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Review Article

Advances in the prevention of Alzheimer's disease: A Review on Role of Amyloid-β pathology

*Parlovich Fletcher*1, Edward Alecto1
Department of Neurophysiology, Taiwan

*Corresponding Author: Parlovich Fletcher, Department of Neurophysiology, Taiwan.

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Abstract

Definitions and diagnostic criteria for all medical conditions are regularly subjected to reviews and revisions as knowledge advances. In the field of Alzheimer's disease (AD) research, it has taken almost three decades for diagnostic nomenclature to undergo major re-examination. The shift towards presymptomatic and pre-dementia stages of AD has brought prevention and treatment trials much closer to each other than before. Here we discuss: (i) the impact of diagnostic reliability on the possibilities for developing preventive strategies for AD; (ii) the scientific evidence to support moving from observation to action; (iii) ongoing intervention studies; and (iv) the methodological issues and prospects for balancing strategies for high-risk individuals with those for broad population-based prevention. The associations between neuropathology and cognition are still not entirely clear. In addition, the risk factors for AD dementia and the neuropathological hallmarks of AD may not necessarily be the same. Cognitive impairment has a clearer clinical significance and should therefore remain the main focus of prevention.

Amyloid-β peptide (Aβ) seems to have a central role in the neuropathology of Alzheimer's disease (AD). Familial forms of the disease have been linked to mutations in the amyloid precursor protein (APP) and the presenilin genes. Disease-linked mutations in these genes result in increased production of the 42-amino-acid form of the peptide ($A\beta_{42}$), which is the predominant form found in the amyloid plaques of Alzheimer's disease.

Keywords

Alzheimer's disease, biomarkers, clinical trials, dementia, prevention.

Introduction

Aβ has been the major target for disease-modifying therapeutic development in AD, driven in large part by studies of Down syndrome and studies of autosomal dominant AD and sporadic, late-onset AD, which implicate increased production, decreased clearance, and Aβ aggregation However, little is known about the proteoforms (*i.e.*, all protein variants of a single gene including post-translational modifications and sequence variants) of Aβ in human AD brain. Previous studies have demonstrated some sequence heterogeneity and post-translational modifications (PTMs) of the Aβ peptide in amyloid-beta plaques. Yet amyloid-beta plaques, one of the pathological hallmark of AD, correlate only moderately with dementia. As a result, focus has shifted in recent years to the most toxic forms of Aβ, soluble aggregates previously termed 'oligomers' and other appellations as they demonstrate a strong correlation with dementia.

The field of Alzheimer's disease (AD) research has advanced to where it is no longer necessary to justify the importance of prevention as the main therapeutic goal. After nearly two decades of research aimed at AD prevention, there is an abundance ofstudies in support of a number of proposed risk and protective factors.The present review was written in response to the evolving changes in the diagnosis and nomenclature of AD. The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) was published in May 2013, and the International Classification of Diseases, 11th revision (ICD-11) is expected in 2015. In addition, two new sets of criteria, formulated by an international workgroup and a National Institute of Aging-Alzheimer Association sponsored group, have been proposed and used in AD clinical research.

A large number of risk and protective factors for dementia and Alzheimer's disease have been investigated, and there are greater and lesser degrees of evidence to support these various factors.

APP, amyloid precursor protein; *APOE*, apolipoprotein E; BMI, body mass index; *CLU*, clusterin; *CR1*, complement component receptor 1; ELF-EMF, extremely low-frequency electromagnetic field; HRT, hormone-replacement therapy; NSAID, non-steroidal anti-inflammatory drug; *PICALM*, phosphatidylinositol binding clathrin assembly protein; PUFA, polyunsaturated fatty acid; SES socioeconomic status; *TOMM40*, translocase of outer mitochondrial membrane 40 homolog; *TREM2*, triggering receptor expressed on myeloid cells 2.

Generation and Clearance of Aβ

Amyloid precursor protein (APP) is a single-pass transmembrane protein which is expressed at high levels in the brain and metabolized in a rapid and highly complex fashion. The APP is cleaved by two pathways. In the nonamyloidogenic pathway, the full-length APP is cleaved by α- and γ-secretases. Cleavage via the β- and γ-secretases can be promiscuous and produces several species of Aβ fragments.

Synthetic and Naturally Secreted Aβ

Aβ assemblies are classified as synthetic and naturally secreted forms. Synthetic Aβ oligomers include 10, 40 or 42 peptides and mimic the most common forms of Aβ which are found in both AD and the normal human brain. It has recently been shown that synthetic Aβ dimers which mimic the natural ones can make some stable protofibrils that persist for a long time and impair synaptic plasticity.

Moreover, these synthetic forms of Aβ are chemically defined and can be readily synthesized and biophysically characterized. On the other hand, for the achievement of adequate memory disruption in animals these forms of Aβ must be used at higher doses.

Aβ and Neurofibrillary Tangles

Tau is a microtubule-associated neuronal protein. It is generated by neurons and is localized in the cell body and axons. Under normal conditions, nerve growth factor increases tau expression during neuronal development. However, in some pathological conditions it is also produced by glial cells.

Methods and Materials

Amyloid-beta (Aβ) Extraction and Separation of Soluble Aggregates from Insoluble Material

Complete methods are described in Esparza *et al*.. Briefly, 1–2 g of frozen CDR3 (severe AD) frontal cortical samples, including both gray and white matter, were weighed, stripped of pia mater, leptomeningeal, and intraparenchymal vessels to the fullest extent possible. and dounce homogenized at a 10:1 buffer volume:tissue weight ratio using a constant 25–40 manual strokes. Homogenization buffer consisted of ice-cold 1X phosphate buffered saline (PBS) (137 mM sodium chloride, 7.76 mM sodium phosphate dibasic, 2.17 mM monopotassium phosphate, 2.7 mM potassium chloride) with 0.45% (w/v) (3-((3-cholamidopropyl) dimethylammonio)−1-propanesulfonate) (CHAPS) and 1X protease inhibitor (2 ug/mL aprotinin and 1 ug/mL leupeptin).

Results

Purification of Soluble Aβ Aggregates

The layers atop the 70% sucrose cushion of the 475,000 × *g* spin were immunoprecipitated with 100 uL/mL of a 50% slurry of beads conjugated to the monoclonal antibodies HJ3.4 and HJ5.1 overnight (22 hrs) at 4 °C. HJ3.4 binds the N-terminus of canonical Aβ, and HJ5.1 binds a mid-domain epitope. Beads were washed 15 times in (1 mL each) 1X PBS and eluted with formic acid at room temperature for 15 min. Total protein and Aβ concentrations were determined by NanoOrange (Molecular Probes, Eugene, OR) and ELISA.

Purification of Insoluble Aβ Aggregates

The pellet of the 100,000 × *g* spin was resolubilized in 5 M guanidine hydrochloride (pH 8.0) overnight at 4 °C. The resulting guanidine solubilized 100 k pellet was centrifuged in a MicroCL 17 R centrifuge at 17,000 × *g* to remove any guanidine insoluble material. Next, the supernatant was diluted 1:10 (0.5 M guanidine, final concentration) in 1X PBS and immunoprecipitated with 100 uL/mL of a 50% slurry of immobilized monoclonal antibodies HJ3.4 and HJ5.1 overnight (22 hrs) at 4 °C. Beads were washed 15 times in 1X PBS (1 mL each) and eluted 3X with 100 uL formic acid at room temperature for 5 min each. Total protein and Aβ concentrations were determined by NanoOrange (Molecular Probes, Eugene, OR**)** and ELISA, respectively.

Conclusion

The most common neurodegenerative disorder and the most important cause of dementia in elderly people appears to be AD, and Aβ peptide has a substantial role in its pathogenesis. The appearance of Aβ occurs many years before the clinical signs and symptoms of the disease, so it could be a reliable biomarker for AD prediction. As indicated, Aβ plays an important role in the formation of both amyloid plaques and NFTs, which gradually leads to AD. Aβ deposition leads to synaptic degeneration and interacts with different types of central nervous system receptors; hence, it disrupts neuronal homeostasis. Moreover, Aβ deposition along the cerebral vessels alters their tonicity and triggers some of the cerebrovascular deficits. Furthermore, its accumulation disrupts intracellular Ca^{2+} homeostasis which ultimately reduces neuronal Ca^{2+} buffering capacity and increases excitotoxicity outcomes. Also, Aβ peptides may fold in different ways and show a prion-like pathology in the brain of AD patients.

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