REVIEW ARTICLE

Amyloid Precursor Protein Processing in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and a leading cause of dementia. The AD is characterized by presence of intraneuronal tangles and extracellular plaques in the brain. The plaques are composed of dense and mostly insoluble deposits of amyloid beta peptide (Aβ), formed by sequential cleavage of the Amyloid Precursor Protein (APP), by two pathways amyloidogenic and non-amyloidogenic. Tangles are composed of paired helical fragments, which aggregate to form, microtubular protein tau. Although Aβ plaques are established to be the cause of the disease, there exist genetic factors and other pathological identifications in addition to these which are an integral part of the disease. This article gives an overview into the mechanism of APP action, genetic factors and other pathological identifications contributing to Alzheimer's disease formation.

Keywords: Amyloid precursor protein; Amyloid plaques; Secretase; Neurofibrillary tangles

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Introduction

Alzheimer's disease (AD) is the most common form of dementia. It is a progressive neurodegenerative disorder characterized by severe memory loss and has afflicted 10% of the world population over the age of 65 years, and 50% of the population over the age of 85 years (1). Health and medical statistical analysis using year 2000 census data showed that about 4.5 million people in the United States suffer from AD and by 2050 there are expected to be 13.4 million people suffering from AD worldwide (2).

The disease was first described by a German neuropsychiatrist Alois Alzheimer in 1906. He found the presence of neurofibrillary tangles and amyloid beta plaques in the brain tissue of Auguste Deter, the first patient who was diagnosed with AD (3). Plaques and tangles are considered to be the hallmarks of the disease (4). Improper cleavage of the amyloid precursor protein (APP) by specific secretases leads to generation of a 4 kDa fragment of an insoluble amyloid beta (Aβ) peptide. The secretases have been described in a subsequent section of this proposal. The aggregation of the resulting Aβ peptide forms plaques, which accumulate within neuronal cells eventually causing death. Neurofibrillary tangles on the other hand are composed of hyperphosphorylated insoluble forms of the microtubule protein-tau. The tau-protein contributes to the development of microtubules which function in cellular transport. The hyperphosphorylation of tau-protein leads to the formation of tangles which destroy the microtubule structure. Neurofibrillary

tangles are formed in neurons and cause neuronal cell death by destroying the intracellular nutrient transport system (5).

Missence Mutations in APP

Missence mutations were identified to be the first genetic cause of AD. Presence of missence mutations have been found in only two dozen families worldwide (6). These mutations have been found to have been located strategically just before the β-secretase cleavage site or shortly after the α-secretase cleavage site. Some of the established mutations are: (1) β-APP mutations on chromosome 21 leading to production of all Aβ40 peptides; (2) ApoE4 polymorphism on chromosome 19 leading to an increase in density of Aβ plaques; and (3) Presenilin1 mutations on chromosome 14 leading to production of Aβ42 peptides. These mutations alter the processing of APP (6).

APP Processing

Amyloid precursor protein (APP) is a type-1 transmembrane glycoprotein (7). The human APP gene is located on chromosome 21. APP has a large extracellular domain and a short cytoplasmic domain. This protein is located partially in the ectodomain and partially in the transmembrane (8). There are three different isoforms of APP, namely APP695, APP751 and APP770 (9). Twenty five different forms of APP mutations are identified to be involved in AD formation. These mutations are known to introduce amino acid changes within the Aβ domain or the region flanking Aβ. The two predicted pathways of cleavage for APP are the amyloidogenic and the non-amyloidogenic pathway. The cleavage is carried out by three types of proteases, namely α, β, and γ (10).

The Amyloidogenic Pathway

This pathway is characterized by the formation of Aβ fragments. A high expression of Beta-site APP Cleaving Enzyme (BACE1), a membrane bound aspartyl protease, stimulates the APP to preferentially undergo cleavage by the amyloidogenic pathway (8). It involves the sequential cleavage of APP by β-secretase followed by γ-secretase. BACE1 cleaves APP within the ectodomain to release a fragment, sAPPβ and a C99 fragment (Figure 1). The γ-secretase subsequently cleaves the C99 region to release Aβ peptides (Aβ40 and Aβ42). sAPPβ is known to induce neuronal death while over production of βCTF causes neuronal degeneration by hampering signal transduction (9).

The γ-secretase mediated cleavage brings about the formation of Aβ40 and Aβ42 fragments, of which Aβ42 is the more amyloidogenic species (11). Substantial evidence suggests that an excessive production of Aβ results in a neurodegenerative cascade leading to initiation of synaptic dysfunction, formation of neuro-fibrillary tangles and finally a loss of neurons in the affected areas of the brain. Aβ40 and Aβ42 are the two main toxic species. Aβ42 is known to be more prone to formation of neuron fibril aggregates (4).

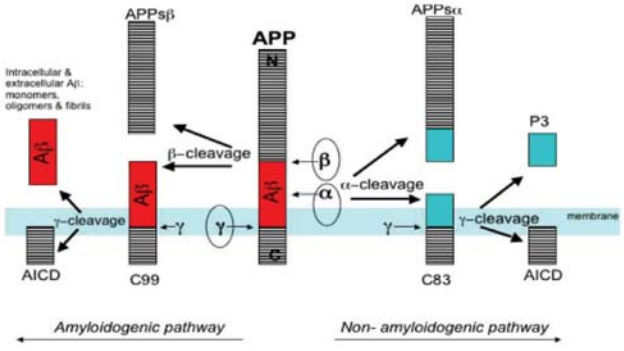

Fig 1. Processing of amyloid precursor protein (APP) by amyloidogenic and non-amyloidogenic pathway

The Non-Amyloidogenic Pathway

APP is cleaved within the transmembrane domain by α-secretases such as TACE or ADAM (a disintegrin and metalloproteinase), thereby generating a sAPPα fragment and an 83 residue long (C83) C-terminal fragment (CTF). The sAPPα only differs from sAPPβ by the presence of the 1-16 residue region at C-terminus (9). Further cleavage by γ-secretase of the CTF leads to the generation of short fragments of p3 peptide and the APP intracellular domain (AICD) (Figure 1). The p3 is rapidly broken down while AICD has activity responsible for regulation of transcription of multiple genes including APP and BACE1. AICD is also known to facilitate the interaction of APP with cytosolic factors (9). The formation of sAPPα is considered to be neuroprotective. The sAPPα is also responsible

for early CNS development, neuronal survival and prevention against excitotoxicity (4).

α and β Secretases

The α-secretase cleaves APP to at Lys 16-Lys 17 bond to release a soluble ectodomain of APP called sAPPα. It is a membrane bound endoprotinase which cleaves APP primarily at the plasma membrane bound endoprotinase. A-secretase is a zinc-metalloprotinase (9). Many members of the ADAM (a disintegrin and metalloproteinase) family, like ADAM9, ADAM10 and ADAM17 have an α-secretase like activity (4). ADAM9 possess α-secreatse like activity and is known to be involved in regulation of α-cleavage. ADAM10 is known to cause an increase in the activity of α-cleavage. sAPPα protects against excitotoxicity and has an important role in neuronal survival (9).

BACE 1 is the most common name given to the β-secretase. It is a membrane bound aspartyl protease as well. Down regulation of BACE 1 induces or inhibits cleavage of APP at known β site locations Asp1 and Glu11. BACE 1 activity is considered to be the rate limiting step in Aβ formation (12). Mechanism regulating BACE 1 has not been fully recognized but it is known that they function best in an acidic environment. BACE 1 is being currently widely validated as a potential therapeutic target and reports have indicated that sAPPβ can rescue gene expression (9).

Promoter of APP Gene

The promoter for APP gene resembles the promoter of many housekeeping genes. It is deficient in the presence of a TATA box and is characterized by the presence of high GC content of nearly 72% in the promoter region. Found upstream of RNA start site are the sequences which are homologous to the AP-1 transcription factor and the control element for heat shock binding protein. The DNA-protein interaction can be mapped to the element which is located in a 9-bp long GC-rich element which can be located in positions 200 and 100 (13). Protein sequencing of the amyloid isolated from the brain tissue of AD patients showed the presence of A4 protein, a part of a larger amyloid precursor which is mapped to chromosome 21. Recent investigation has further revealed a nuclear factor-binding domain designated as DAPB located in the 5'-UTR of the APP gene may have a function in post-transcriptional regulation, including nuclear export of mRNA due to the fact that elimination of factor-binding correlated with an overall decline in expression from the APP promoter while in vitro transcription and the total amount of in vivo transcribed RNA remained unaffected (14).

Prospects

All currently available research has been targeted towards knowing the processing of amyloid precursor protein. It would be immensely resourceful if research could come up with answers for validating these findings. Manufacturing drugs targeting the receptors such NMDA which are involved in bringing about APP processing would be one of the methods of validating the viability of the findings. Finding the functions of APP intracellular domain (AICD) and the C-terminal fragment regions would also shed more light into the Aβ hypothesis. It has been demonstrated recently in a successful establishment of the possible involvement of AICD in mouse models, that amyloid (α/β/) peptides are potentially the primary cause of AD (15). We expect that this theory of AD pathogenesis will bring a better understanding of the molecular mechanism of AD pathogenesis and will lead to the invention and development of new technologies and medicines for AD prevention, control, and final cure in near future. It now remains to be seen if reproducible results can be produced in humans as well. Drugs for AD such as Flurbiprofen and Tramiprosate which were targeted towards AB plaques have failed. This suggests the involvement of another synergistic factor which shows pathological identification in addition to AB plaques. It is therefore possible to hypothesize that AICD a by-product of APP processing is involved in Alzheimer's disease formation.

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