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Inhibition of secretase: A promising technique for Alzheimer's disease patients

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A B S T R A C T

Alzheimer's is a globally known neurodegenerative disease. Aβ is a cleavage product of the 695-770 amino acid, single mem-brane-spanning protein known as the Aβ-precursor protein (APP), which is highly expressed in the nervous system. The most abundantly produced isoform of A by neurons is A40, while A42 has two C-terminal hydrophobic residues that increase its propensity to self-assemble into amyloid. As a consequence, despite differences in the relative numbers of plaques stained for A40 and A42, more plaques are immunoreactive for A42 than for A40. In addition to plaques and amyloid angiopathy, Aβ multimerizes into a range of oligomeric species that can interact with cells and impact brain function. Because all established risk factors for AD enhance its quantity and/or inclination to aggregate, A has taken on a key role in Alzheimer research. The Aβ plaque formation and hyperphosphorylation of Tau protein are key hallmarks of this disease. The maturation of Aβ occurred by two golden enzymes β secretase and γ secretase. In this review we discuss about some strategies which suppress these enzymes for prevention of Aβ plaque formation.

Keywords: Alzheimer's disease · Neurofibrillary tangles · Aβ plaque · Amyloid Precursor Protein · β Secretase · γ secretase

1. Introduction

Alzheimer's disease is a type of neurodegenerative disease cause characterized by loss of memory, progressive cognitive and behavioral disorder. A study of global prevalence of dementia revealed that near about 50% - 70% of dementia caused by the Alzheimer's disease (AD) [1]. The World Alzheimer's disease Report on 2018 suggests that about 50 million people worldwide suffering dementia. With every 3 s worldwide new case arise, so now AD become convert an epidemic disorder, so it can predict that on 2050 there about 152 million of new cases occur [2]. Alzheimer's disease has numerous biomarkers such as deposition of β-amyloid (Aβ) peptides, this deposition occurs in the extracellular matrix between neurons which cause of Aβ plaque formation. Deposition of Aβ peptide is the main component of amyloid plaque and Aβ derived from the APP (Amyloid precursor protein) by proteolytic cleavage. Aβ accumulation mainly occurs within the hippocampus, neocortex and cerebrovasculature region of the brain [3]. The most prevalent cause for a loss in cognitive capacity is Alzheimer disease (AD). Alzheimer's disease causes modest memory loss in the initial phases, but by the latter stages, people are unable to response.

The main clinical feature of this disease loss of memory associate with dementia, change of personality, mood swing, anxiety. Some other pathological symptoms with AD brain contain neurofibrillary tangles (NFTs) occurred by Amyloid Aβ aggregation, hyperphosphorylation of tau protein, number of synapse is drastically reduced [4].

The most prevalent form of dementia in older people, Alzheimer's disease (AD) is characterised by the buildup of intracellular tangles of the abnormally hyperphosphorylated microtubule-associated protein tau (P-tau) and extracellular deposits of aggregated β-amyloid (Aβ) peptides [5]. Amyloid plaque formation Extracellular amyloid plaque development is a frequent patho-biochemical process that underlies a number of crippling human illnesses, including Alzheimer's disease (AD). There is a lot of evidence to suggest that small oligomeric amyloid forms of the Aβ peptide are the main cause of Alzheimer's disease (AD) damage, although the exact pathogenic process is still unknown. Aβ -peptide that has been internally processed is sorted to multivesicular bodies, where fibrils emerge and penetrate the vesicular membrane. An essential membrane protein called amyloid precursor protein, or APP, is processed by secretases, which are proteolytic enzymes. Secretases are a broad class of proteases that selectively breakdown membrane proteins. The limited cleavage is sometimes enforced by the release of large products from the membrane during initial endoproteolysis because their substrates are membrane-bound. There are three varieties of secretases i.e. α, β, and γ and these enzymes break down APP into nonamyloidogenic and amyloidogenic fragments. The cleavage of APP into the several amyloid fragments, among them the amyloid beta fragment, the main element of the senile plaques, is carried out by a number of membrane-bound secretase enzymes. Here a review of current ideas in Alzheimer's AD, with respect to inhibition of secretase is provided and future therapeutic strategies are considered.

2. Overview of inhibition process of secretase and Alzheimer's disease (AD)

A smaller protein known as amyloid beta (Aβ), which is typically 40 or 42 amino acids long, is released from a larger parent protein known as the Aβ-precursor protein (APP).

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The Aβ segment of the APP is located both within and outside of the membrane. In the body, Aβ-precursor protein (APP) is produced by a variety of cell types, although it is prevalent in neurons. It is a transmembrane protein that only makes a single pass-through cellular membrane. Two enzymes successively cleave APP, the beta secretase (or β-amyloid cleaving enzyme (BACE)), outside the membrane, first, and gamma secretase (γ-secretase), an enzyme complex inside the membrane, second [6]. The activation of synapses increases the discharge of Aβ. Aβ can be chemically altered in a number of ways and the length of the protein as well as chemical alterations can affect a protein's toxicity and susceptibility to aggregation [7]. β -amyloid (A β) peptide extracellular deposits are linked to Alzheimer's disease [8-10]. Dementia-related acquired progressive cognitive impairment that interferes with daily life activities and is a leading contributor to dependency, disability, and mortality is Alzheimer's disease (AD). The risk for familial types of AD can be increased by mutations in the β-cleavage sites of the APP [11].

3. Research Methods

The β secretase, also known as beta-site amyloid precursor protein splitting enzyme 1 (BACE1), starts the synthesis of the harmful amyloid β (Aβ), which is a key early stage in the aetiology of Alzheimer's disease. β-secretase is a transmembrane aspartyl protease, this enzyme has an immense importance in Alzheimer's disease (AD) as it is one among the primary enzymes in the production of amyloid beta plaques (A β), a pathological sign of the condition. Aβ is a cleavage product of the 695-770 amino acid, single membrane-spanning protein known as the Aβ-precursor protein (APP), which is highly expressed in the nervous system. The most abundantly produced isoform of A by neurons is A40, while A42 has two C-terminal hydrophobic residues that increase its propensity to self-assemble into amyloid. As a consequence, despite differences in the relative numbers of plaques stained for A40 and A42, more plaques are immunoreactive for A42 than for A40. Aβ multimerizes into a variety of oligomeric species in addition to plaques and amyloid angiopathy [12, 13], which can interact with cells and affect brain function [14-16]. Because all established risk factors for AD enhance its quantity and/or inclination to aggregate, A has taken on a key role in Alzheimer research. The relationship between Alzheimer's disease and secretase inhibition has been thoroughly examined in academic literature and the study includes some recommendations as well.

4. Results and Discussion

4.1 Formation of Aβ associate to AD

Amyloid precursor protein (APP) is a type I membrane protein which ultimately generate Aβ by some enzymes such as β secretase, Aph1, Pen2, nicastrin, γ secretase. APP is cleaved by β secretase and form two fragments N-terminal APP, membrane bound C- terminal APP. This C terminal APP further cleaved by γ secretase to form mature Aβ which is 40 to 43 amino acid long. γ secretase encoded by PSEN 1 and PSEN 2 gene, gain of functional mutation of these genes can cause hyper production of γ secretase which led to high production of amyloid β [17]. Hyperaccumulation of Aβ can cause the formation of amyloid plaque and Aβ oligomer. Aβ oligomers are directly affect long term potentiation (LTP) which ultimately prevent synaptic transmission, loss of memory, affect cognitive behaviour [18]. Glial cell proliferation is induced by hyper formation of Amyloid β plaque. These glial cells release some cytotoxic factors which have neurodegenerative effect [19].

4.2. Some therapeutics involve to remove Aβ plaque

4.2.1. β *secretase*

One of the significant therapeutic to remove Amyloid β is to target β secretase for AD. The inhibition of β secretase is to involve in prevention of $A\beta_{42}$ production which become a remarkable strategy in AD therapeutics. β secretase also known as BACE1 (β site APP Cleaving Enzyme) [20]. It is difficult to design any drug for inhibition of BACE1 because of the catalytic site of this enzyme is more hydrophobic in nature [21]. In dividing and nondividing cell's gene silencing occurred by a novel genetic tool known as lentiviral derived siRNA [22]. This siRNA mediated gene therapy gives outstanding result in AD by suppressing of BACE1 expression [23]. SiRNAs are originated from shRNA, contain 21-23 nucleotide and have a complementary sequence to silence the transcript [24]. The siBACE1-6 is one of the most potential sequences among the seven different sequences of siBACE1 which remarkable worked on mouse cells as well as human cells BACE1 suppression [25]. The nuclear factor κB is transcription factor which composed of five protein such as NF- κB1 (p105/p50), NF- κB2 (p100/p52), ReIA (p65), ReIB, c-Rel [26]. NF κB acts on inflammatory response as well as it also performs neuroprotective factor or neurodegenerative factor by hyper production of β secretase [26-28]. The FDA approved drug on AD patients work either NMDR (N-methyl-D-aspartate receptor) antagonist or inhibit acetylcholinesterase. Memantine is NMDR antagonist which inhibit the expression of NF-κβ, this inhibition act on reduction of Aβ, increase the impermeability of BBB (Blood Brain Barrier) [29]. Some other components such as ibuprofen, aspirin, indomethacin, Lipoxin A4, tetracycline, minocycline, curcuminoid, forsythoside B affect on expression of NF – κβ, BACE1, which ultimately prevent Aβ plaque formation [28,30-32].

4.2.2. γ Secretase

The final development of Aβ protein occurs by γ secretase. This enzyme cleaves cytosolic C - terminal domain which is 99 amino acid long [33]. Presenilin 1 and Presenilin 2 are key proteins which help in catalytic core formation for γ secretase [34]. Apart from PS1 and PS2 protein, APH1 (anterior pharynx-defective 1), Pen-2 (PS enhancer protein 2) and Nicastrin play significant role for γ-secretase complex formation [35]. Some drugs which act as γ secretase inhibitor helps in reduction of Aβ but these

drugs also affect Notch signalling [36,37]. The early endoplasmic reticulum is where the gamma secretase complex is expected to assemble and mature through proteolysis. The complexes are subsequently taken to the late ER where their substrate proteins are interacted with and cleaved. Gamma secretase is a multi-subunit protease complex, is additionally essential in the processing of several other integral membrane proteins, such as Notch [38], N-cadherin [39], E-cadherin [40], ephrin-B2 [41], ErbB4 [42] or CD44 [43]. Notch signalling, which represents a highly conserved cell signalling mechanism, plays several important roles such as neural survival, synaptic plasticity, protooncogene and tumor suppressor gene regulation, neural stem cell proliferation [44,45].

4.3. Some promising drugs and Alzheimer's disease (AD)

Some promising drugs like begacestat, avagacestat, PF-3084014 and piperidine have γ secretase inhibition activity on AD [46]. The Begacestat contains sulfonamide which show reduction of Aβ activity on cell based and cell free assay. A specific inhibitor of γ -secretase, begacestat prevents the cleavage of the amyloid precursor protein (APP) over notch. It exhibits notch intracellular domain inhibition activity in cell-based assay. Some of the cardinal diseases connected with Alzheimer's disease include congophilic angiopathy, senile plaques, and neurotoxic oligomers, which are formed when amyloid beta-peptides (Abeta peptides) assemble. However, nonselective inhibition of the enzyme may result in serious adverse outcomes due to defective Notch receptor processing, even if inhibition of this protease working on APP may reduce neurotoxic Abeta peptides in a manner that is potentially therapeutic. The transmembrane receptor known as Notch plays a crucial role in lymphocyte maturation and intestinal cell fate decisions. Notch functions in the skin as a tumour suppressor in preclinical models. The prior clinical medication semagacestat was terminated due to side effects believed to have been brought on by Notch inhibition; thus, following drug-development programmes have sought to achieve a stronger dissociation between APP and Notch inhibition. In a parallel, untreated, nonrandomized observational cohort (NCT00890890) in a randomised, placebo-controlled phase 2 clinical trial, the safety of avagacestat, a -secretase inhibitor, for treating Alzheimer's disease was assessed [47]. The idea that early involvement with a disease-modifying agent will be necessary to most effectively affect symptom emergence and disease progression is supported by a recent investigation among people with dominantly inherited AD that found that structural and biochemical alterations related to AD begin years before the onset of clinically evident symptoms [48]. The avagacestat contains aryl sulfonamide group which inhibit γ secretase. It has the ability to bind N terminal domain of PS 1 and inhibit γ secretase complex formation. Inhibition of γ secretase activity. The PF-3084014 exhibits blood brain barrier permeability activity. It shows weak potency to inhibit notch signaling pathway. It also acts as γ secretase inhibitor. The Piperidine contains N-aryl sulfonamide. It is a most common orally taken γ secretase inhibitor. It acts on mild Aβ level.

5. Conclusion

In this review we discuss some strategies which helps to block Aβ plaque formation by affect the functionality of two enzyme β secretase and γ secretase. But all the strategies are economically very high and some strategies are not still proceeded on any human trail. In future we should focus on developing single drug which is extremely potent for inhibition of both β and γ secretase. The study reflects that the BACE1 (-secretase, memapsin 2, Asp2) has become noted as a viable Alzheimer's disease therapeutic target. The initial stage of the process leading to the formation and deposition of amyloid- peptide (Aβ) is carried out by the aspartic protease known as BACE1. Despite the fact that designing and developing BACE1 inhibitors has proven to be extremely challenging, there is a considerable body of data indicating BACE1 inhibitors can work as disease-modifying medicines, and their usage deserves to be pursued to treat AD patients. It will take more research to come up with effective ways to reduce the negative consequences of long-term BACE1 inhibitor use.

Conflict of interest

The authors declare that there is no conflict of interest in this manuscript.

Data availability

The authors confirm that all data collected or analyzed during this study are included in this published article.

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