

Amyloid β protein and Alzheimer's disease

Introduction

Alzheimer's disease (AD) is a disease that causes deficits in memory and learning and is the major cause of cognitive deterioration in the elderly. Throughout the world, approximately 10% of people in their 70s and 30% in their 80s suffer from Alzheimer's disease. Its symptoms include forgetfulness, estrangement of the family members and friends, depression, loss of homing instinct and time sensitivity. AD has two neuropathological hallmarks: extracellular formation known as senile plaques (SP, a dense heterogeneous extracellular deposit) and intracellular silver-stained formations called neurofibrillary tangles (NFT). Filamentous brain lesions could occur within neurons (neurofibrillary tangles), in extracellular cerebral (amyloid plaques), and in meningocerebral blood vessels (amyloid angiopathy).^{1,2}

Amyloid β protein, amyloid protein precursor and Alzheimer's disease

Amyloid β protein ($A\beta$) has been identified as a 4 kDa hydrophobic non-glycosylated peptide consisting of 39-43 amino acid residues and derived from a 700 amino acid residue of a membrane-associated glycoprotein, the amyloid precursor protein (APP) by specific endoproteolytic cleavages.^{2,3} $A\beta$ appears in bundles of amyloid fibrils surrounded by abnormal neurites and is believed to be the major subunit of the vascular and plaque filaments in individuals with Alzheimer's disease, elderly people, and patients with trisomy 21 (Down's Syndrome). In vitro studies recently indicated that synthetic $A\beta_{1-42}$ could form insoluble aggregates and produce neurotoxicity after incubation for several days.¹ The $A\beta_{1-42}$ assemblies are positive in Congo red and thioflavine S staining similar to that observed in AD brain. The synthetic peptide $A\beta_{1-40}$ was found to enhance the aggregation of $A\beta$ and exhibit neurotoxic effect in vitro.⁴ More interesting, peptide $A\beta_{25-35}$ showed strong self-aggregation activity and reproduced both the neurotoxic and the neurotrophic effect in tissue culture, indicating that this portion of $A\beta$ may be responsible for biological effects of $A\beta$.¹ The aggregation state of $A\beta$ seems to play a critical role in developing AD: as $A\beta$ is aged, it spontaneously aggregates and self-assembles into higher-

order structure. This conformation change transforms $A\beta$ into a stimulus which initiates neuronal cell death.⁵

Amyloid protein precursor (APP), encoded by a gene on human chromosome 21, serves as an integral transmembrane cell-surface receptor. It binds and inhibits a number of factors in plasma and proposed to act as a signal for membrane extension. APP missense mutations have been studied in vitro transfection system and are found to increase $A\beta$ secretion, particularly $A\beta_{1-42}$.⁶ Furthermore, plasma $A\beta$ level significantly increased in some APP mutation carries. As a result, it is believed that APP mutations cause AD by enhancing cleavages to generate more $A\beta$, thereby promoting the amyloidogenesis.⁷

ApoE, Presenilin 1, 2 and Alzheimer's disease

Inheritance of one or two apoE4 alleles increases risk factor for familial and sporadic AD. AD patients carrying apoE4 show a significant increase in the density of $A\beta$ deposit compared to patients carrying no apoE4 alleles. In vitro studies have indicated that ApoE4 can promote amyloid fibril formation by $A\beta$ and binding of human apoE4 to synthetic $A\beta$ peptide has been identified. Precisely how apoE4 enhances $A\beta$ aggregation is still under intensive investigation.⁷ Presenilin (PS) 1 and 2 belong to highly homologous, multitransmembrane proteins. To date, more than 30 mutations in PS1 and PS2 have been identified. It was found that $A\beta_{42}$ secretion increases after transfection of mutant PS cDNA into cultured peripheral cells. Transgenic mice expressing mutant PS1 also show increased $A\beta_{42}$ levels in the brain. Finally, direct analysis of the brains of patients bearing PS1 mutations demonstrated a significant increase in the density of $A\beta_{42}$ -containing plaques compared to that found in patients with sporadic AD.^{6,7,8}

Prospects

Current therapeutic strategies for Alzheimer's disease involve decreasing the rate at which patients decline. In the course of AD, patients' cholinergic neurons that produce acetylcholine are lost in the brain. An obvious

therapeutic approach is to attempt to enhance the activity of the remaining acetylcholine. The existence of amyloid β protein also provides attractive target for drug discovery. At least four broad classes of AD drugs can now be envisioned: (I) protease inhibitors: that decrease the activities of the enzyme which cleave A β from APP; (II) compounds that bind to extracellular A β and prevent

its aggregation into cytotoxic amyloid fibrils; (III) brain specific anti-inflammatory drugs that block the microglial

activation, cytokine release and acute-phase response that occur in affected brain region; (IV) compounds such as antioxidants, neuronal calcium channel blockers, or antiapoptotic agents that interfere with the mechanisms of A β -triggered neurotoxicity. Recently, many AD research laboratories have been involved in developing the animal model that might provide insights into the pathology and phenotype characteristics of Alzheimer's disease.

Literature References

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American Peptide Company, Inc

Headquarters

777 East Evelyn Ave.
Sunnyvale, CA 94086
USA

Phone: (408)733-7604
Fax: (408)733-7603

cGMP Manufacturing

1271 Avenida Chelsea
Vista, CA 92081
USA

Phone: (760) 597-8820
Fax: (760) 597-8816

Toll free phone: (800) 926-8272 fax: (888) 670-0070

Email: sales@americanpeptide.com,

URL: www.americanpeptide.com