between free radical production and the body's detoxification capabilities causes oxidative stress, which in turn is caused by ROS formation. Damage to lipids, proteins, and DNA caused by oxidative stress results in genetic mutations, decreased protein function, and a breakdown of cell membrane integrity. The viability and health of neurons may be severely compromised by this kind of injury. The continued elevation of intracellular Ca^{2+} interferes with mitochondrial activity and causes oxidative stress as well (Puranik & Song, 2024).

4.4. The Link Between Microglia Deterioration and Alzheimer's

Microglia, in a way, acts like an immune cell and cellular debris, damaged neurons and toxic protein aggregates like $\text{A}\beta$. $\text{A}\beta$ is generated in neurons and then released to the extracellular space, where it can be degraded or cleared by microglia and astrocytes (Guo et al., 2020). Research has established that

microglia employ autophagy when responding to amyloid plaques in brains affected by Alzheimer's disease.

A study conducted by Shahidehpour and his team found that tau was the initiating factor leading to the development of dystrophic microglia, which was then associated with the spread of amyloid- β and tau. These results suggest that a loss of the protective role of microglia could contribute to the spread of Alzheimer's disease (Shahidehpour et al., 2025). Microglia exert protective function by phagocytosing and clearing pathological protein aggregates and play detrimental roles due to excessive uptake of protein aggregates, which would lead to microglial phagocytic ability impairment, neuroinflammation, and eventually neurodegeneration if there is a dysfunction (Gao et al., 2023).

4.5. The link between the Blood-Brain-Barrier (BBB) and AD

The blood-brain barrier (BBB) is highly selective in the brain. It protects the brain from exogenous substances by strictly regulating the transport of molecules from the blood vasculature into the brain. The BBB has a multicellular structure. It mainly comprises endothelial cells (ECs), pericytes, and astrocytes (Cui & Cho, n.d.). Endothelial cells are a natural barrier between the blood and tissues. Deterioration of Endothelial cells can relate to neurodegenerative diseases, such as AD. Pericytes are specialized cells in blood vessel walls that regulate capillary blood flow and maintain the BBB. Additionally, Pericytes control blood vessel development and contribute to tissue repair and homeostasis. Depletion as well as dysfunctional Pericytes have been observed in the cerebral cortex and hippocampal region in AD patients (Zhang et al., 2024).

The BB dysfunction induces the failure of A β transport from the brain to the peripheral circulation across the BBB. Additionally, the failure of A β transport to the brain is the result of decreased levels of LRP-1 (low-density lipoprotein receptor-related protein 1) and increased levels of RAGE (receptor for advanced glycation endproducts). The pathogenesis of AD is related to the BBB structural components, including pericytes, astrocytes, vascular endothelial cells, and tight junctions. Tight junctions among adjacent cells form the basic structure of the BBB. They limit paracellular permeability. A study conducted by Yamazaki and his team found that as AD progressed, the tight junction proteins drastically decreased as A β and Tau numbers increased (Yamazaki et al., 2019).

BBB dysfunction will trigger neuroinflammation and oxidative stress. Then it enhances the activity of β secretase and γ -secretase, and finally promotes $A\beta$ generation. A progressive accumulation of $A\beta$ in the brain and BBB dysfunction may become a feedback loop that gives rise to cognitive impairment and the onset of dementia. The correlation between BBB dysfunction and tau pathology has been well-reported. Therefore, regulating BBB function may be a new therapeutic target for treating AD (Cai et al., 2018).

Analyses of Cellular Processes Resulting in Alzheimer's Disease

All the cellular mechanisms interconnect with each other and play a role in triggering AD progression. The overproduction of Amyloid Beta results in the accumulation of Amyloid Beta Plaques results in neuronal damage and dysfunction, leading to the development of Alzheimer's disease symptoms, such as memory loss and cognitive impairment. These plaques disrupt synapse signaling, trigger inflammation, which can decrease memory formation.

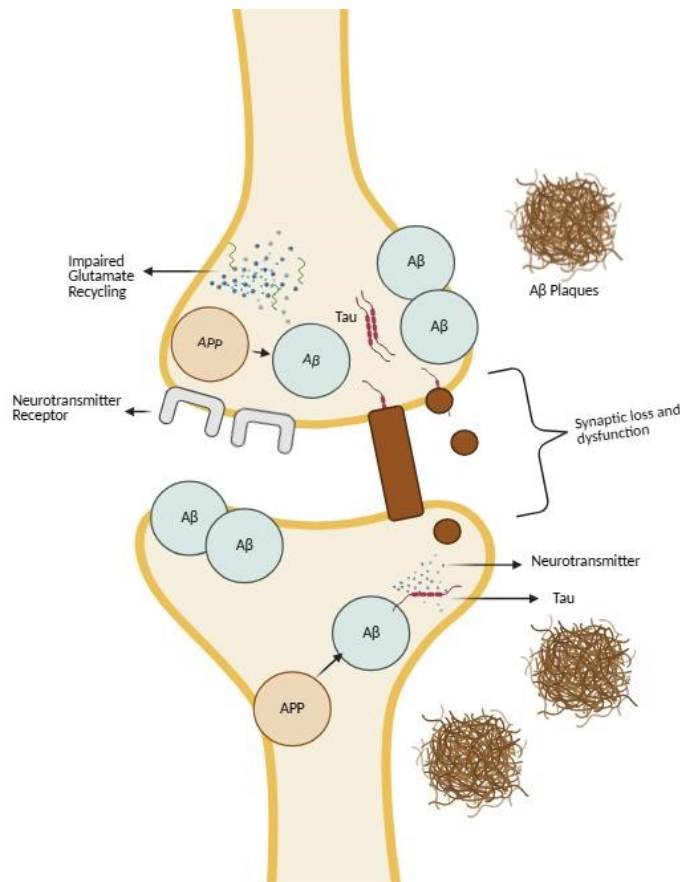


Figure 3: The cellular impact of amyloid beta plaques and tau tangles on the synapse, leading to Alzheimer's disease

The Amyloid Precursor Protein (APP) is processed into amyloid beta peptides, which accumulate inside and outside the neuronal cells, and form an accumulation of A β Plaque. The A β Plaque, in addition to hyperphosphorylated tau proteins, causes synaptic loss and dysfunction in the neuron. As there is an accumulation of the A β levels, the glutamate recycling becomes irregular and dysregulated. The soluble, hyperphosphorylated tau protein will directly move across the plasma membrane or through the formation of nanotubules, which helps the translocation of tau intracellularly. Taken from Rawat al., 2022, and adapted using Biorender.

5. Methodology

5.1 Exploring Disease Models to Model Alzheimer's

5.1.1. Mouse models

A mouse model is a laboratory mouse used to study some aspect of human physiology or disease. There are a variety of different model organisms. The more common one is a transgenic mouse (Drummond & Wisniewski, 2018). They are used to represent the human brain with AD as they share mammalian features with humans and suffer from many of the same diseases, such as Alzheimer's (National Human Genome Research Institute, n.d).

Common modeling conducted with mice is Transgenic mice, which involves inserting a mutation into the mice's genes. Transgenic modeling has been pursued on the basis of the amyloid hypothesis. It has taken advantage of mutations in the amyloid precursor protein and the presenilins that cause familial forms of Alzheimer's disease (Elder et al., 2010). There are different types of transgenic models. In saying that, some of the most commonly used models to examine Alzheimer's disease are Tg2576, 5xFAD, and 3xTg.

Model 1: Tg2576 Understanding the Model

The Tg2576 model expresses the 695-amino acid isoform of human APP with the Swedish mutation inserted into the hamster prion protein (PrP) cytoplasmic vector. The results show a fivefold increase in A β 40 and a 14-fold increase in A β 42/A β 40. The Tg2576 mouse model is considered a modest neurodegenerative model, possibly due to the promoter used in overexpressing APP. This model is reasonably suited for studying the pathogenic processes of amyloid initiating AD (Zhong et al., 2024).

Findings and How They Relate to AD and Mortality

A study conducted on the Tg2576 model by Michael Z. Zhong and his team in 2024 found that other studies observed that around 6 to 7 months of age, Tg2576 mice accumulated A β 40 and A β 42 species that were resistant to Sodium Dodecyl Sulfate (SDS). Furthermore, around 7 - 8 months of age, amyloid plaques became dense and visible, with a wide spread of plaque having accumulated and deposited on the mouse brain parenchyma, and vascular structures by 11 to 13 months of age. Research indicated that female Tg2576 were more susceptible to developing plaques compared to their male counterparts. Unlike most other APP models, cognitive decline in Tg2576 mice manifested months before the onset of pathology. At the same time, cognitive decline occurred in proximity to other models (Zhong et al., 2024).

In addition, cognitive impairment in Tg2576 mice can be manifested as impaired spatial and working memory measured by behavioral tasks, such as the Y-maze, the Morris water maze, and the contextual fear conditioning tests. The Y-maze test is used to measure the short-term spatial memory of animals as a type of recognition. The test is based on the mice's curiosity to explore new environments while there are no positive or negative stimuli in the maze (Kraeuter et al., n.d). Sex-specific differences in cognitive impairment showed a rapid progression in females. Similarly, a greater degree of cognitive impairment was observed in female mice with the Tg2576 mouse model (Zhong et al., 2024).

Alongside cognitive deficits, other behavioral disturbance was reported in the Tg2576 mouse model, such as non-rapid eye movement (NREM) sleep disorder and an increased susceptibility to seizures. At 22 months of age, male Tg2576 mice had disrupted sleep EEG rhythms, and female Tg2576 mice had decreased REM sleep and delayed sleep onset. It was speculated that cholinergic dysfunction may contribute to sleep and circadian rhythm abnormalities. Moreover, when compared to wild-type (WT) littermates, Tg2576 mice at the age of 12 to 14 months were more susceptible to electrically evoked seizures and an increased sensitivity to kindling epileptogenesis. Another study reported a high susceptibility to audiogenic-induced seizures in Tg2576 mice that was reduced by passive immunisation with an anti-A β antibody therapy. Overall, this increased susceptibility to seizures may contribute to a higher mortality rate in Tg2576 mice (Zhong et al., 2024).

In addition, while synaptic loss was absent in Tg2576 mice, changes in synaptic plasticity were reported with impaired Long Term Potentiation (LTP) that was measured in the dentate gyrus and CA1 region of the hippocampus. LTPs play a role in memory formation and learning by strengthening the synapse

persistently between neurons. Additionally, the dentate gyrus permits information to enter the forming hippocampus. In the hippocampus, the CA1 neurons play a role in retrieving memories. The study of the hippocampus and cortex of aged Tg2576 mice conducted by Zhong and his team showed a reduction in the process where acetylcholine, the primary neurotransmitter in the cholinergic system, binds to two main types of receptors: nicotinic and muscarinic, and decreased choline uptake (Zhong et al., 2024) .

In other words, AD, which results from a loss in choline signaling, can affect the nicotinic and muscarinic receptors. In addition, cortical neurons derived from Tg2576 mice were found to have an impaired retrograde trafficking of Brain-Derived Neurotrophic Factor (BDNF). Thus, leading to cholinergic degeneration, even though the mouse model did not show any neurofibrillary tangles. Cortical neurons store long-term memories by forming stable, permanent changes in their synaptic connections through synaptic plasticity. However, in the case of AD, cortical neurons cannot store long-term memories as the synaptic connections are destroyed (Zhong et al, 2024).

This model was observed as being highly lethal, and it was shown that male mice tended to be aggressive, which required single housing. However, this model is reasonably suited for understanding the pathogenic processes of amyloid in AD (Zhong et al, 2024).

Model 2: 5xFAD

The 5xFAD mouse is a genetically modified mouse model of Alzheimer's Disease (AD), which has a mutation that speeds up APP processing and rapidly develops amyloid plaque disease. The 5XFAD transgenic mice overexpress the following five FAD mutations: the APP(695) transgene harbors the Swedish (K670N, M671L), Florida (I716V), and London (V717I) mutations. The PSEN1 transgene harbors the M146L and L286V FAD mutations (Oblak et al., 2023).

Research conducted in the Vassar laboratory, where 5xFAD mice were generated, has reported that these synergistic mutations lead to fast disease progression within the 5xFAD mice. In addition, the research indicated that 5xFAD mice show high expression of cerebral A β 42 after 1.5 months of age, and amyloid deposition at 9 months of age. This resulted in neurodegeneration and neuronal loss, as well as an increase in glial cells immediately after 2 months (Broek et al., 2022).

Model 3: 3xTG

The triple transgenic 3xTg-AD mouse is one of the most studied mouse models of AD. The mouse model possesses three mutations in homologous mouse genes, which are similar to some extent to human Alzheimer's disease (Falangola et al., 2022). Research conducted by Barber and her team (2024) found that there was a difference in the detection of AD pathways between the genders of the mouse models. For instance, 3xTg-AD females significantly outlived 3xTg-AD males and exhibited progressive Alzheimer's nervous system. 3xTg-AD males demonstrated progressive inflammation of the liver, an enlargement of the spleen, circulating inflammatory proteins, and minimal Alzheimer's neuropathological hallmarks. However, 3xTg-AD males experienced an accelerated upregulation of immune-related gene expression in the brain. This was different from what the females experienced.

The limitations of the scientists' study were that the sample size of 3-8 3xTg-AD transgenic mouse model of 3 to 8 mice per gender, strain, and age group was used to investigate the effects of how gender and age play an important role in diagnosing AD. The team experimentally examined nearly 30 subcohorts of mice between the ages of 3 and 24 months old, which made it particularly challenging to achieve larger sample sizes in each grouping. This is especially true in older mice with higher rates of mortality. Despite constraints on sample size, our histology data established age and gender specific effects of moderate and large size. The sequencing data revealed differentially expressed genes with a high degree of statistical significance (Barber et al., 2024).

General Limitations of Mouse Models

Mice are less reliable as models of human disease. This is because the networks linking genes to disease are likely to differ between the two species (Perlman, 2016). Mice are not fully representative of humans, especially in terms of brain structure. Two-dimensional (2D) culture models and animal models are used as standard techniques for drug development and mechanism research. However, none of these gold standard methodologies can perfectly mimic the physiological settings and complexity of the human brain. Therefore, there is a technological gap that needs to be addressed (Rodrigues et al., 2024).

2D systems are in vitro models that enable fast and less costly modelling experiments. In saying that, there are several limitations to emulating the complex structure of the human brain. This includes cell-cell interaction and organized three-dimensional (3D) neuronal populations. They have proven to be ineffective in the prediction of neuro-cytotoxicity and drug screening. On the other hand, animal models,

such as the ND-induced mouse, can provide more valuable physiological and mechanistic insights for the understanding of molecular and cellular pathogenesis. Nonetheless, due to species-specific differences between humans and animals, the prediction of drug/nanoformulation (NFs) efficacy and accurate recapitulation of ND are limited (Rodrigues et al., 2024).

Organoid Models to model AD:

Limitations of 2D Models and Strengths of 3D Models

Despite their successes, 2D and animal models can only capture a fraction of AD mechanisms due to their inability to recapitulate human brain-specific tissue structure, function and cellular diversity. Recently, the emergence of three-dimensional (3D) cerebral organoids using tissue engineering and induced pluripotent stem cell technology has paved the way for developing models that more accurately resemble the features of human brain tissue compared to prior models (Sreenivasamurthy et al., 2022).

The Importance of Brain-On-a-Chip (BoC)

Today, Organ-on-a-chip (OoC), specifically Brain-on-a-chip (BoC), emerges as an advanced microfluidic platform combined with 3D tissue culture techniques to recapitulate human physiology and homeostasis. This is at a lower cost and higher reproducibility, and additionally bypasses the ethical concern regarding the use of animals for testing of human products, which is in line with the 3Rs' animal principle. Additionally, it can overcome the low capability of animal tests to predict the effects of drugs and NFs (Rodrigues et al., 2024).

Brain-on-a-chip is an engineered model platform to replicate the structural and functional aspects of brain tissue (Liu et al., 2022). Brain-on-a-chip platforms offer an in vitro approach to replicating brain function, allowing for the real-time investigation of disease onset, progression and potential therapeutic interventions. These systems employ patient-derived neurons, which can be cultured and differentiated directly on the chip. Using human cells significantly enhances the model's relevance compared to traditional animal models, making it more suitable for studying diseases. In addition, the device architecture, material selection and biochemical functionalization support the control of cell proliferation and organization within the chip environment (Rodrigues et al., 2024).

The Developments of BoC

Recent studies have highlighted that there is a development of a brain-on-a-chip with human brain tissue. The scientists at the Morgridge Institute for Research in Wisconsin, who are supported by the NIH, generated multiple types of brain cells from a single stem cell source. Stem cells have the remarkable potential to develop into many different cell types. Stem Cells play a crucial role during early life and for embryonic growth. In adults, stem cells function in tissue repair and maintenance as a source of replacement for damaged cells. When these brain cells are added together in a nutrient-rich framework, they form complex, layered tissue, complete with nerve structures and blood vessels.

The goal is to use the model to predict the effects of potential toxins on brain development. By conducting the initial testing in a laboratory setting with human tissue, the scientists may be able to predict potential toxic compounds on the brain with greater accuracy than current testing methods allow (National Center for Advancing Translational Sciences, 2024).

Future Implications of Research

Researchers can plan to generalize the Brain-to-Chip model to other organs outside the brain. Additionally, link the brain and blood-brain barrier models with chips based on other human organs. This will contribute to our knowledge about the 'downstream' effects of experimental brain treatments on other organs. The processing of drugs by other organs of the body (for the liver) could affect the ability of drugs to cross the blood-brain barrier, and also provide crucial information for scientists working to develop new and more effective treatments (Kawakita et al., 2022).

Using Microfluidic Technologies

The advancements in microfluidic technologies have significantly improved brain modeling capabilities as the model includes factors such as the asymmetric spatial organization of dendrites and axons, the capacity to model the blood-brain barrier (BBB), and the incorporation of interstitial flow dynamics (Timofeeva et al., 2025). A research team at Vanderbilt University (supported by NIH) is developing a device that scientists could use to test compounds for their ability to cross the blood-brain barrier. The researchers used stem cell technology to generate brain tissue and blood vessels for the device (National Center for Advancing Translational Sciences, 2024). The team generated brain cells and blood vessels from induced stem cells, specifically pluripotent (iPSCs) derived from adult donor cells.

iPSCs can develop into various types of brain cells and organize themselves into layers, complete with nerves and blood vessels. Other iPSCs develop into cells that form tiny blood vessels. On the chip, the brain cells and blood vessels are separated by a membrane that acts like the blood–brain barrier (National Center for Advancing Translational Sciences, 2024). Organ-on-a-chip technology, a microphysiological system where cells and tissues can be cultured, has been applied to overcome limitations of conventional in vitro BBB models. It is composed of microfluidic devices that can simulate tissue-and organ-level physiological function (Cui & Cho, n.d.).

The limitations of the brain chip can only interact with certain areas of the brain. While this limitation could be improved in the future, it currently limits treatment possibilities. This technology is currently in the very early stages, which makes the timeframe for possible developments and when this technology will reach peak performance uncertain. In addition, studies to understand the possible effects of the chip on human health are still ongoing. Studies on the safety and effectiveness of this technology have not yet been completed (Nurali, 2025). Another limitation includes focusing on a single person only, and it needs to be further generalized to the population.

Computational Models:

Computational modeling of AD involves the use of simulation studies of complex systems using Mathematics, Physics and Computer Science. Computational models contain numerous variables that characterize the system being studied. They are modeled through simulations by changing the variables independently or in combination, and observing the outcomes. Computer modeling allows scientists to conduct thousands of simulated experiments by computer (National Institute of Biomedical Imaging and Bioengineering, n.d). Mathematical models of complex diseases, such as Alzheimer's disease, have the potential to play a significant role in personalized medicine. The models can be personalized by fitting parameters with individual data for the purpose of discovering primary underlying disease drivers, predicting natural history, and assessing the effects of theoretical interventions (Petrella et al, 2024).

Research conducted by D. Jones and his team on a computational model of neurodegeneration in Alzheimer's disease attempted to link low-dimensional patterns of neurodegeneration to the existing neuroscience literature. This includes describing gradients of functional connectivity, task activation patterns, a variety of AD biomarkers, brain aging and distinct clinical syndromes that selectively impair cognitive functions. The goal of the experiment was to report a low-dimensional representation of

neurodegeneration and characterize the relationship to fundamental features of AD. Therefore, linking the relationship to the neuroscience literature and clinical syndromes related to brain function (Jones et al., 2022).

The goal is accomplished through patient data, which is used to derive the low-dimensional manifold through a latent space representation of glucose uptake across the AD clinical spectrum. The mental functions are significant for observing manifolds by using a functional meta-analysis and compared to functional connectivity data. In addition, application and external validation of the predictive ability of the observed manifold in a large multi-site study, and additional clinical construct validation of the functional-anatomic mapping. This can be conducted by projecting data from normal aging and clinically defined dementia syndromes, selectively targeting memory, executive functions, language, behavior, movement, perception, semantic knowledge, and visuospatial abilities. In the experiment, the team analyzed 423 AD patients using FDG-PET and validated findings in a separate cohort of 410 individuals. The experiment concluded that degenerative patterns can be associated with computational principles in our model. In this computational model of mental functions, the observed low-dimensional representation of neurodegeneration is interpreted as quantifying latent parameters within the manifold (Jones et al., 2022).

Limitations of Computational Models

One limitation of computational models is that experimentally assessing such a global theory is logistically impossible to achieve, as the number of variables is substantial. This leads to ethical, logistical and financial difficulties when studying human patients. This includes the lack of causal studies, the long duration of neurodegeneration, and the always incomplete selection of biomarkers in clinical studies due to resource and time constraints.

6. Findings & Discussion What the Results Indicate

The research has found that, unlike the other models, Brain on Chip (BoC) can model the complexity of the brain structures and include other factors, such as the flow of blood into the brain in multiple directions. This can play a significant role in realism. The BoC is designed to predict the effects of potential toxins on brain development.

In addition, the BoC can combine a microfluidic platform with 3D tissue culture techniques that can simulate human physiology and homeostasis at a lower cost and higher reproducibility. The microfluidic

device can be used without animal testing, without human subjects, and just with human cells. The BoC uses human tissue, which can predict potential toxic compounds on the brain with greater accuracy than current testing methods. This is unlike the mouse models that the paper has found to be least accurate, as mouse brains do not have the same networking system and brain functions as humans.

Computational models are less effective in modeling AD, as using mathematical computations to model the human brain is less accurate if the computations are not precise. The models lack the ethics of analyzing human brains and fail to incorporate other factors, such as the brain barrier, despite the model's complexity, which is similar to the BoC. Despite the microfluidic device's advancement in modeling the brains of AD patients to predict the tissue's reactions to the brain, the brain chip is a recent model. Thus, the model needs to have more research conducted on it.

Another limitation of this research is the potential development and advancements in the newer technology, such as organoids and recent improvements of BoC, to model AD. This incorporates the complexity of the brains of patients with Alzheimer's disease, which needs to be further studied. The challenges that were faced in this study included the lack of studies on the cognitive functions and cellular mechanisms, specifically AD pathways. With further studies, there can be in-depth knowledge, which benefits the development of medicines for patients with AD and/or other neurodegenerative disorders.

The limitations of this study include the fact that not enough research was conducted in terms of BoC being a recent model. Thus, this needs further investigation in the future. In addition, the study needs to incorporate more factors that may play a role in initiating the progression of AD. For instance, Tau hyperphosphorylation, glial contributions, and rapid production of Amyloid-Beta plaques, and investigating why these processes occur. With a better understanding of Brain On Chips, scientists can incorporate ethical issues that can arise with the new advancement. Furthermore, more trials need to be conducted to get a deeper and accurate knowledge of how BoC can be helpful to simulate the brains of AD patients in a simpler yet deeper approach.

6. Conclusion

The paper has analyzed the main cellular mechanisms underlying Alzheimer's disease (AD). The paper evaluated the different disease models that are used to model AD, and compared their advantages and disadvantages. The paper has found that the brain-on-chip is more effective in modeling Alzheimer's

disease. Primarily, this is because it provides an overall understanding of how cellular mechanisms work in the case of AD, offering a more realistic, comprehensive, and interactive modeling of the brain and each of the processes that occur. The processes include the Blood Brain Barrier and the production of A β , which improves accuracy and reduces errors compared to other models. Additionally, the Brain on Chip will enable observing drug reactions within the brain simulation.

Out of all the methods of modeling, the Brain-On-Chip models, along with Organoid models, are hypothesized to be proven effective in disease models compared to other models, despite some of their drawbacks. For example, BoC was shown to include specific details of the brain, the Blood-brain barrier, and complex veins, unlike other modeling methods. The hypothesis was proven to be correct, as the paper proves that BoC is the most effective method of modeling the AD brain. The paper evaluated the pros and cons of each model and determined which model is more effective in modeling AD. The paper interprets various models used to effectively model the brains of AD patients, aiming to enhance understanding of AD and inform future studies. on AD, for better treatments.

The findings of the results point out that although the brain-on-chip is a recent model, it plays a larger role in simulating AD through drug reactions of cells. Additionally, with the use of human cells rather than human/ animal test subjects, there is a better understanding of treatments for AD. BoC can also account for post-mortem trials on patients with AD, since cells can be generalized to the population.

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