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REVIEW ARTICLE

Alzheimer's Disease: What Do We Know About It and How Can We Tackle It?

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ABSTRACT: Alzheimer's Disease (AD) is one of the leading causes of death in the global senior population, yet its pathology is still not completely understood. Treatment opportunities are hindered by this lack of knowledge and heavy controversy around the cause of AD. This review aims to provide information about the origins of AD, molecular and pathological underlining of the disease, as well as addressing the current state of treatments. Additionally, it includes the challenges that are still prevailing within this frame of research and a thorough and backed evaluation of the current state of AD research, which personalizes this review. With treatment approaches being such a broad topic, this article intends to portray select and different approaches for pharmacological intervention. Methods of research, such as animal models, are thoroughly explained with detailed examples. Furthermore, links to pressing modern issues such as the COVID-19 pandemic are also highlighted. Though it covers a wide scope of Alzheimer's Disease research, its main focus is to emphasise the debate and uncertainty about its pathology to be able to close with an evaluation on how treatment approaches can work around this.

KEYWORDS: Cellular and Molecular Biology; Neurobiology; Neuroscience; Neurodegeneration; Alzheimer's Disease.

Introduction

Being a disease primarily affecting those above 65 years of age, an increasing aging population and life expectancy play an important part in the prevalence of Alzheimer's Disease. The United Nations stated that the global population of citizens older than 60 years in 2017 was over twice than what it was in 1980 – 962 million in comparison to 382 million. Another key concept that was pointed out was, that between 2017 and 2050, the number of people aged 80 years or over is expected to increase more than threefold – from 137 million to 425 million.[1] With an increased number of vulnerable people, the number of Alzheimer's cases is certain to escalate.

According to the Global Health Observatory, an initiative by the World Health Organisation (WHO), life expectancy has increased by over 6 years between 2000 and 2019; it stood at 66.8 years in 2000, and 73.4 years in 2019. However, an important factor to be considered is that healthy life expectancy (HALE) has not kept up to speed, and has only increased by 5.4 years - from 58.3 in 2000, to 63.7 in 2019. HALE refers to the average number of years that can be lived without disease or injury – in complete health.[2] Despite the 8 % increase in HALE, it was not indicative of fewer years spent with afflictions or disability, but instead a declining mortality rate. This is further testimony to the notion that an extended life expectancy is likely to bring complications such as neurodegeneration.

Based on this information, it can be easily deduced that the reason such a disease is so much more rampant in our modern medical setting than it was in the past can be attributed to both this increase in life expectancy, without health moving in synchronisation, and the number of elderly citizens. It is thus also understandable why most of the progress in understanding, identifying, and observing AD increased in the late 20th century. Taking all of this into account, communal understanding on a widespread disease as such is necessary to scientifically progress. In specific, in this review article the aim is to cover the underlying mechanisms known in Alzheimer's Disease, and to search for therapeutic approaches, and finally, conclude with a critical evaluation of the ambiguity around its cause and future treatment possibilities.

Discussion

Recognition of a Novel Disease of the Cerebral Cortex:

A brief outline into the history of dementia would date as far back as 2000 B.C. At this point in time, the ancient Egyptians were already conscious of memory declining with age - though this remained the extent of their knowledge on the topic for a long period of time.[3] Over the years, the concept of dementia was debated and often believed to have religious ties, like in the theocratic Middle Ages, when dementia or senility was viewed to be a punishment for sin.[4] It was not until 1797 when dementia was finally accepted as a medical term by Philippe Pinel.[5] In 1910 Emil Kraepelin, later classified dementia into presenile and senile dementia; the onset of presenile dementia is before the age of 65 and the onset of senile dementia is after the age of 65. He was also the first to name "Alzheimer's disease" in honour of Alois Alzheimer, who Kraepelin was the student of.[6]

The patient of Alois Alzheimer, Auguste Deter, was presented to the clinic in 1901 at 51 years of age with signs of delusion and memory impairment. Her conversation and writing skills deteriorated and she had a change in behaviour as she became more suspicious and started having hallucinations. Her condition only exacerbated with failures in her declarative memory and psychological social disability. She was seemingly aware of her delusion, as when she could not respond to Alzheimer's questions she would repeat, "So to speak, I lost myself." Taking

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into account all these symptoms, he was able to diagnose her with presenile dementia.[7]

In return for the hospital expenses over years of admission, the patient's medical records and brain were consented to be used for research upon her death. Alzheimer performed post-mortem analysis of his patient with progressive cognitive disorder as he named it and identified pathological features which he connoted as might be the reason for the disease. The regions in her brain as we know now responsible for memory, language, judgement, and thinking had shrunk to a great degree, and her cerebral cortex was also thinned. The two things that institute the main hypotheses for AD onset today were the senile plaques he found in neurons, stirring the amyloid hypothesis, and the tangles in the nerve fibres, which are the focus of the tau hypothesis. These neurofibrillary tangles were nothing like ever seen before, and the senile plaques were something known to be found in patients above 70 years of age, much older than Auguste was at her death.

It was only later after more research into memory and memory stores when it was discovered that AD typically causes a loss of semantic knowledge and even retrograde amnesia in later stages.[8,9] However, the location of the dementia could cause this to vary; for example, subcortical or frontotemporal dementia patients only had difficulty with systematically retrieving information from their semantic memory stores, but could still retain the knowledge well.[10, 11] Studies on Auguste, however, were not this in depth, as it was merely a first insight into Alzheimer's Disease.

Neurobiology of AD: Underlying its Pathology:

There are several hypotheses that are the roots of heavy debate between researchers and exemplify the mystery of this disease itself. The first approach explaining the molecular pathology of AD to be studied was the cholinergic hypothesis. Defined as a key degenerative process for more than 30 years, it describes the selectively damaged groups of cholinergic neurons in regions of the brain that are fundamental to learning, memory, conscious awareness, attention, and alternate similar processes, namely the hippocampus, frontal cortex, amygdala, nucleus basalis, and medial septum.[12] Aging typically results in cholinergic hypofunction, but pathological aging, such as in Alzheimer's disease, is where neuronal cell loss is predominantly found. Severe loss of cortical cholinergic innervation has consistently been recorded both in the advanced stages of AD and presenile AD. However, patients with mild cognitive impairment (in which some form of cognitive decline more than healthy aging, but less than serious dementia is observed) or any early form of AD have only a loss of cholinergic function, without any neurodegeneration.[13] Nonetheless, this loss of function is still suggestive of the cholinergic hypothesis being a valid explanation of the pathogenesis of AD. In this hypothesis, there are a few main alterations in cholinergic neurons considered: high-affinity choline uptake, impaired acetylcholine release, deficits in expression of nicotinic and muscarinic receptors, dysfunctional neurotrophin support, and deficits in axonal transport.[14,16]

Linking back to two of the main histopathological hallmarks in A – β-amyloid plaques and neurofibrillary tangles – there is plenty of evidence implying that β-amyloid plaques may potentially be a trigger to cholinergic dysfunction through affecting NGF signalling by acting on α7 nicotinic acetylcholine receptors. This in turn mediates tau hyperphosphorylation and interacts with acetylcholinesterase, which mainly affects the proteome in cholinergic neurons.[13] These points all indicate that implementing an early anti β-amyloid strategy could prevent cholinergic deficits and cognitive impairments associated with normal and pathological aging.

The amyloid cascade hypothesis focuses on amyloid neuritic plaques, which are due to the abnormalities in the function and secretion of the amyloid precursor protein (APP). Essentially, the APP is encoded by the APP gene and while remaining rather elusive, many studies suggest that it directs neuron migration during early brain development. Enzymes fragment the protein into peptides, two of which being soluble amyloid precursor protein (sAPP) and amyloid beta (Aβ) peptide.

It is speculated that sAPP may have a role to play in the early formation of neurons in the brain, and may also be able to control protein function and activity, as well as having an age-dependent role in synaptic growth and plasticity.[17] Aβ peptide focuses on neuronal plasticity and has a high resistance to proteolytic degradation. It consists of 37-43 amino acids, but the most common isoforms are 1–40 and 1–42.[18] The 1–42 isoform has the greatest toxicity and is the most hydrophobic isoform, and generally forms the core of the amyloid plaques due to its tendency to aggregate.[19, 20]

As one of the reasons for the plaque formation, the mutations in the APP gene can bring rise to one of two issues: an increased amount of amyloid β peptide, or production of a stickier and longer form of it. Upon being released from the cell, these fragments can accumulate into plaques – amyloid plaques.[21] There are also other differences between normal and aged subjects that are involved in plaque formation. In normal individuals, β- and γ-secretase extracts amyloid β from APP, and it immediately gets degraded when released outside of the cell. Under the pathological conditions of an Alzheimer's patient, individuals will have a decreased metabolic ability to remove amyloid β, causing accumulation of these peptides, hence creating plaques.[22]

Masses of Aβ are mostly made up of Aβ 40 and Aβ 42, which are, respectively, composed of 40 and 42 amino acid residues. Amyloid fibrils can be formed when there is more Aβ 42, and these can also gather into senile plaques.[23] These plaques can cause neurotoxicity, neurodegeneration, and cell death by inducing tau pathology. Furthermore, it was even suggested that amyloid oligomers may be more neurotoxic, rather than Aβ plaques being what causes neuronal cell death.[24] Recent research induces AD pathology by injecting these Aβ oligomers into mice's hippocampi, where oxidative stress, inflammation, and tau phosphorylation are induced as oligomers interact with both neurons and glial cells.[25]

(MAPT) and are able to handle events like phosphorylation or other post-translational modifications.[27] However, upon being hyperphosphorylated, tau detaches from these microtubules, and forms NFTs and paired helical filaments (PHFs) as it accumulates. This hypothesis is often argued to be more

reasonable than the amyloid hypothesis due to the pathology of NFTs and the τ protein coming before Aβ plaque formation, suggesting that the aggregation and phosphorylation of tau predominantly causes neurodegeneration.[23]

Microtubules are unstable and dynamic structures, which constantly undergo assembly and disassembly. When tau is bound to microtubules in healthy neurons, it promotes polymerisation and stability.[28] Studies have suggested that the tau protein plays a role as a recruiter of EB proteins to the +ends of microtubules, which contribute to microtubule dynamics regulation.[29] Microtubule-Associated Proteins (MAPs) such as MAPT are involved in the modulation of microtubule dynamics, and thus are associated with its neuronal function.[30] Dynamic microtubules are necessary for synaptic plasticity, hence they are important for proper neuronal function.[31] Synaptic plasticity is key in memory formation, which is why impairment of memory is an early AD symptom.[32] Given the neurodegenerative nature of tau, and its consequences of neuronal loss and synaptic dysfunction upon phosphorylation, it is possible that this neurodegeneration could occur through microtubule effects, as tau is only present on stable microtubules.[39,33,34] However, neurodegeneration mediated by the tau protein could also be happening through defective signalling or axonal transport, or alterations in gene regulation.[35,37]

Similarly, NFTs are a direct cause of neuronal dysfunction and death. Tau tangles can also be seen in the brains of patients with mild dementia, without any Aβ pathology present, which goes against what the amyloid hypothesis suggests.[25] Additionally, the pathology of the τ protein correlates more with the progression of the disease than the amyloid explanation does.[38]

Aβ plaques can be a product of healthy aging, and individuals who possess them do not have to be experiencing neurodegeneration. Contrarily, NFTs are only seen in frontotemporal dementia and other tauopathies, not in regular aging subjects. NFTs are located intracellularly, within neurons, gradually but severely damaging axonal transport, whereas amyloid plaques remain in extracellular space.[40] Brier and colleagues managed to produce scans showing where tau proteins build up in the brains of patients with early AD (2016). Despite beta-amyloid and tau concentrating in different parts of the brain, it was found that tau accumulation in the temporal lobe more closely correlated with the symptoms of memory loss, measured via pencil and paper cognitive ability tests, than beta-amyloid scans. It was overall suggested that tau may be a more useful predictor of cognitive decline and possible AD development than Aβ plaques. Nevertheless, beta-amyloid still remains an early and reliable sign of AD.[40]

Approaches to Prevent, Delay, or Treat AD:

Understanding the hypotheses and causes of Alzheimer's is crucial when it comes to deciding approaches to overcome it - either by preventing it before onset, or by delaying the progression, or by curing the disease. For example, cholinergic system damage can be pharmacologically tackled by using cholinergic intervention methods. New drug development approaches for AD that have arisen as a result of knowledge on the cholinergic hypothesis include acetylcholinesterase inhibitors, cholinergic precursors, cholinergic receptor agonists, and allosteric cholinergic receptor potentiators.[41, 42] This hypothesis has established that decreased cholinergic function has a role to play in the pathology of Alzheimer's Disease, but there is no definitive sign of it being a direct cause.

The amyloid hypothesis, being the one with the highest scientific acceptance rate, has several mechanism-based treatments based around it. Four commonly studied ones were aggregation inhibitors, β-secretase inhibitors, γ secretase inhibitors, and antibody approaches.[43] Inhibitors of amyloid aggregation were the first interventional approach targeting amyloid formation that was studied. Its aim is to either prevent aggregation or at least disrupt existing amyloid plaques.

The β secretase enzyme (BACE 1) splits APP, releasing N-terminus from the amyloid beta peptide.[44, 45] As this is significant in the generation of β-amyloid, inhibition of this proteolytic enzyme may decrease the cleavage, which is why it was explored more as a potential treatment opportunity. Mice in which BACE1 gene was knocked out survived into adulthood without any serious neuronal defects.[46] Without the BACE1 gene, even the mice which overexpressed mutant human APP were not found to produce a measurable amount of amyloid beta, overall suggesting that β secretase was necessary for β-amyloid production.[47] The gene knockout of BACE1 did not show any serious issues in the mice, which may suggest that β secretase inhibitors might be a safe method of treatment lacking severe side effects. However, there are significant problems with relying on evidence from animal models such as mice, as they do not display some of the other features of AD. As AD pathology in mice will not completely parallel that of humans, the efficacy of these β secretase inhibitors cannot be truly tested unless they are tested on humans, which may instigate harm.

γ secretase inhibitors are similar to β secretase ones, however, γ secretase cleaves more proteins than just APP, which makes it harder to test, as some of these proteins, like Notch1,[48] are crucial for healthy brain development. Despite these problems, neurodegeneration is evident in adult animals when two vital components of γ secretase, presenilin 1 and 2 are knocked out.[49, 50] Both the success of γ secretase inhibitors and β secretase inhibitors would be widely dependent on the validity of the "toxic gain of function" model, which is when mutations in coding regions of a protein cause altered interactions, possibly causing aggregation. Mutations in both APP and presenilin 1 can potentially accelerate AD progression as they also can reduce cleavage rates.[43] Treatment worsening the disease is a significant concern, suggesting there is still room for more research into this area.

Human amyloid peptide immunization of transgenic mice can invoke B-cell and T-cell responses, which is the model for antibody treatment approaches for AD. In studies by Schenk and colleagues, significant amyloid deposition reductions were found in mutant human APP transgenic mice immunized with β-amyloid peptides.[51] Humans immunized with human peptides showed encephalitis, which was likely to be from the T-cell responses.[52-54] Some other studies also show that passive immunization, with direct antibodies to β-amyloid penetrating the brain, can reduce β-amyloid deposition

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due to the antibody binding potentially activating microglial mechanisms.[55, 56]

The β-amyloid peptide uses receptors, such as advanced glycation end products (AGE) and receptors for advanced glycation end products (RAGE), to transit through the blood-brain barrier.[57] Both are multi ligand receptors, and the concentration of ligands controls the expression of RAGE. With high levels of β-amyloid, RAGE expression also increases. Induction of inflammatory responses at the endothelium is caused by β-amyloid and RAGE interaction, as well as apoptosis in endothelial cells, decreased cerebral blood flow, and long-term potentiation (LTP) suppression, all pointing towards the notion that RAGE may contribute to the neurovascular changes in the progression of Alzheimer's Disease.[57,60]

Research into microglia has significantly increased recently, due to their important role in the pathogenesis of Alzheimer's Disease. Microglia are the resident macrophage cells, representing the main immune cells of the brain, and have been shown to play a part in neuroinflammation.[61] The release of cytokines is a major hallmark of brain inflammation, and activated microglia stimulates their production.[62] Microglia activation tends be conducive to the activity of inflammasomes, which contribute heavily to this, and which tend to be important pathological features of AD.[63] The NLRP3 can easily be classified as the most important inflammasome, made up of protein NLRP3 and the adaptor protein ASC (apoptosis-associated Speck-like protein). This adaptor protein activates pro-caspase-1, which is cleaved into caspase-1. This mechanism triggers the further cleavage of pro-IL-1β and IL-18, which are then released into the extracellular space.[64] IL-18 has been shown to indirectly cause amyloid plaques and neurodegeneration, through inducing NO and TNFα secretion.[65] This correlation to the pathology explains why AD patients tend to display increased caspase-1, which tends to be involved in reducing the effect of Aβ peptide phagocytosis.[66, 67]

Activated microglia and astrocytes could possibly be neurotoxic in certain circumstances. As microglia plays a key role in causing inflammation in the brain, they have provoked research into anti-inflammatory agents. However, these agents would only be effective when administered to patients who aren't in late stages of AD.[68] It is important to assess the relative stages of neuritic plaques and NFTs, as well as the microglia, in the subject's hippocampus and entorhinal cortical sections, as well as correlating this with their Clinical Dementia Rating (CDR) scores, which can give a relative idea as to how advanced the disease is, which is what two studies did.[69, 70] The CDR is scored on a scale of 0-3, 0 being no dementia, when CDR = 1 or 2, there is moderative cognitive impairment, and severe cognitive impairment is when CDR = 3. Something that both studies show in their findings is a decline in microglia scores while plaques and NFTs are still both progressing (NFTs more than the plaques), suggesting that microglia activation could potentially "burn out".[68] Through assessing all features of the pathology, it is clear that anti-inflammatory approaches would have optimal usage in the early or moderate stages of

AD, as it would be easiest to reduce not just inflammation, but plaque and tangle formation as well.

Several trials have been carried out for anti-inflammatory agents, including nonsteroidal anti-inflammatory drugs (NSAIDs). Epidemiological studies have shown that NSAIDs bring about a noticeable decrease in the risk for AD development.[71, 72] However, in formal trials testing out different NSAIDs, drugs like prednisone,[73] naproxen,[74] celecoxib,[75] triflusa,[76] and hydroxychloroquine[77] all failed to show any significant effect, in spite of the nonblinded studies initially having some form of positive results. Additionally, in a large clinical trial, R-flurbiprofen, which was reported to be both a derivative of an NSAID and work as a γ-secretase inhibitor, was shown to have no effect.

Another study on patients at high risk of AD, based on age and genetic susceptibility, tested the effectiveness of NSAIDs naproxen and celecoxib. The main findings of the study were that participants, including asymptomatic ones, who had already begun neurodegeneration and were showing AD pathology had the disease accelerated and worsened by the NSAIDs.[78] However, upon analysing the 4-year follow-up data, it was found that the patients who received naproxen with an initially healthy brain were 67 % more protected from developing AD than the control group with a placebo. While, 21-42 months after treatment, the CSF biomarkers values of the participants even showed low tau and high Aβ42 levels, alongside the clinical observation of these participants having lower incidence of AD. Based on these findings, it is possible that NSAIDs or anti-inflammatory agents may only be effective treatments in early AD due to Aβ deposition being minimal and microglia activation stimulates the release of pro-inflammatory mediators. In long-term, activated microglia can act as a mediator of the clearance of Aβ, and so the inhibitory activity of NSAIDs on this may worsen disease progression if administered in late stages.[79]

Therapies targeting tau and NFT formation focus on two main categories: preventing tau aggregation and preventing tau phosphorylation. However, in addition to this, there is some research into antibody approaches to tau pathology that has been conducted. Drug development opportunities tend to focus on targeting the mechanisms that convert soluble monomeric tau proteins into insoluble tau aggregates.[80, 81] These tau aggregates are often made up of nonphosphorylated tau, encouraging a search for potential tau aggregation inhibitors. Polyanions like heparin, RNA,[80] and arachidonic acid[82] are often what is used to provoke the aggregation of tau, allowing studies to test different inhibitors; methylene blue is speculated to inhibit tau aggregation, whilst also preventing progression of AD.

Significant research has been put into inhibiting the hyperphosphorylation of tau, which typically forms NFTs. The activation of protein kinase activity is what is generally accepted as the cause of accelerated tau phosphorylation, and thus protein kinases such as glycogen synthase kinase (GSK)3β, cyclin-dependent kinase (CDK)5, and extracellular signal-related kinase (ERK)2 are often targeted due to their correlation to the presence of NFTs.[83] The more active kinases, GSK3β

particularly, have been found to induce tau phosphorylation in cells in a culture.[84] During mice tests, it was found to do the same in the brains of transgenic mice,[85] as well as accelerating the aggregation of tau in them.[86] Unexpectedly, GSK3β caused less aggregation in certain mice, with the reason for this remaining unknown.[85, 87]

Other, more recent anti-tau therapies include tau aggregation inhibitor TRx0237, which aims to alleviate tau-related neuronal damage by reducing the aggregation of tau proteins.[88] After the first study, it was reported that TRx0237 was not an effective additional treatment for AD.[89] However, certain analyses suggest that better outcomes are shown when administered to patients who aren't on background therapies, yet this analysis needs to be confirmed through future studies.[90]

Another treatment opportunity for AD is the integrated stress response (ISR). ISR is an intracellular signalling pathway in eukaryotic cells that uses the logistics of evolutionary conservation to help an organism, or its cells and tissues, to maintain health in a new environment.[92] It reprograms gene expression to restore cellular homeostasis. Four specialised kinases are used to recognise multiple stresses; these include: (PERK, GCN2, PKR and HRI). The kinases converge on phosphorylation of one serine on the eIF2 (eukaryotic translation initiation factor). Protein synthesis is reduced when the eIF2 phosphorylation blocks eIF2's guanine nucleotide exchange factor (eIF2B), yet it also induces the translation of specific mRNAs, like the key transcription factor, ATF4. These processes allow ISR to instil balance and re-establish homeostasis within the cell, yet there are other solutions, such as apoptosis, that ISR may resort to if stress cannot be alleviated.[92]

Though AD is generally sporadic and not genetically linked, there is certain evidence to suggest that alleles such as the apolipoprotein E ε4 allele (ApoE4) can play a role such as promoting key features of AD pathology, like Aβ production and tau aggregation.[91] ISR elements, such as protein kinase RNA-activated (PKR), have been shown to assist memory suppression in Alzheimer's, and so a recent study used a mouse model to test if PKR could intervene with the harmful effects of ApoE4 on memory.[93] In this mouse model, the murine homologs were replaced with two copies of either ApoE3 or ApoE4 alleles, and found that ApoE4 mice suffered declines in their contextual memory.[94] Later, it was shown that PKR inhibition prevents this memory impairment in ApoE4 mice, stressing upon the idea that the integrated stress response is a crucial preventative approach. Segev and colleagues overall confirmed that utilising ISR could potentially prevent ApoE4-related cognitive impairment, which is associated with AD.

Pharmacological Interventions and New Drug Opportunities:

Extending upon drug opportunities within Alzheimer's Disease research, several drugs are currently undergoing clinical trials with the potential of being used as treatment methods. Additionally, there are drugs already in use, like Aricept® (donepezil), which has been FDA approved and in use since 2010. Likewise, very recently, Aducanumab has also been FDA approved and in use since 2021.

Aricept® (donepezil) has been approved to treat mild, moderate, and severe cases of AD, yet generally improves it symptomatically rather than slowing the disease progression or cognitive decline.[95] It is a cholinesterase inhibitor, preventing the hydrolysis of acetylcholine so that it is not broken down, and more of it is available at the synapses for increased cholinergic transmission.[96] This in turn prevents the loss of working cholinergic neurons through stabilizing acetylcholine levels, thus treating AD symptoms.

Aducanumab was approved for use in 2021, and is a monoclonal antibody that removes amyloid plaques to slow cognitive decline in AD patients, if administered at early stages of the disease.[97] However, due to the debate surrounding whether or not the amyloid cascade theory is true caused this drug to be equally criticised as it was praised. Entire amyloid removal exemplifies great scientific progress, yet the FDA stated that there were "uncertainties regarding clinical benefit".[98] However, it was still approved with the belief that amyloid removal generally slows cognitive decline.[99]

Three drugs that are currently undergoing clinical trials include Nabilone, Tricaprilin, and Donanemab. Nabilone is a synthetic cannabinoid that generally works as an antiemetic drug, and has the potential to relieve agitation in AD, through its anti-inflammatory effects.[100] Tricaprilin is a caprylic triglyceride, which is meant to induce ketosis to improve mitochondrial metabolism and neuronal function.[101] This is due to reduced cerebral glucose utilization being associated with early AD and a boost in cellular metabolism would provide an alternative to using glucose as a fuel.[102] Finally, Donanemab is an antibody that targets Aβ peptide. Studies conducted so far have shown a great impact on the cognitive ability of patients who have taken Donanemab compared to control groups taking a placebo, suggesting positive initial results, yet longer trials are still necessary.[103] Nabilone, Tricaprilin, and Donanemab are only a few of the many compounds currently undergoing clinical trials. All five of the aforementioned drugs are outlined and summarised in Table 1 below.

Table 1: Selected compounds in Alzheimer's Disease treatment at various clinical stages.

DRUG NAME	DRUG TYPE	HOW IT WORKS	CLINICAL TRIALS STAGE
Aricept® (donepezil)	Cholinesterase inhibitor	Stops acetylcholine from being broken down in the brain.	FDA approved – in use since 2010
Aducanumab	Monoclonal antibody	Targets Aβ plaques, reducing it and slowing cognitive decline.	FDA approved – in use since 2021
Nabilone	Synthetic cannabinoid	Antiemetic drug, reduces agitation through mimicking the euphoric effects of cannabinoids	Phase 3
Tricaprilin	Caprylic triglyceride	Induces ketosis and improves mitochondrial metabolism and neuronal function.	Phase 2/3
Donanemab	Antibody	Targets Aβ peptides, clearing the excess protein plaques.	Phase 2

Significance of Animal Models:

As can be interpreted by their frequent mention in previous sections, animal models play a crucial role in Alzheimer's Disease research. These are quite often transgenic mice which have undergone a genetic intervention in their genome. Although the majority of AD cases are sporadic, genetic mutations as

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sociated with familial AD provide the basis for the generation of transgenic animal models mimicking Alzheimer's Disease in humans. An overproduction of the mutated amyloid precursor protein results in Aβ accumulation, which manifests in the form of extracellular plaques. When transgenic mice overproduce mutant APP, a similar pathology to what is found in human patients develops, making them good models to test on or experiment on for the purpose of Alzheimer's research.[104]

A limitation within transgenic mouse modelling is that it cannot be directly compared to human pathology. For example, APP-overexpressing mouse models can show an increase in tau hyperphosphorylation, but do not develop neurofibrillary tangles.[105] Understandably, rodents are unlike humans, with a different lifespan as well, which could possibly not provide the time for enough hyperphosphorylation. Another difference is the structure and sequence of their tau, which could potentially not form NFTs, and simply manifest in alternate ways. However, these results could also reject what the amyloid cascade hypothesis posits, and suggest that NFT formation is not a downstream consequence of Aβ accumulation.[104]

Several APP transgenic mice models are successful in producing cognitive impairment that parallels what is experienced in a human patient. For example, Games *et al.*'s study using the human Indiana mutation on APP minigene as the transgene, found pathology such as neuronal loss in the hippocampus and dentate gyrus at 3-4 months, Aβ plaques at 6-9 months, gliosis, synaptic loss, and general behavioural deficits.[106] Additionally, many laboratories have tried to generate transgenic mice overexpressing human wildtype tau. Brion *et al.* conducted a study using the human wildtype tau transgene, which, despite showing no NFTs, brought about results of AT180, PHF1, AT270 positive phosphorylated tau deposits in the mice's somatodendritic compartments after 6 months.[107]

As scientific research progressed, there was a need for a more comprehensive approach to studying AD in mouse models, by incorporating both Aβ and tau pathology. In 2007, Bolmont *et al.* used both the APP23, with the Swedish mutation, and JNPL3, expressing human P301L-mutant tau, transgenes and found accelerated tau pathology forming around the plaques, suggesting there is exacerbation of tau when Aβ is aggregating.[108]

Mutations in the presenilin-1 (PSEN1) gene very commonly leads to familial AD (FAD).[109] Herzig *et al.* experimented on several different transgenic mice, including one line expressing APP-Dutch crossed with a FAD mutant of PS1, creating APP/PS1 mice. Parenchymal amyloid plaques with little vascular deposition was observed in these mice, which had about half the Aβ40/Aβ42 ratio that just APP-Dutch mice did.[110] Alternate studies on APP/PS1 mice examined the levels of Aβ and tau in the cerebrospinal fluid (CSF).[111] The CSF concentrations of tau increased by 5-fold between 6 month and 18 months of age in this study, and both Aβ42 and Aβ40 concentrations decreased, with Aβ40 decreasing less. The pathology of Human APP, Human wildtype tau, APP23 x JNPL3, and APP/PS1 mouse models are all illustrated in Figure 1.

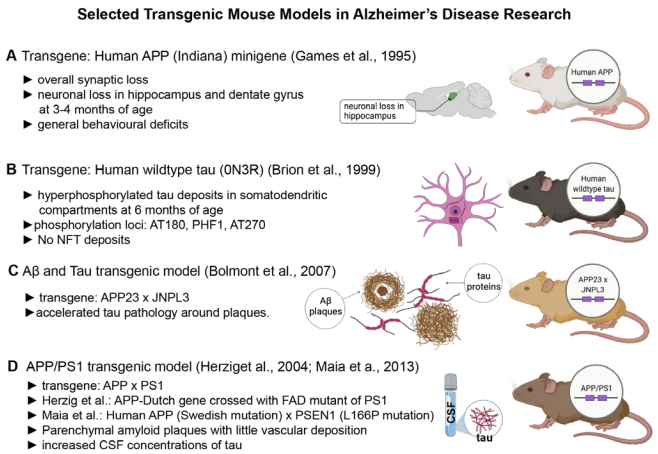

Figure 1: Selected transgenic mouse models in Alzheimer's Disease research. A. Human APP transgenic mouse model. B. Human wildtype tau transgenic mouse model. C. Transgenic mouse model with both APP23 transgene and JNPL3 (P301L-mutant tau) transgene. D. Transgenic mouse model with APP crossed with Presenilin-1, a part of γ- secretase. (APP: amyloid precursor protein; NFT: neurofibrillary tangles; FAD: Familial Alzheimer's Disease; CSF: cerebrospinal fluid). Cartoons are created with BioRender.com.

COVID-19 Implications on AD:

Whilst research into Alzheimer's Disease has been a continuous subject in science since its discovery, it has tied in significantly to modern medical settings, such as the severity of the Coronavirus Disease (COVID-19) pandemic.[112] Recent research into their links have shown that SARS-CoV-2 virus causing COVID-19 has the ability to invade the central nervous system, causing neurological symptoms to be seen as a potential comorbidity.[113] Apart from the biological comorbidities, the demanding nature of the pandemic means the need for caregivers for AD management clashes with that of COVID-19, putting a burden on the economy, patients, and families.[114, 115] Other similar factors include that AD patients are unable to properly care for themselves, and hence cannot protect themselves from the pandemic. These patients often fail to follow social distancing guidelines, or wear masks.[116]

In terms of pathology and features of the disease, a study conducted in Spain suggested that 29.1 % of the comorbidities of deceased COVID-19 patients was cognitive impairment – a key feature of AD. These patients particularly had a shorter survival rate than those without.[117] Furthermore, the aforementioned ApoE e4 allele may be involved in the pandemic, whilst also being the strongest risk gene for AD.[118] In the UK Biobank community cohort, it was predicted to heighten the risk of a severe and highly symptomatic SARS-CoV-2 infection,[119] extending the notion that AD and COVID-19 have notable correlations.

Furthermore, AD and COVID-19 seem to have similar inflammatory responses. Increased cytokine levels occur due to microglia in AD patients, including TNF-α, IL-1β, and IL-6. Likewise, COVID-19 tends to induce inflammatory responses and a promotion of cytokines.[114] Concerningly, patient serum with higher cytokine levels seems to be associated with COVID-19 fatality.[120] When coinciding, an AD patient's existing neuroinflammation may influence and speed up cytokine elevation and therefore heighten the risk of mortality

from a COVID-19 infection. A further reason for the comorbidity of AD and viruses such as SARS-CoV-2 might be the increase in expression of angiotensin, a viral receptor that converts pro-inflammatory molecules and enzyme 2, in AD patients, increasing their vulnerability to a severe form of the infection.[112]

Conclusion

It can be generally inferred by the scope of this review that research into AD has expanded greatly over time. With a very minimal understanding in the early 20th century, when Auguste Deter was first presented to Alois Alzheimer, scientific progress has consistently progressed over time, even reaching into modern contexts like the correlation between AD and COVID-19. However, regardless of the extent of research, one aspect of Alzheimer's Disease that is still heavily debated is its pathology. These AD hypotheses – Aβ aggregation or neurofibrillary tangles – have been briefly discussed in earlier sections. There are several aforementioned arguments for both sides.

The fundamentals of both the amyloid cascade hypothesis and the tau hypothesis were previously outlined. Many treatment opportunities are viewed as evidence for the amyloid cascade hypothesis, such as Aducanumab, which has been proven to slow cognitive decline through inhibiting Aβ accumulation. However, clinical trials also tend to provide evidence against the amyloid hypothesis, due to their more frequent failure than success. Aβ targeting antibodies like solanezumab, bapineuzumab, and gantenerumab all failed to slow cognitive decline in phase III of their clinical trials.[121,123] Ponezumab, another antibody targeting Aβ, was abandoned before it could even reach that stage, due to its significant failure.[124] Additionally, as previously discussed, Aβ is present in normal aging, so it does not necessarily suggest neurodegeneration than cognitive decline.

NFTs, on the other hand, are not seen in individuals not experiencing neurodegeneration. This could be due to NFTs forming intracellularly, within neurons, whereas Aβ plaques reside in extracellular space. Furthermore, as discussed in the second section of this review and Braak's and Braak's research, tau pathology more closely corresponds with the severity of AD than amyloid plaques do, due to processes such as microtubule assembly. AD can be classified as a tauopathy, due to its pathogenesis involving the abnormal hyperphosphorylation of tau. Inhibiting these intracellular lesions can be a promising therapeutic strategy for AD and related tauopathies. Tau has generally been showing quite hopeful results in terms of treatment opportunities, and seven anti-tau therapies are in phase II of clinical trials.[125] In spite of this, there are a few that did fail clinical trials. A protein kinase that plays a role in the phosphorylation of tau, glycogen synthase kinase 3 beta (GSK-3β), was initially thought to be a good target for treatment targeting tau, but Tideglusib, a GSK-3β inhibitor, did not display significant enough effects in phase II of the clinical trials.

Clinical trials for AD treatment generally fail for several reasons, including mistargeting or nonoptimal timing. In treatments targeting Aβ, there are several questions that arise on what specifically to target – monomeric, oligomeric, protofibrillar, or plaque Aβ – and the location – either the N-terminus, C-terminus, or mid-domain.[126] The approach taken to target the pathological substrates could lead to these drugs failing clinical trials. Additionally, the administration of treatment could be too late. The peak of Aβ deposition and other pathological changes tends to be in the mild cognitive impairment stage, as neurodegeneration and the pathology of AD tends to occur in the brain long before a diagnosis has been made. Often, clinical trials fail when participants have severe or late-stage AD.[126]

The presence of the debate itself exemplifies the room for progress and research that still prevails in Alzheimer's Disease research. It suggests that research into treatment should keep focusing on both hypotheses to remain multifaceted in their research and maximise their chances of success. Whilst this review covers a large breadth of what is known and innovative new treatment approaches, there is also still no official cure for AD, like many other serious diseases. To summarise, it is clear that research has brought joy to patients and families through its treatment applications, but nevertheless, much like other areas of science, more breakthroughs can be expected in regards to this medical enigma.

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