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The Role and Therapeutic Potential of α-secretase in Alzheimer's Disease

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ABSTRACT

Currently, more than six million Americans suffer from Alzheimer's Disease (AD), a number that is set to become 12.7 million by 2050. But despite killing more people than breast cancer and prostate cancer combined, there are no available pharmaceuticals that can cure AD, halt its pathogenesis, or reverse its effects. Therefore, the need for a thorough understanding of the physiological mechanisms behind AD progression has captured the attention of countless researchers and clinicians worldwide. In the last 30 years alone, the scientific community has made unprecedented progress towards an effective therapeutic. Notably, the amyloid cascade hypothesis has been one of the most dominating theories in recent AD research and drug discovery. The hypothesis suggests that AD's main trigger lies in the accumulation of amyloid-beta protein fragments within brain tissue. Here, I present a review of some of the latest efforts to inhibit the production of these neurotoxic amyloid-beta peptides through the modulation of α-secretase enzyme activity in APP proteolysis.

Introduction

Alzheimer's Disease is an incurable, progressive neurodegenerative disorder that is characterized by the loss of neurons, primarily in the hippocampus and cerebral cortex [1,2]. AD contributes to 60-70% of all dementia cases, and the percentage of individuals living with Alzheimer's dementia increases with age [3]. AD symptoms commonly include impaired cognition and memory erosion in patients with a clinical diagnosis. Hallucinations, personality changes, and seizures are observed in more severe cases of AD [4]. Sporadic Alzheimer's Disease (SAD) makes up more than 90% of all AD cases and is characterized by the lack of hereditary links within the patient's family [5,6]. Familial Alzheimer's Disease (FAD) is a rarer, inherited form of AD. Patients with FAD usually have an earlier clinical onset than those diagnosed with sporadic AD [7].

Our physiological understanding of AD began in the early 20th century, when the German Physician Dr. Alois Alzheimer first noticed aggregations of beta-amyloid plaques and neurofibrillary tangles in the brain of a patient suffering from dementia [8,9]. After more than a century of careful study, we now know those senile plaques and neuronal tangles to be the two major physiological characteristics of Alzheimer's. Neurotoxic amyloid-β (Aβ) peptides are the primary proteinaceous component of the amyloid deposits and are derived from larger amyloid precursor proteins (APP) [10]. Neurofibrillary tangles are accumulations of hyperphosphorylated tau proteins that are mainly concentrated in the hippocampus and cerebral cortex of AD patients [9,2,11]. The aggregation of these notorious plaques and tangles in the brain can interrupt intercellular communications between neurons and trigger an immune response, which can cause inflammation and neuron death [12].

The Amyloid Hypothesis

The amyloid hypothesis was introduced in 1991 by John Hardy and David Allsop. The model theorized the build-up of excess Aβ peptides in the brain to be the direct cause of AD pathogenesis and neurodegeneration [13,14]. Even under "normal" circumstances, Aβ peptides are primarily produced in the neurons. However, the amyloid hypothesis proposed that an imbalance between the production of Aβ and its clearance can result in the build-up of insoluble Aβ plaques and neurofibrillary tangles, the hallmarks of AD. According to the amyloid hypothesis, the excessive deposition of the Aβ peptides in the brain is the first trigger of Alzheimer's – a claim that has prompted scientists to study the mechanisms behind Aβ generation and disposal for a potential therapeutic [2,15]. Several such studies have produced valuable results for AD research. Still, it is important to note that the amyloid hypothesis is a theory of intense debate within the scientific community. This controversy will be further examined later in this section.

The proteolytic cleaving of the transmembrane amyloid precursor protein (APP) by several enzymes leads to the production of amyloid-β peptides 1-40 and 1-42 in neuronal tissue. Although Aβ40 is more common, Aβ42 is more neurotoxic and especially quick to aggregate [16,17]. Despite the harmful effects of Aβ, APP itself is not neurotoxic and is widely expressed throughout the central nervous system [18]. APP has three cleaving sites, each associated with a secretase enzyme: α-secretase cleaves APP within the Aβ domain, β-secretase at the N-terminal of the Aβ domain, and γ-secretase at the C-terminal of the Aβ domain [2,19]. APP processing by β-secretase and γ-secretase produces Aβ peptide isoforms that can aggregate into plaque deposits. APP proteolysis by α-secretase, however, does not produce a complete Aβ peptide as the enzyme cleaves the protein in the middle of the Aβ domain. Therefore, the enzyme does not contribute to the pathogenesis of AD [15].

Before examining the validity of the amyloid hypothesis, it is important to understand its purpose. The hypothesis aims to guide AD drug development strategies to topics likely to yield useful results. In that sense, the theory has shown significant success and has been a source of great advancement in AD research. Nevertheless, much remains unanswered about the amyloid hypothesis [21,22,23]. For example, one of the hypothesis' principal implications is that Aβ peptides are neurotoxic and represent the primary causative agent behind AD pathogenesis. Under this assumption, the degree of Aβ burden in the brain should directly correlate to the clinical progression and severity of the disease and its symptoms [24]. However, several studies demonstrated a lack of such a relationship, and some found links to AD risk factors that were not suggested by the amyloid hypothesis [25,26]. Moreover, the physiological connection between the development of Aβ plaques and that of neurofibrillary tangles in neuronal tissue is still yet to be concluded [2]. Despite its drawbacks, the amyloid hypothesis is one of our most robust models for AD. It has led to the development of several viable AD drugs that have recently progressed to human clinical trials. One promising direction to designing such therapeutics is the secretase targeting approach. Here, we look at the function of one of the primary secretases involved in APP processing and examine its therapeutic potential.

α-secretase

Enzymatic α-secretase activity is localized to the plasma cell membrane and the trans-golgi network [27]. Unlike β-secretase, α-secretase activity precludes the formation of toxic amyloid-β peptide by cleaving APP at the Lys16-Leu17 bond in the middle of the Aβ domain. This results in the extracellular release of a large, soluble ectodomain of APP called "sAPPα" through a process called "ectodomain shedding" [28,29]. Interestingly, scientists have found strong neuroprotective properties in soluble sAPPα metabolites [30]. In rat traumatic brain injury (TBI) models, sAPPα induced axonal elongation and neuroprotection, improved motor outcome, and attenuated neuron loss. It also appeared to rescue synaptic plasticity deficits in AD mouse models and inhibit tau phosphorylation through the GSK3β signaling pathway [31,32]. After proteolysis by α-secretase, γ-secretase cleaves the remaining membrane-bound C-terminal APP fragment (C83) and releases the APP cytoplasmic domain and a nontoxic p3 peptide [2].

APP processing by α-secretase is referred to as the nonamyloidogenic pathway while APP processing by β-secretase is referred to as the amyloidogenic pathway [33]. Two major proteolytic pathways of APP processing occur through the putative α-secretase metalloprotease enzymes: constitutive and regulated cleavage. Constitutive cleavage occurs rapidly at the cell membrane surface, and regulated cleavage takes place in the Golgi complex. Since then, several candidate enzymes for α-secretase have been identified, including ADAM10, ADAM17, and ADAM9. All three candidates are part of the a-disintegrin and metalloprotease (ADAM) family and have been confirmed as active α-secretases since their initial discovery. Of the three secretases, ADAM10 is essential for the constitutive α-secretase cleavage of APP and is the most physiologically important ADAM to APP processing [2].

ADAM10

α-secretase's ability to prevent Aβ production while releasing neurotrophic sAPPα has made it an attractive therapeutic target among AD researchers. Moreover, BACE1 (the putative β-secretase) and α-secretase compete for APP cleavage. Therefore, α-secretase activation in APP processing is speculated to lower the chances and frequency of amyloid-beta aggregation while promoting neuroprotection in the nervous system [34]. Several studies observing the moderate neuronal overexpression of ADAM10 in AD mouse models have supported this theory [35,36]. ADAM10 levels in platelets and spinal fluid of AD patients was also reported to have an inverse relationship with the disease's progression [37]. Additionally, the presence of ADAM10 prodomain missense mutations attenuated α-secretase activity and increased Aβ peptide levels in the brain [38].

ADAM10 has proven to be an attractive therapeutic target for AD, but the possible effects of extensive ADAM10 activation are still uncertain [2]. ADAM10 is widely expressed in neuronal and non-neuronal tissue and seems to play a significant role in the development of other diseases, including cardiovascular-related disorders. ADAM10 has also been connected to over 40 substrates that belong to three distinct classes of membrane-bound proteins and operate in diverse body systems and cells [39,40]. However, mutagenesis experiments on ADAM10 have found multiple residues in the enzyme's S1' pocket active site that strongly influence substrate specificity – something that we may be able to manipulate to target specific substrates of ADAM10 [41]. Moreover, ADAM10's widespread expression and its substrates' wide range of cellular function make the secretase a potential therapeutic target for a number of medical disorders, including inflammatory disorders, cardiovascular diseases, skin disorders, epilepsy, and tumor development in several types of cancer [42,43,44,45]. Future studies with ADAM10 should consider the mechanisms by which the enzyme's expression is controlled, the subcellular localization and activity of ADAM10, and how it defines its substrate specificity. A better understanding of the aforementioned interests will aid us in discovering appropriate drug targets to better modulate ADAM10's roles in various medical diseases [46].

Although the development of a direct α-secretase activator as a pharmacological therapeutic for Alzheimer's Disease seems unlikely in the near future, drugs that indirectly stimulate α-secretase activity have advanced as far as Phase II in human clinical trials [33]. For example, Etazolate (EHT 0202) is a selective GABAA receptor modulator that stimulates ADAM10 activity and the α-secretase non-amyloidogenic pathway [47]. The drug induced sAPPα secretion and protected against Aβ-induced neurotoxicity in guinea pig and rat models. However, since Etazolate did not seem to contribute to downsizing Aβ peptide burdens in AD, it cannot be classified as an Aβ-lowering drug [48,49]. EGCG (epigallocatechin gallate) is a naturally occurring polyphenol that has been discovered to boost ADAM10 activity and reduce Aβ in the hippocampus of AD model mice induced by D-gal (50). Although target receptors are yet to be discovered, tyrosine kinase inhibitors have been demonstrated to prevent EGCG-induced ADAM10 activation [47]. Finally, Am80 (Tamibarotene) is a synthetic retinoid and ADAM10 activator that has reached Phase II in Clinical Trials [46]. Already approved for APL treatments in Japan, Am80 administration in AD model mice decreased Aβ(42) deposition and significantly improved memory in rat scopolamine-induced memory deficit models. The drug also facilitated recovery in spinal cord-injured rats and reduced inflammatory cytokines in a rat experimental autoimmune encephalomyelitis model [51].

ADAM17

Also known as tumor necrosis factor-converting enzyme (TACE), ADAM17 is similar to ADAM10 in its function and potential to inhibit the amyloidogenic pathway. Like ADAM10, ADAM17 is found in many body systems and is known to cleave a wide range of substrates – most of which link the sheddase to major contemporary pathologies, including inflammatory disorders, vascular diseases, and cancer. As such, the enzyme is a subject of intense research in various medical fields, including neurodegeneration and dementia [52]. In a 2021 study, ADAM10 and ADAM17 upregulation by quercetin stimulated the non-amyloidogenic pathway in AlCl3-induced AD rat models while also ameliorating behavioral and neurotransmission impairment [53]. ADAM17 overexpression has also improved cerebrovascular vasoreactivity and cognitive performance in APP/PS AD mice [54]. On the other hand, ADAM17 is a key ectodomain sheddase for many proinflammatory factors (including microglial activation). It therefore plays a crucial role in AD-related neuroinflammation and neurodegeneration [55]. The secretase's dual character in AD pathogenesis makes the strong and widespread modulation of ADAM17 tricky in AD drug development. Furthermore, ADAM17 overexpression in diabetic mice has been demonstrated to aggravate cardiac fibrosis while its knockdown attenuated it [56]. The enzyme's additional involvement in pulmonary emphysema and some tumor pathogenesis makes it a complicated drug target for medical disorders [55,57].

Nevertheless, there have been many advancing efforts in targeting ADAM17 activity regulation. AF267B - a low molecular weight compound and artificial agonist of ADAM17 - has been verified to improve cognitive deficits and postpone AD progression by reducing the Abeta(42) burden and decreasing tau pathology in triple transgenic (3xTg-AD) mice [58]. No further advances have been made for testing AF267B in human clinical trials. The same model has been treated with ADAM17-activating acetylcholinesterase inhibitors huprine X and huperzine A, with results showing improved cognition without significant adverse effects. There have been no further reports [59]. Although many more efforts have been aimed at developing selective ADAM17 inhibitor compounds for Alzheimer's Disease, the majority of them are unavailable on the market as drugs. Several compounds made it to early clinical trials, but they were later withdrawn [60].

ADAM9

ADAM9 sheddase (metalloprotease/disintegrin/cysteine-rich protein 9; MDC9) shares a number of characteristics with ADAM10 and ADAM17. Like the latter two, ADAM9 is ubiquitous, cleaves a wide range of cell surface substrates, and influences physiological processes and disorders, including organismal development, inflammation, degenerative disorders, and tumor pathogenesis in several cancer types [61]. Also similar to ADAM10 and ADAM17, ADAM9 upregulation is the subject of research efforts aimed at activating the non-amyloidogenic pathway in APP processing. A 2012 study supporting this conjecture found that neuroprotective Substance P (SP) neuropeptides can stimulate ADAM9 mRNA expression and induce α-secretase-mediated APP proteolysis [62]. Even more interesting, ADAM9 can also cleave another α-secretase, ADAM10. Inhibiting ADAM9 function reduces ADAM10 shedding activity, and as a result, ADAM10 was reported to generate more soluble APP and fewer amyloid-beta peptides [61,63]. Another study learned that genetic polymorphisms in promoter regions of ADAM9 can influence ADAM9 transcription and have been suggested to affect one's risk of AD. Specifically, the promoter polymorphisms demonstrated to protect against Sporadic Alzheimer's Disease onset [64]. Estrogen treatment by ERα (Estrogen Receptor α) activation has also boosted ADAM9 transcription in cultured human neurons, highlighting another potential indirect ADAM9 activator for AD drug development [65].

Such evidence shows major signs that ADAM9 could be a useful therapeutic target for AD, but the enzyme's biological pertinence has also been questioned. MDC9 is widely expressed during mice development, but mice lacking the protease seem to develop normally and in the same way as wild-type mice. The *Adam9*−/− mice were viable, fertile, and showed no differences in p3 peptide (a product of the non-amyloidogenic pathway) or amy-

loid-beta levels [66,48]. While the results of the study undermined MDC9 to have an essential role as an α-secretase in mice, it also supported the argument that several ADAM proteases participate in APP processing and in the absence of one, the other two can still mediate APP α-secretase cleavage. There have been little to no substantial efforts in producing indirect ADAM9 modulators as an AD drug target.

Future Perspectives

When it comes to developing viable pharmaceuticals for Alzheimer's Disease, the secretase targeting approach has been a major contender for nearly 20 years now. Recent therapeutic strategies for precluding Abeta formation, averting its aggregation into plaques, lowering its soluble levels in brain tissue, and disassembling preexisting amyloid plaques are some of the principal areas of study in slowing and reversing AD progression – and despite large gaps in the literature, the scientific community has seen incredible gains and breakthroughs in such a short amount of time. Recent insights in APP processing pathways and ADAM10 characteristics pave the way for rational drug designs in coming years, and ongoing clinical trials show promising results for an effective therapeutic. Still, the vast unmet medical need for AD demands even more quality studies to answer several remaining questions for current and future AD patients. Further studies aimed at elucidating the involvement and mechanisms of each APP proteolysis-participating secretase are required for advancements in the secretase targeting approach, but this has been a challenge due to the lack of selective alpha-secretase inhibitor compounds and the lethality that comes with slicing the genes that code for the secretases. Developing proper, selective ADAM inhibitors and conditional transgenic animal models can guide our research to appropriate target enzymes for AD drug design [33]. Recent failures in high-profile clinical trials and AD treatments have also undermined the validity of the amyloid hypothesis while discouraging many AD researchers and clinicians. But it seems that the study group may be the issue as the Alzheimer's in the patients was too far advanced in its pathogenesis. Newer trials are focusing on targeting patients at earlier stages of AD. The results of these trials may reinforce or undermine the amyloid hypothesis and its role in future AD research (2).

Conclusions

In 21st-century America, Alzheimer's Disease is one of the most dangerous and common medical disorders in adults. It is reportedly the sixth leading cause of death in adults, but dementia is often under-reported in death certificates. So, the proportion of individuals who die from Alzheimer's may be significantly higher than reported. In 2010, the costs of treating AD in the United States were estimated to fall between $159 and $215 billion. By 2040, these projections have jumped to more than $500 yearly. Between 2020 and 2030, 1.2 million additional direct healthcare workers will be required to care for the growing population of dementia patients – representing the largest worker gap in the nation. As these alarming numbers continue to climb and early diagnoses for AD patients become more commonplace, the need for effective therapeutics has reached its all-time high. But with the world's finest researchers and healthcare professionals working towards reducing AD stigma, breaking through socioeconomic barriers in treatment administration, and developing a cure, significant hope lies for present and future AD patients.

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