Amyloid Deposition in Alzheimer’s Disease*

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ABSTRACT

Alzheimer’s disease (AD), a progressive neurodegenerative disorder, accounts for approximately 60 percent of all victims of dementia and affects greater than 10 percent of the population over 65 years old. Although the cause is unknown, there is evidence that beta-amyloid plays an important role in its pathogenesis. The deposition of this type of amyloid in the brain and its implications in AD are discussed.

Introduction

Alzheimer’s disease (AD), a progressive neurodegenerative disorder, accounts for approximately 60 percent of all individuals with dementia and affects greater than 10 percent of the population over 65 years old. It is the fourth major cause of death in the developed world. The diagnosis of Alzheimer’s disease is not always straightforward. Only a “probable,” not a definitive diagnosis can be made without histologic confirmation, and many of the pathologic changes are found to a lesser degree in normal aging.

Alzheimer’s disease is characterized microscopically by neuritic (senile) plaques (containing tortuous argyrophilic neuritic processes around a central core of beta amyloid), neurofibrillary tangles (composed of intraneuronal paired helical filaments owing to a hyperphosphorylated microtubular tau protein), amyloid angiopathy, and neuronal cell loss. The amyloid protein in neuritic plaques and blood vessels is essentially the same. Recently, much attention has been given to the role of beta-amyloid protein (A4) in the pathogenesis of Alzheimer’s disease. Whether or not the excess accumulation of beta-amyloid in the brain is the causative agent of the neurodegeneration or a by-product of the process is not known.

Amyloid Precursor Protein

Amyloid precursor protein (APP) is a transmembrane glycoprotein coded by a gene on the long arm of chromosome 21. Its functions include protease inhibition, cell adhesion, and regulation of cell growth. Splicing of ribonucleic acid (RNA) of the APP gene produces several isoforms designated by
the number of amino acids, i.e. 770, 751, 714, 695, 563, and 365.2,4,6,8,12,13,20,26
Amyloid precursor protein770 is the most abundant form in the body. The predominant variant in the brain has 695 amino acids and lacks the serine protease (Kunitz-type) inhibitor region that is present in other APPs.4,5,6

Without the Kunitz Protease Inhibitor (KPI) region, APP functions primarily in the stimulation of cell adhesion. The variants of APP containing the KPI insert share the same properties as protease nexin II (a growth regulating molecule secreted by fibroblasts) and bind with several serum proteases in the blood to play an important role in coagulation inhibition.22

**Formation of Beta-Amyloid**

Beta-amyloid protein is a 4.2 kD peptide15 containing 39 to 43 amino acids.6,16 It is located near the carboxyl-terminal region of APP.13 The processing of APP can occur through two pathways (figure 1). Amyloid precursor protein can be inserted into the cytoplasmic membrane (or into the membrane of an organelle)

**Figure 1.** The amyloid cascade hypothesis. Processing of amyloid precursor protein (APP) can occur via two pathways: (1) Cleavage within amyloid-beta protein (ABP), the secretase, which generates peptide products that do not precipitate to form amyloid and (2) Cleavage in the endosomal-lysosomal compartment, resulting in intact ABP that precipitates to form amyloid and, in turn, causes neurofibrillary tangles and cell death, the hallmarks of Alzheimer’s disease.6 (Permission to reprint figure 1 granted by the American Association for the Advancement of Science and Gerald A. Higgins, Ph.D. Figure 1 is taken from Hardy, J. A. and Higgins, G. A.: Alzheimer’s disease: The amyloid cascade hypothesis. Science 256:184—185, April 10, 1992. Copyright 1992 by the AAAS.)
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and subsequently cleaved at amino acids 15-17 to form beta-amyloid by APP secretase.\textsuperscript{6,13,25} The NH\textsubscript{2}-terminus extends extracellularly or intralumennally, depending on the cell type. The COOH-terminus lies within the cytoplasm. The NH\textsubscript{2}-terminus of beta-amyloid lies at Asp 672 (in reference to APP\textsubscript{770}) and the COOH-terminus lies within the membrane-spanning sequence.\textsuperscript{13} Since this enzymatic degradation results in fragments that do not contain intact beta-amyloid, deposition of amyloid does not occur. Amyloid precursor protein can also be processed via the endosomal-lysosomal pathway, resulting in an intact beta-amyloid sequence near the COOH-terminus of APP. This, in turn, may lead to amyloid deposits.\textsuperscript{6}

**Beta-Amyloid in Alzheimer's Disease (Alzheimer's Amyloidosis)**

Excess accumulation of beta-amyloid in the brain may cause the microscopic lesions resulting in the clinical features of Alzheimer’s disease.\textsuperscript{5,6} Beta-amyloid has been shown to be toxic to cultured neuronal tissue and \textit{in vivo} to mature neurons in regions typically affected by Alzheimer’s disease. Neve et al\textsuperscript{19} and Yanker et al\textsuperscript{28} demonstrated that the beta-amyloid fragment of the APP is toxic to neurons in primary hippocampal cultures. While beta-amyloid was toxic to mature neurons, it was trophic to undifferentiated hippocampal neurons at lower concentrations.\textsuperscript{29} Kowall et al\textsuperscript{14} suggested that beta-amyloid alone exerts toxic effects in the adult cerebral cortex, resulting in neuronal loss and degeneration of neurites. This toxic effect can be blocked by intracerebral and systemic administration of substance P, which has an amino acid sequence similar to parts of the APP.\textsuperscript{14}

The segment of beta-amyloid required for the toxic and trophic neuronal effects is found within an 11 amino acid internal sequence homologous to a conserved region in the tachykinin family of neuropeptides.\textsuperscript{29,30} Beta-amyloid does not appear to bind to the tachykinin receptor that binds substance P; it is recognized instead by the serpin protease inhibitor-enzyme complex (SEC) receptor.\textsuperscript{9,10,30} The SEC receptor specifically recognizes an amino acid sequence conserved in serpin protease inhibitors, tachykinins, and beta-amyloid. Alzheimer’s disease may represent over-production of beta-amyloid which may competitively inhibit binding of the protease complex to SEC receptors, thereby impairing the ability to clear extracellular protease. This enzyme, in turn, could lead to cell membrane damage and eventual neuronal degeneration.\textsuperscript{30} Substance P competes with beta-amyloid for binding to the SEC receptor,\textsuperscript{10} thereby potentially blocking its effect.

Mattson et al\textsuperscript{16} maintain that beta-amyloid is not neurotoxic directly, but destabilizes calcium homeostasis, rendering neurons more sensitive to excitotoxic damage. The neuritic lesions in Alzheimer’s disease show immunoreactivity with antibodies to the microtubule associated protein (tau).\textsuperscript{13} Abnormal phosphorylation of the tau protein gives rise to the excessive numbers of paired helical filaments characteristic of patients with Alzheimer’s disease. Since the phosphorylation of tau can be controlled by intracellular calcium concentration, this may explain formation of neurofibrillary tangles and dystrophic neurites.\textsuperscript{6,13}

**Etiologic Considerations**

Alzheimer’s disease is primarily sporadic. Mutations in the COOH-terminus of APP have been associated with hereditary early onset Alzheimer’s disease\textsuperscript{1,3,18} and hereditary cerebral hemorrhage with amyloidosis of Dutch type (HCHWA-D).\textsuperscript{15,21,27} Mutations in early onset hereditary Alzheimer’s disease
occur on codon 717 of the amyloid precursor protein and involve a single amino acid substitution near the COOH terminus of beta-amyloid (Val → Phe, Val → Ile, Va → Gly).1,3,18 This substitution lies within the transmembrane domain of APP.1,3,6,18 The exact mechanism of subsequent amyloid deposition is not known. The mutation may make that peptide area more hydrophobic, and, therefore, anchor the protein more firmly into the membrane.3 Other theories involve inhibiting the breakdown of a COOH-terminal fragment that contains beta-amyloid or stabilizing beta-amyloid containing amyloidogenic fragments within the lysosomes.6 The mutation involved in HCHWA-D is a guanidine to cysteine transversion resulting in the substitution of glutamine for glutamic acid at codon 693 (in reference to APP770). Exactly how this mutation leads to subsequent amyloid deposition is not known.15,21,27 However, inhibiting secretase cleavage of APP may be a possibility.5

All patients with Down’s Syndrome (trisomy 21) will inevitably develop extensive neuropathological changes of Alzheimer’s disease by their fifth decade.4,5,23 Even though they may not be demented, amyloid deposition occurs by the fourth decade, considerably earlier than in the normal population. In addition, elevated levels of APP are found in the brain and blood of patients with Down’s victims, but not in Alzheimer’s subjects. This increase seems due to over-expression of the APP gene. Accumulation of excess beta-amyloid also occurs in non-demented Down’s patients in their middle teens and twenties.23

Conclusion

Recent advances in molecular genetics support a strong correlation between the accumulation of beta-amyloid in the brain and the development of Alzheimer’s disease. The continued understanding of the biochemical and biophysical cascade leading to beta-amyloid deposition will facilitate pharmacologic intervention. With no current effective treatment and an aging population, Alzheimer’s disease is becoming a major cause of chronic disability and rising medical costs.

References


