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# Alzheimer's disease as oligomeropathy

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ABSTRACT

Alzheimer's disease (AD) is the most common age-related neurodegenerative disorder and is characterized by pathological aggregates of amyloid β-protein (Aβ) and tau protein. On the basis of genetic evidence, biochemical data, and animal models, Aβ has been suggested to be responsible for the pathogenesis of AD (the amyloid hypothesis). Aβ molecules tend to aggregate to form oligomers, protofibrils, and mature fibrils. Although mature fibrils in the final stage have been thought to be the cause of AD pathogenesis, recent studies using synthetic Aβ peptides, a cell culture model, Aβ precursor protein transgenic mice models, and human samples, such as cerebrospinal fluids and postmortem brains of AD patients, suggest that pre-fibrillar forms (oligomers of Aβ) are more deleterious than are extracellular fibril forms. Based on this recent evidence showing that oligomers have a central role in the pathogenesis of AD, the term "oligomeropathy" could be used to define AD and other protein-misfolding diseases.

In this review, I discuss recent developments in the "oligomer hypothesis" including our research findings regarding the pathogenesis of AD.



**Contents**



*Abbreviations used:* Aβ, amyloid β-protein; AD, Alzheimer's disease; ADDL, Aβ-derived diffusible ligands; AFM, atomic force microscopy; APP, Aβ precursor protein; APP OSK mice, APP transgenic mice expressing the Osaka E693Δ mutation; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; EM, electron microscopy; LMW, low molecular weight; low-n, low molecular weight order; LTD, long-term depression; LTP, long-term potentiation; mAb, monoclonal antibody; NFT, neurofibrillary tangles; PFs, protofibrils; PICUP, photo-induced cross-linking of unmodified proteins; RA, rosmarinic acid; RIF, rifampicin; SDS, sodium dodecyl sulfate; SEC, size exclusion chromatography.

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## 1. Introduction

Many neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease, or spinocerebellar ataxia, are characterized by the presence of abnormal protein aggregates in the brain. In the case of AD, amyloid plaques formed of amyloid β-protein (Aβ) and neurofibrillary tangles (NFT) formed of tau are the two neuropathological characteristics in postmortem human brain tissue of this neurological disorder (Lesne, 2014).

From genetic evidence, biochemical data, and animal models, Aβ has been suggested to be responsible for the pathogenesis of AD (Selkoe and Hardy, 2016; Walsh and Selkoe, 2007). Aβ is derived from the Aβ precursor protein (APP) by the action of two aspartyl proteases referred to as β- and γ-secretases (Haass et al., 1992; Selkoe and Hardy, 2016) (Fig. 1). Although two forms of Aβ comprising 40 and 42 amino acid residues are produced, the relative amount of $Aβ_{1-42}$ is particularly critical for AD progression because this longer form of Aβ is more prone to aggregate than is the shorter $Aβ_{1-40}$ peptide (Jarrett et al., 1993; Walsh and Selkoe, 2007). Aβ molecules tend to aggregate and form oligomers, protofibrils (PFs), and β-amyloid fibrils, which have been suggested to cause neuronal dysfunction in the brains of AD patients (Fig. 1A) (Ono et al., 2006; Yamin et al., 2008). These Aβ aggregates may cause neuronal injury directly by acting on synapses or indirectly by activating microglia and astrocytes (Selkoe and Hardy, 2016; Walsh and Selkoe, 2007); therefore, pharmacological interventions have been developed to target the sequential events originating from Aβ synthesis (Ono et al., 2006; Yamin et al., 2008).

Although these deposited final aggregates (mature fibrils) have long been thought to be the cause of AD, accumulating evidence over the last 15 years suggests that soluble multimers of these pathogenic proteins, referred to here as"oligomers," might initiate the synaptic and neuronal dysfunction associated with AD and the other protein-misfolding diseases described above (oligomer hypothesis) (Cheng et al., 2007; McLaurin et al., 2006; Ono et al., 2009; Ono and Yamada, 2011; Selkoe and Hardy, 2016; Shankar et al., 2008; Walsh et al., 2002; Walsh and Selkoe, 2007). Aβ oligomers are mainly classified as low molecular weight order (low-n) oligomers, such as dimers, trimers, or Aβ*56 (~dodecamer), and high molecular weight order (high-n) oligomers, such as PFs.

In addition, multiple lines of evidence suggest that an abnormal change in the biology and subcellular localization of another pathogenic protein, tau, might be responsible for neuronal dysfunction and cognitive decline as well as potentially being mediated by Aβ oligomers, such as dimers and trimers (Ittner et al., 2010; Tomiyama et al., 2010).

Because of the unstable nature of oligomers and lack of tools to specifically detect oligomers, it has been very difficult to detect stable oligomers in actual human samples, such as of brain tissue, blood, and cerebrospinal fluid (CSF). However, several groups have attempted to identify several specific oligomers of Aβ, such as dimers (Klyubin et al., 2008; Lesne et al., 2013; Shankar et al., 2008), trimers (Lesne et al., 2013), Aβ*56 (Lesne et al., 2013), and PFs (Kayed et al., 2009; Lasagna-Reeves et al., 2011b) in human samples by developing immunological and biochemical methods. The direct evidence from these studies showing that several species of Aβ oligomers are involved in the pathogenesis of AD may strengthen the oligomer hypothesis in its complexity.

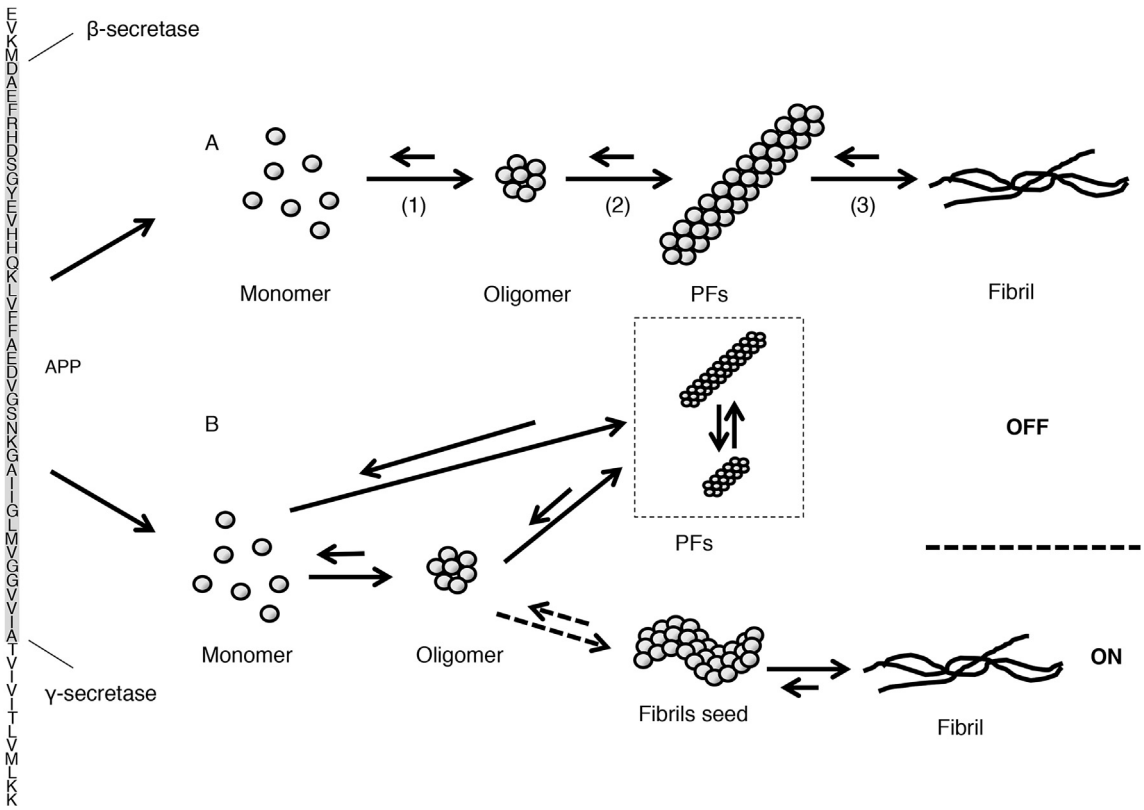


**Fig. 1. Models for the formation of Aβ fibrillogenesis.** Aβ is produced by the sequential cleavage of APP. β-secretase cleavage produces the Aβ N-terminus, after which γ-secretase releases the Aβ C-terminus from APP. **(A)** Classical model. Aβ fibril formation is a nucleation-dependent polymerization process in which monomeric Aβ forms oligomers (step 1) from which PFs emanate (step 2). These PFs give rise to full-length fibers (step 3). **(B)** New model. PFs are incapable of forming fibers directly. In addition, the addition of Aβ to PF ends does not lead to formation of mature fibers from PFs through simple end-to-end annealing. Instead, PFs may simply provide precursors for productive pathways of fibrillogenesis.

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