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Role of Amyloid Beta in Alzheimer's Disease: A Review

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ABSTRACT

One of the most serious brain conditions affecting senior people is Alzheimer's disease. A significant public health issue is emerging from a condition that is both undertreated and under recognized. An effort that has been progressively growing over the past ten years has been made to identify the disease's genesis and create pharmaceutical treatments. Improved clinical diagnostic standards and better behavioural and cognitive disorders therapy are recent breakthroughs. Randomized, double-blind, placebo-controlled, parallel-group studies evaluating performance-based assessments of cognitive function, activities of daily living, and behaviour have been used to clinically evaluate symptomatic treatment that primarily focuses on cholinergic therapy. Patients with Alzheimer's disease are advised to use cholinesterase inhibitors, such as donepezil, tacrine, rivastigmine, and galantamine, to address cognitive impairment. Anti-inflammatory drugs, antioxidants, and oestrogen replacement therapy are controversial topics that require more research. Behavioral disturbances are treated with antidepressants, antipsychotics, mood stabilisers, anxiolytics, and hypnotics. The development of new classes of medications that target various neurotransmitter systems (cholinergic, glutamatergic, etc.), both for the treatment of the cognitive deficit and the treatment of the behavioural disturbances, as well as the development of preventive methods (amyloid p-peptide immunisation), are some future directions in the research and treatment of patients with Alzheimer's disease.

Keywords: Alzheimer's disease, etiology, epidemiology, apolipoprotein E4, cholinesterase inhibitor, antioxidant, anti-inflammatory agent, estrogen replacement therapy, behavioral disturbance.

INTRODUCTION

A complex and severe brain condition known as Alzheimer's disease (AD) affects millions of individuals worldwide [1] Several studies have been conducted with a focus on understanding the underlying causes of AD and creating novel therapies to prevent or delay the disease's progression. One of the key features of AD is the accumulation of beta-amyloid protein in the brain. This protein forms plaques that disrupt normal brain functioning and cause the death of neurons [2]. According to a 2012 study that was published in Nature, the build-up of beta- amyloid protein is probably an early stage in the onset of AD and takes place years before symptoms appear. Another study, published in the journal AD in 2020, found that chronic inflammation may also play a role in the development of the disease [3]. The study found that people with a history of chronic inflammation were more likely to develop AD than those without. Despite these findings, there are still no treatments that can cure or reverse AD.

However, there are a number of drugs on the market that can assist treat the disease's symptoms [4]. For example, cholinesterase inhibitors, such as rivastigmine, used to treat mild to moderate dementia can improve thinking ability in some patients. There are also many treatments in development that slow the progression of the disease [5] Acetyl cholinesterase inhibitors, which are used to treat the symptoms of mild to severe Alzheimer's disease, include donepezil (also known as Aricept), rivastigmine (Exelon), and galantamine (Reminyl). Donepezil is also used to treat more severe Alzheimer's disease. The second is a beta-amyloid protein-targeting therapy called monoclonal antibody therapy, which is presently undergoing clinical trials [6]

Other than medicinal treatments, lifestyle changes may also be helpful in managing or controlling the symptoms of AD. For instance, a 2018 study that appeared in the journal of Alzheimer's disease suggested that adopting a Mediterranean-style diet, increasing physical activity, giving up smoking, and drinking excessively could all help lower the chance of getting AD [7]. However, despite the fact that AD is still a difficult and harmful condition, science is finally making progress in figuring out the underlying reasons and creating novel therapies. Continued research is needed to ultimately find a perfect cure for this devastating disease [8].

Two proteins play key roles in the causes of Alzheimer's disease, according to researchers.

Plaques: A smaller protein is the source of beta amyloid. When these fragments cluster together, they appear to have toxic effects on neurons and disrupt cell-to-cell communication. These accumulations, known as amyloid plaques, which also contain other cellular waste, grow into these clusters.

Tangles: Tau protein play a role in the internal structure of a neuron's support and transport system, which carries nutrients and other necessary components. Neurofibrillary tangles are formed when tau proteins alter shape and assemble themselves in Alzheimer's disease. The tangles poison cells and interfere with the transport system [9]**.**

SYMPTOMS-One of the main signs of Alzheimer's disease is memory loss. Early warning indications include having trouble recalling previous conversations or occurrences. Memory impairment worsen as the disease advances, and new symptoms appear [10] A person with Alzheimer's disease may initially be aware of having trouble organising their thoughts and remembering things. It's possible that a friend or family member would notice the symptoms getting worse first. Brain changes associated with Alzheimer's disease led to growing trouble with

- Confusion
- Poor judgment
- Language disturbance
- Agitation
- Withdrawal
- Hallucinations

CAUSES- It is unclear what causes Alzheimer's disease exactly. But on a fundamental level, brain proteins malfunction, which interferes with the functioning of brain cells (neurons) and sets off a chain of harmful events [11].Damaged neurons lose their connections to one another and finally pass away.

Alzheimer's is only 1% of the time brought on by certain genetic abnormalities that practically insure a person will develop the disorder. These rare occurrences usually result in disease onset in middle age. Most frequently, the memory-controlling area of the brain is where the damage first manifests itself, however the damage actually starts years before any symptoms show up [12]. Some parts of the brain experience the death of neurons in a pattern that is largely predictable. The brain has greatly contracted during the disease's late stages.

Researchers trying to understand the cause of Alzheimer's disease are focused on the role of two proteins: plaques and tangles.

RISK FACTORS

There are various kinds of risk factors that are associated with associated with AD [13], which are mentioned below:

- Age
- Sex
- Heredity
- Mild cognitive impairment
- Head trauma
- Air pollution
- Excessive alcohol consumption
- Poor sleep patterns
- Lifestyle and heart health
- Obesity
- Down's syndrome
- Vascular disease

Prevention: There is no cure for Alzheimer's disease. A few lifestyle risk factors for Alzheimer's can be changed, though [14]. There is evidence that altering your food, exercising more, and changing your habits could lower your chance of acquiring cardiovascular disease as well as dementia-causing diseases like Alzheimer's [15]. The following are heart- healthy lifestyle behaviours that may lower the risk of Alzheimer's:

- Exercising regularly
- Consuming a diet high in fresh fruits and vegetables, nutritious oils, and foods low in saturated fat, such a Mediterranean diet,
- Adhering to recommended treatment regimens for high cholesterol, diabetes, and blood pressure
- Asking your doctor for help to quit smoking if you smoke

Studies have shown that preserved thinking skills later in life and a reduced risk of Alzheimer's disease are associated with participating in social events, reading, dancing, playing board games, creating art, playing an instrument, and other activities that require mental and social engagement [16].

Pathogenesis of Alzheimer's disease: The two core pathological hallmarks of Alzheimer's disease are amyloid plaques and neurofibrillary tangles According to the amyloid cascade hypothesis, the build- up of amyloid (A) in the brain causes neuronal malfunction and death [17]. Other major points that affect or trigger AD are:

- Beta amyloid aggregation and deposition: plaque formation.
- Hyper phosphorylation of tau protein: NFT development
- Inflammatory processes.
- Dysfunction of the neurovasculature.
- Oxidative stress.
- Mitochondrial illness

The differences between a healthy brain and the brain of a person who is suffering from Alzheimer's disease are shown in the figure given below:

Neurodegeneration:

Neurodegeneration can be considered an umbrella term for the progressively greater loss of structure and function of neurons, including the eventual death of [18] Many neurodegenerative diseases, including amyotrophic lateral sclerosis, Parkinson's, Alzheimer's, and Huntington's, occur as a result of the loss of structure and function of neurons, eventually leading to the death of neurons. Such diseases are incurable due to the progressive degeneration and/or death of neuron cells they cause. As research progresses, on a subcellular level, many similarities appear that relate these diseases to one another. The emergence of these similarities offers great hope for therapeutic advances that could ameliorate many diseases simultaneously. There are many parallels between different neurodegenerative disorders, including atypical protein assemblies and induced cell death. Ranging from molecular to systemic, neurodegeneration is found at many different levels of neuronal circuitry [19]. A chronic neurodegenerative condition that often becomes worse over time is Alzheimer's disease (AD). AD is the main cause of 60% to 70% of cases of dementia. The commonest early symptom of AD is difficulty remembering recent events (short-term memory loss). As the illness progresses, symptoms alter over time and might include behavioural problems, linguistic difficulties, disorientation (including a tendency to get lost easily), mood swings, loss of motivation, and loss of self-control [20]. Withdrawal from family and society occurs with patients whose condition gradually declines; bodily functions are lost, ultimately leading to death. Although the speed of progression can vary, the average life expectancy following diagnosis is three to nine years [21].

Amyloid beta and neurodegeneration

In the brains of Alzheimer patients, amyloid beta is considered the main component of amyloid plaques, which denote peptides of 36–43 amino acids. The peptides result from the amyloid precursor protein (APP), which is cleaved by beta secretase and gamma secretase to yield Aβ [22]. Aggregation of A, which can exist in several forms, results in the formation of flexible soluble oligomers. Other molecules are induced to also take the misfolded oligomeric form by certain other misfolded oligomers known as seeds, leading to a chain reaction akin to a prion infection. The seeds or the resulting amyloid plaques are toxic to nerve cells. Such prion-like misfolded oligomers are also formed by tau protein, another protein implicated in Alzheimer's disease, and there is some evidence that misfolded Aβ can induce tau to misfold [23]. Several potential activities have been discovered for Aβ, including activation of kinase enzymes [24], protection against oxidative stress regulation of cholesterol transport;functioning as a transcription factor and anti-microbial activity [25]

Formation

The amyloid precursor protein (APP), a trans membrane glycoprotein, forms Aβ by undergoing sequential cleavage. APP can be cleaved by the proteolytic enzymes and secretases the successive action of β and γ secretases generates the Aβ protein. A number of isoforms of 30-51 amino acid residues in length are generated when the - secretase producing the C-terminal end of the Aβ peptide cleaves within the Trans membrane region of APP [26] The two most common isoforms are A40 and A42; the longer form is typically produced by cleavage that occurs in the endoplasmic reticulum, while the shorter form is produced by cleavage in the trans-Golgi network [27] The Aβ 40 form is the more common of the two, but Aβ 42 is the more fibrillogenic and is thus associated with disease states. Mutations in APP associated with early-onset Alzheimer's have been noted to increase the relative production of Aβ 42, and thus one suggested avenue of Alzheimer's therapy involves modulating the activity of and secretases to produce mainly Aβ 42 [28] Several amyloid-degrading enzymes like neprilysin are found to destroy Amyloid beta [29]

Diseases associated

Aβ is the main component of amyloid plaques (extracellular deposits found in the brains of patients with Alzheimer's disease) [30].In some variants of Lewy body dementia and in inclusion body myositis (a muscle disease), similar plaques are found to appear. The aggregates that coat cerebral blood vessels in cerebral amyloid angiopathy are formed by Aβ. Aβ tangle of regularly ordered fibrillar aggregates called amyloid fibres constitutes these plaques [31].These fibrillar aggregates are a protein fold shared by other peptides such as the prions associated with protein misfolding diseases. In the

development of Alzheimer's disease, soluble oligomeric forms of the peptide may be the causative agents [32] It is generally believed that oligomers are the most toxic.[33]

According to the ion channel hypothesis, membrane ion channels are formed by oligomers of soluble, non-fibrillar Aβ, allowing the unregulated calcium influx into neurons that underlies disrupted calcium ion homeostasis and apoptosis seen in Alzheimer's disease[34]. A number of genetic, cell biology, biochemical, and animal studies support the concept that Aβ plays a central role in the development of Alzheimer's disease pathology [35]

The tau hypothesis of Alzheimer's disease

The phosphorylation of tau is also developmentally regulated. For example, in the embryonic CNS, fatal tau is more highly phosphorylated than adult tau [36] Due to the activation of phosphatases, the degree of phosphorylation in all six isoforms decreases with age [37].Like kinases, phosphatases too play a role in regulating the phosphorylation of tau. For example, PP2A and PP2B are both present in human brain tissue and have the ability to dephosphorylate Ser396 [38]. Tau's association with MTs is affected by the binding of these phosphatases to tau.

The tau hypothesis states that the transformation of normal adult tau into PHF-tau (paired helical filament) and NFTs (neurofibrillary tangles) is performed by excessive or abnormal phosphorylation of tau. Tau protein is a highly soluble microtubule-associated protein (MAP). The microtubule assembly is stabilized when phosphorylation of tau protein interacts with tubulin through its isoforms. A family of six isoforms constitutes tau proteins, with a range of 352-441 amino acids [39] The longest isoform in the CNS has four repeats (R1, R2, R3, and R4) and two inserts (441 amino acids total), whereas the shortest isoform has three repeats (R1, R3, and R4) and no insert (352 amino acids total). All six tau isoforms are present in an often hyper phosphorylated state in paired helical filaments in AD[40]

Mutations that alter the function and isoform expression of tau lead to hyper phosphorylationQW3A4. The process of tau aggregation in the absence of mutations is not known but might result from increased phosphorylation, protease action, or exposure to polyanions, such as glycosaminoglycan' hyper phosphorylated tau disassembles microtubules and sequesters normal tau, MAP 1 (microtubule-associated protein 1), MAP 2, and ubiquitin into tangles of PHFs. This insoluble structure damages cytoplasmic functions and interferes with axonal transport, which can lead to cell death [41]

BACE1

Various enzymatic digestions, including - and -secretases, cleave amyloid precursor proteins into various types of amyloid precursor proteins. An integral membrane aspartyl protease originates most of the - secretase activity encoded by the -site APP cleaving enzyme 1 gene (BACE1). A sensitive and specific BACE1 assay was led by Dr. Zetterberg for the purpose of assessing CSF BACE1 activity in AD. In subjects with AD, there is an increase in BACE1 expression and enzymatic activity. The amyloidogenic process in Alzheimer's disease is mainly due to elevated levels of BACE1 activity. A potential candidate biomarker to monitor amyloidogenic APP metabolism in the CNS is CSF BACE1 activity[42].

Soluble Aβ precursor protein (sAPP)

Proteolysis of APP, which is an integral membrane protein, generates beta amyloid ranging from 39- to 42-amino acid peptides. APP may play a potential role during neurodegeneration and the regulation of neural activity, connectivity, plasticity, and memory, although the biological function of APP is not known. Novel potential biomarkers of Alzheimer's disease are found to be large soluble APP (sAPP) that is present in CSF [43].In a study published in Nature, a team led by Lewczuk tested a soluble form of APP to see how it worked. When compared to normal subjects, patients with Alzheimer's disease have a significant increase in sAPP and sAPP. However, the CSF level of - sAPP and -sAPP has a contradictory result; more studies need to be performed to confirm the validity of sAPP as a biological marker for AD. Although many researchers have revealed that the CSF level of sAPP increases in AD patients, A protein dominates the cortical plaques found in AD brains. A is created by breaking down APP, the protein that is A's parent. The APP gene is located on chromosome 21. Although the precise.[44]

Physiologic functions of APP are not fully understood, it is generally believed to support healthy neuronal activity and maybe cerebral growth. A peptides are produced by the proteolytic cleavage of the trans membrane protein amyloid precursor protein (APP) by the enzyme complexes,, and -secretases. APP cleavage occurs via two distinct routes. The non- The amyloidogenic pathway creates neurotoxic A peptides and benefits the nervous system in a neurotropic manner. The A peptides formed via the amyloidogenic pathway can misfold and aggregate to form deposits that contribute to Alzheimer's disease pathology [45].

Proteolytic processing of amyloid precursor protein (APP)

The 37–43 amino acid amyloid -peptide

(A) is generated by proteolytic processing from its precursor, the -amyloid precursor protein (APP), in a physiologically normal pathway. APP is a type-I membrane protein with its amino terminus within the lumen/extracellular space and its carboxyl terminus within the cytosol).Although APP is initially targeted into the secretory pathway (see below), it is proteolytically processed at several different subcellular sites. Three protease activities called -, -, and -secretase are involved in specific processing steps. The name "secretases" refers to the secretion of the proteolytically cleaved substrates [46].

There are two principal processing pathways: the amyloidogenic pathway, which leads to A generation, and the anti- amyloidogenic pathway, which prevents A generation. A is produced in the amyloidogenic pathway by the consecutive action of - and -secretase. The -secretase activity initiates A generation by shedding a large part of the ectodomain of APP (APPs) and generating an APP carboxy- terminal fragment (CTF or C99), which is then cleaved by -secretase. The latter cleavage occurs within the hydrophobic environment of biological membranes [47]

The non-amyloidogenic pathway

The non-amyloidogenic process involves the cleavage of APP by -secretase to produce two fragments: an N-terminal ectodomain (sAPP) that is released into the extracellular space and an 83 amino acid C-terminal fragment (C83) that stays in the membrane. Three enzymes, ADAM9, ADAM10, and ADAM17, have been found to exhibit -secretase activity. It's significant to note that -secretase cleaves APP within the Aβ domain, which prevents the synthesis of Aβ peptide. It should be noted that -secretase has the ability to cleave the C83 membrane fragment in the future, producing the P3 peptide and the C terminal fragment (CTF). The P3 peptide is thought to be inconsequential in terms of pathology at this time.[48]

The amyloidogenic pathway

The neurotoxic Aβ generation is produced by the amyloidogenic pathway. The initial stage of proteolysis is mediated by - secretase (BACE1), which discharges a sizable N-terminal ectodomain (sAPP) into the extracellular space. The membrane still contains a 99-amino acid C-terminal portion (C99). The first amino acid in Aβ corresponds to the recently revealed C99 N-terminus. The A peptide is released via successive cleavage of this fragment by -secretase (between residues 38 and 43). Presenilin (PS1 and PS2), nicastrin, anterior pharynx deficient (APH-1), and presenilin enhancer 2 make up the complex of enzymes known as -secretase (PEN2). The majority of the A peptides (A 1–40) have 40 residues, but a minor subset has 42 residues (A 1–42).[49]

Mechanisms for Alzheimer's disease - amyloid peptide (Aβ) is formed by the amyloidogenic pathway after the cleavage of amyloid precursor protein by the - secretase and the -secretase (52). Excess amyloid -peptide (A) production leads to the dysfunction and degeneration of neurons that occur in Alzheimer's disease (AD). A is a 38–43 amino acid peptide that is derived from the -amyloid precursor protein (APP) through sequential cleavages by β and γ secretase enzyme activities. The amino terminal fragment generated through -secretase is called secreted APP (sAPP), respectively. The carboxy terminal fragments (CTF) generated by - and -secretases are called CTF83 and CTF99, respectively.[50] β Secretase cleavage of CTF83 and CTF99 will result in the generation of p3 and Aβ, respectively, as well as the amino-terminal APP intracellular domain (AICD). - Secretase activity is mediated by one or more enzymes from the family of disinterring and metalloproteinase domain proteins (ADAM), with ADAM 10, 17, and 19 being the most likely candidates. Beta-site APP cleaving enzyme 1 (BACE1) is the major -secretase in the brain (52). Amyloid plaques are formed by the accumulation of amyloid fibrils, and the deposition of amyloid beta is a hallmark of AD [51] subsequent intramembranous cut by secretase liberates a truncated Aβ peptide called p3, which apparently is pathologically irrelevant. The APP intracellular domain (AICD), which is released into the cytosol and may play a role in nuclear signalling, is produced by secretase in addition to liberating Aβ (from C99) and p3 (from C83). While increasing

-secretase activity in animal models of Alzheimer disease (AD) or in cultured cells can considerably reduce Aβ production and even amyloid plaque formation, the amyloidogenic and the anti- amyloidogenic processing pathways compete with one another at least in some subcellular loci [52].

Cholesterol homeostasis in the brain

A proper availability of cholesterol is important for optimal neuronal function and shape; neuronal cells function is compromised not only owing to a deficit but also a surplus of cholesterol [53].Defects of cholesterol homeostasis in the adult brain are linked to neurodegenerative diseases like Niemann-Pick type C disease. or Alzheimer's.It is generally known that neuronal cells use a sophisticated feedback process to balance biosynthesis, import, and excretion to control the amount of cholesterol they produce. Sterol regulatory element-binding proteins (SREBPs), which control the transcription of genes encoding cholesterol and fatty acid biosynthesis enzymes as well as lipoprotein receptors, help cells sense their level of cholesterol. They either increase cholesterol synthesis and uptake in sterol- depleted cells or decrease cholesterol- synthesizing enzymes when sterols are overloaded in cells. When the requisite amount of cholesterol is reached, 24- hydroxylase catalyses the conversion of cholesterol to 24-hydroxycholesterol (24- OHC) which can be eliminated when HDL is present as a lipid acceptor and guards against the negative consequences of 24- OHC build-up in neurons (58). In addition to being a metabolite for the removal of cholesterol, 24-OHC activates nuclear transcription factors [54]. As a result, cholesterol outflow rises. One of the key mediators for cholesterol homeostasis is ABCA1. The net cholesterol flux increases quickly throughout the early stages of development, when the majority of growth and myelination occurs. Following myelination, the CNS continues to produce cholesterol, although at a very low level. Neurons do not efficiently synthesize cholesterol after myelination is complete and mainly rely on external sources of cholesterol.Conditional ablation of cholesterol synthesis in mouse neurons leads to significant transfer and uptake of glia-derived cholesterol by neurons.[55]

However, under certain conditions, when brain-derived neurotropic factor (BDNF) is present, the endogenous synthesis of cholesterol in neurons is partially restored Cholesterol synthesis ablation in neuronal precursor cells during embryonic development leads to reduced brain size, perinatal lethality, and newly generated neurons.All these evidences indicate that cholesterol synthesis in neurons is essential at the early development stage [56]. This suggests that adult neurons do not require cholesterol production. In this mouse model, the level of lipoprotein- related protein (LRP) likewise stays constant, supporting the notion that adult neurons already produce enough LRP to import cholesterol as apoE-containing lipoprotein particles. All the evidence suggests that some adult neurons do not require cell autonomous cholesterol synthesis, which is very likely to rely on oligodendrocytes and astrocytes for cholesterol provision, especially astrocytes, as they express apoE *in vivo* and neuronal cells can import cholesterol through receptor-

mediated endocytosis of lipoproteins such as apoE-binding forms. The apoE-cholesterol particle is processed to free cholesterol in the lysosome after being endocytosed and then transported to the membrane. The cholesterol transport between cells is influenced by the fluidity of cell membranes and the distribution of microdomains such as lipid rafts [57]

Although it has long been assumed that glia simply serve to passively support neurons, research now suggests that glia actively participate in supporting neuronal processes like synaptogenesis. In neuronal culture, cholesterol in apoE particles produced by astrocytes significantly improves the generated synaptic responses by enhancing presynaptic function and dendritic development Neuronal culture in the presence of astrocytes showed about a 10-fold increase in excitatory synapse activity and a 5–7-fold increase in synapse numbers. The removal of TSPs from astrocyte-conditioned medium diminishes the synaptogenic activity of the medium TSPs are a necessary and sufficient synaptogenic factor for the development of synapse, according to all of them. Moreover, astrocytes generate messenger RNAs that code for a number of synaptic adhesion proteins, such as neurexins, neuroligins, and cadherins [58]

Glycosylation of amyloid precursor protein

APP in the ER undergoes post- translational modification, called glycosylation of proteins. Mainly N- glycosylation occurs in the ER, where covalent attachment of oligosaccharides to asparagine (Asn) side chains is called N- glycosylation of proteins. N-glycans are added to proteins in the ER, resulting in protein modification. Protein N- glycosylation occurs in two stages: the assembly of glycan molecules and the subsequent transfer of glycan to nascent proteins. In stage 2, Glc3Man9GlcNAc2 is assembled on dolichol phosphate. On dolichol phosphate, three glucose, nine mannose, and two N-acetylglucosamine were assembled.The initial transfer of GlcNAc-P from uridine diphosphate (UDP)-GlcNAc to a Dol-P, generating Dol-P-P-GlcNAc, is catalyzed by GlcNAc- 1-phosphotransferase. [59]. The endoplasmic reticulum developed a surveillance system called the ER quality control system; this system involved in folding and modification as well as eliminating misfolded proteins through ER-associated degradation.N-glycans are oligosaccharides by their chemical nature and are branched chains of sugar residues attached to each other by - and - glycosidic linkages [60]

One of the most frequent and intricate types of post-translational modification of proteins is glycosylation. Although glycosylation abnormalities have been noticed in AD patients, the significance of protein glycosylation in the disease has not been fully explored. This review attempts to shed light on this issue. Amyloid plaques and neurofibrillary tangles are the two main pathological features of AD. Phosphorylated tau makes up neurofibrillary tangles, and amyloid peptide, which is produced from amyloid precursor protein, makes up plaques (APP) [61]. There have been reports of errors in the glycosylation of APP, tau, and other proteins in AD [61]. Another intriguing finding is that the two proteases, -secretase and -secretase, which are necessary for the production of amyloid -peptide, also play a part in protein glycosylation (71). For instance, complex N-glycosylation and sialylation of APP are both influenced by - secretase and -secretase, respectively. Given that appropriate intracellular sorting, processing, and export of APP depend on how it is glycosylated, these activities may be crucial in the pathophysiology of AD [62].

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