Chapter 80
Aβ Monomer, Oligomer and Fibril in Alzheimer's Disease

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ABSTRACT

*Alzheimer's disease (AD), the most prevalent disease of aged people, is a progressive neurodegenerative disorder with dementia. Amyloid-β (also known as β-protein and referred to here as Aβ) is a well-established, seminal peptide in AD that is produced from the amyloid precursor protein (APP) by consecutive digestion with the β secretase of BACE (beta-site amyloid cleaving enzyme) and gamma secretase of the presenilin complex. Abnormal cerebral accumulation of Abeta in the form of insoluble fibrils in senile plaques and cerebral amyloid angiopathy (CAA) is a neuropathological hallmark of AD. In contrast to insoluble fibrillary Aβ, a soluble oligomeric complex, ADDL, consists of low-n oligomers of Aβ, such as Aβ*56. Despite their different names, it is currently proposed that oligomeric Aβ is directly involved in synaptic toxicity and cognitive dysfunction in the early stages of AD. This chapter identifies a novel APP mutation (E693delta; referred to as the Osaka mutation) in a pedigree with probable AD, resulting in a variant Aβ lacking glutamate at position 22. Based on theoretical predictions and in vitro studies on synthetic mutant Aβ peptides, the mutated Aβ peptide showed a unique and enhanced oligomerization activity without fibrillization. This was further confirmed by PiB-PET analysis on the proband patient. Collectively, the chapter concludes that the Osaka mutation is the first human evidence for the hypothesis that oligomeric Aβ is involved in AD.*

INTRODUCTION

Alzheimer's disease (AD) is a well-known, progressive neurodegenerative disorder with dementia. The neuropathological features of AD include senile plaques and neurofibrillary tangles in addition to cerebral atrophy from massive neuronal loss. Amyloid-β (also known as β-protein and referred to here as Aβ) is a well-established, seminal peptide in AD that is produced from the amyloid precursor protein (APP) by consecutive digestion with the β-secretase of BACE and gamma-secretase of the presenilin complex. Abnormal cerebral accumulation of Aβ in the form of insoluble fibrils

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in senile plaques and cerebral amyloid angiopathy (CAA) is widely believed to cause AD. In contrast to insoluble Aβ fibrils, a soluble, nonfibrillary oligomeric complex is currently claimed as a new pathological Aβ species. It has been termed ADDLs (Lambert et al, 1998), low-n oligomer Aβ, dimer (Walsh et al, 2002), Abeta*56 (Lesne et al, 2006) (here, Aβ oligomer collectively together). Despite these different names, it has recently been proposed that Aβ oligomer directly causes synaptic toxicity and cognitive dysfunction in the early stages of AD (Selkoe, 2002). To discuss Aβ oligomers in depth here, the relationship among ADDLs, Aβ oligomer, single oligomers of Aβ (mainly the dimeric form), and Aβ*56 should be explained. It is not easy to compare one Aβ oligomer with other morphologically characterized nonfibrillary Aβ species such as protofibrils (Walsh, Lomakin, Benedek, Condron, & Teplow, 1997), Globulomer (Gellermann et al, 2008), AβO (Kayed et al, 2003), Paranucleus (Bitan, Kirkitadze, Lomakin, Vollers, Benedek & Teplow, 2003), Annulus (Caughey & Lansbury, 2003), amyloidspheroid (Hoshi, 2003), β amyball (Westlind-Danielsson & Arnerup, 2001), (for review in detail, see [Roychaudhuri, Yang, Hoshi & Teplow, 2009]). With these views, new concepts focusing on nonfibrillary and soluble Aβ complex based on synaptic dysfunction are emerging regarding the cause of AD. Here, I review and discuss the Aβ oligomer, particularly based on our current knowledge of patients with early onset familial AD as the sole human evidence in support of the so-called "oligomer hypothesis" and its importance to advancing the research of AD etiology.

A FAMILIAL CASE WITH THE EARLY ONSET ALZHEIMER'S DISEASE

The Osaka Mutation of Amyloid Precursor Protein

The proband was a 62-year-old woman with a history of suspected familial AD. She noticed memory disturbance at the age of 56, and she had no history or symptoms of other neurological disorders. Her Hachinski's ischemic and Mini Mental State Examination (MMSE) scores were normal. MRI and PET scans showed no cortical atrophy or abnormal metabolism, while SPECT demonstrated bilateral mild hypoperfusion in the temporal lobes. An electroencephalogram showed bilateral, intermittent, generalized slow theta activity. Thus, she was diagnosed as having mild cognitive impairment at that time. At the age of 59, she showed ideomotor apraxia, and her MMSE score was 22/30 points. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IIIR) and the criteria of the National Institute of Neurological and Communicative Disorders and Stroke, AD and Related Disorders Association (NINCDS-ADRDA), she was diagnosed as having AD. At the age of 62, her MMSE score dropped to 5, and she exhibited cerebellar ataxia. The axial T1-weighted MRI images showed only mild parietal lobe atrophy. Genetic analysis was performed after an appropriate consultation, at which the caregiver gave informed consent to participate in this study. This study was approved by the institutional ethics committee of Osaka City University Graduate School of Medicine. Exons 16 and 17 of APP and all exons of presenilins-1 and -2 were amplified from the patient's genomic DNA by PCR. The DNA sequence of each product was analyzed using a BigDye Terminator v1.1 Cycle Sequencing Kit (Applied Biosystems, Tokyo, Japan) and an ABI PRISM 310 genetic analyzer (Applied Biosystems). Because this patient was found to have a mutation in exon 17 of the APP but not in the exons 1 or 2 of presenilin, only APP exon 17 was examined from other family members. Apolipoprotein E (ApoE) genotyping was performed by detection of the restriction site polymorphism, as described previously (Gellermann et al, 2008).

From the patient and her family members, we identified a novel mutation (hereafter referred to as the Osaka mutation) in APP exon 17. This muta-

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