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The β-Amyloid Hypothesis in Alzheimer's Disease: Seeing Is Believing

Hank F. Kung*

Departments of Radiology and Pharmacology, University of Pennsylvania, 3700 Market Street, Room 305, Philadelphia, Pennsylvania 19104, United States

INTRODUCTION—ALZHEIMER'S DISEASE AND THE β-AMYLOID HYPOTHESIS

Alzheimer's disease (AD) is a form of dementia that gradually worsens over time. The disease is not a part of normal aging, and it is likely caused by various processes that damage neurons of the brain. Many clinical symptoms are associated with AD, including cognitive decline, irreversible memory loss, disorientation, language impairment, etc. Major neuropathology observations of postmortem AD brain include the presence of senile plaques—containing primarily β-amyloid (Aβ) peptide aggregates—and tangles comprising highly phosphorylated τ proteins.[1] The "Aβ hypothesis" proposes that development of AD is driven by the accumulation and deposition of Aβ peptide aggregates in the brain. The amyloid precursor peptide (APP) is degraded by several proteases, α-, β-, and γ-secretases (Figure 1A). A sustained imbalance between production and clearance of Aβ40−42 fragments by β- and γ-secretases leads to accumulation of Aβ peptide monomers, oligomers, and finally large aggregated Aβ plaques that "gum up" the parenchymal space between neurons in the brain (Figure 1B). Although there are many theories and hypotheses for the pathogenesis of AD, the Aβ hypothesis is considered the most important and pivotal, because it spearheads a cascade of pathological events detrimental to neurons in the brain.[1]

DIAGNOSIS OF AD AND CONFIRMATION OF Aβ PLAQUES

Currently, there is no definitive method to diagnose AD, except by postmortem biopsy sampling and staining of the brain tissue to confirm the existence of Aβ plaques. Novel positron emission tomography (PET) imaging agents specifically targeting the Aβ plaques may lead to "seeing" this key AD pathology, which may inform differential diagnosis of patients with dementia and enable monitoring of patients who are undergoing drug treatment designed to reverse the Aβ buildup in the brain. In the past decade, Aβ plaque-specific PET imaging has generated great anticipation and high hopes for "seeing the culprit" in living human brains (see the following discussion).

DEVELOPMENT OF DRUGS FOR AD

There are five medications approved by the U.S. Food and Drug Administration (FDA) to treat AD patients. Donepezil, rivastigmine, galantamine, tacrine, and memantine are used to treat moderate to severe AD patients. The approved AD drugs only treat the symptoms; they do not halt disease progression or cure AD. There are urgent needs for new AD drugs. On the basis of the Aβ hypothesis and the significant roles of Aβ peptides in the pathogenesis of AD, "anti-plaque" drug treatment has attracted a great of deal of attention. The fundamental principle of the hypothesis is that abnormal amyloid precursor protein processing and the formation of Aβ plaque is the central process in the development of AD (Figure 1). A major thrust in developing a "cure" for AD is to remove and

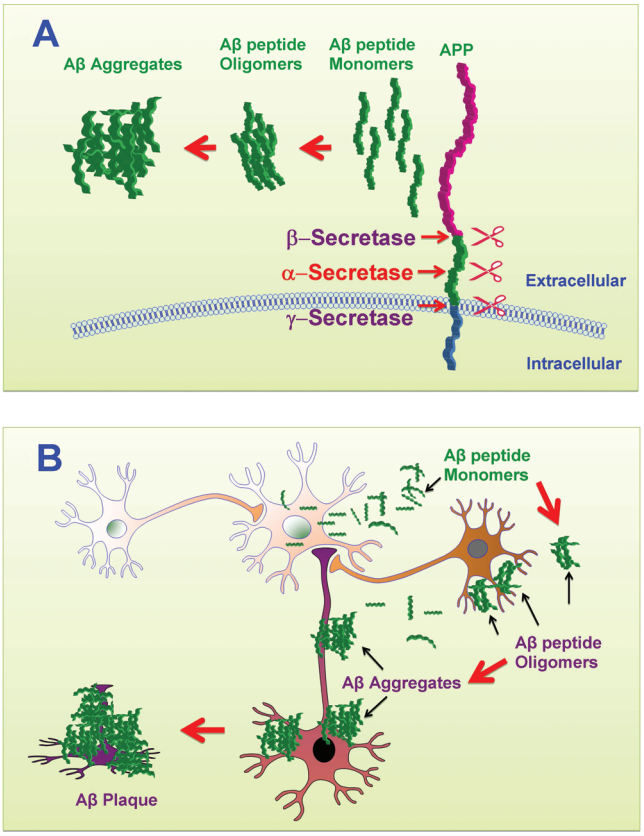

Figure 1. (A) Simplified model of the excessive Aβ peptide production leading to the formation of Aβ plaques. Normally, amyloid precursor protein (APP) of neurons is metabolized by three proteases (α-, β-, and γ-secretases). Increasing production or decreasing clearance of Aβ peptides leads to the formation of Aβ aggregates in the brain. The fibrillar aggregates of amyloid peptides, mainly Aβ40 and Aβ42 (in green), are major metabolic peptides found in the Aβ plaques, and they are believed to be responsible for initiating a cascade of events leading to neurotoxicity and AD.[1] (B) Aβ hypothesis suggests that Aβ peptides participate in AD pathogenesis. The peptides, produced by neurons and other brain cells, stick together like glue and aggregate (formation of β-sheet structures) into a variety of toxic assemblies, neurofibrillary tangles, and neuritic plaques.[1]

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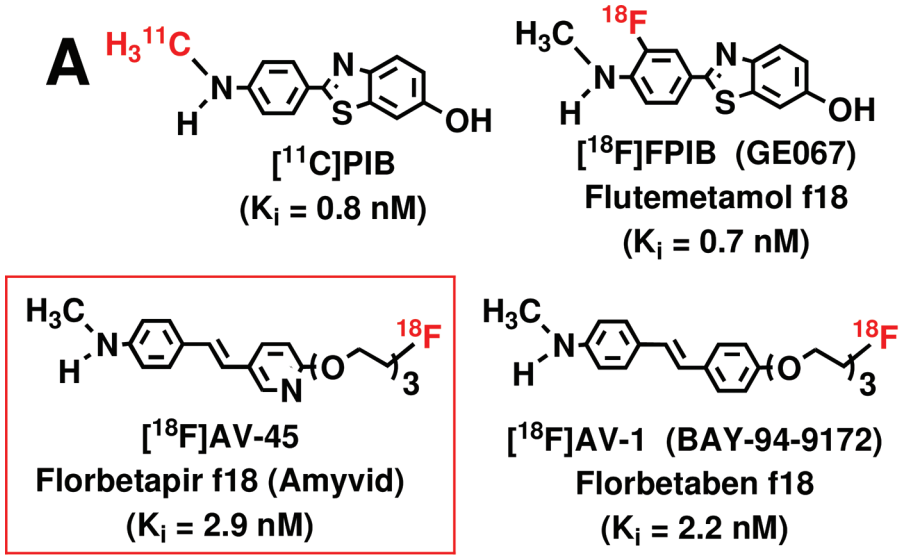

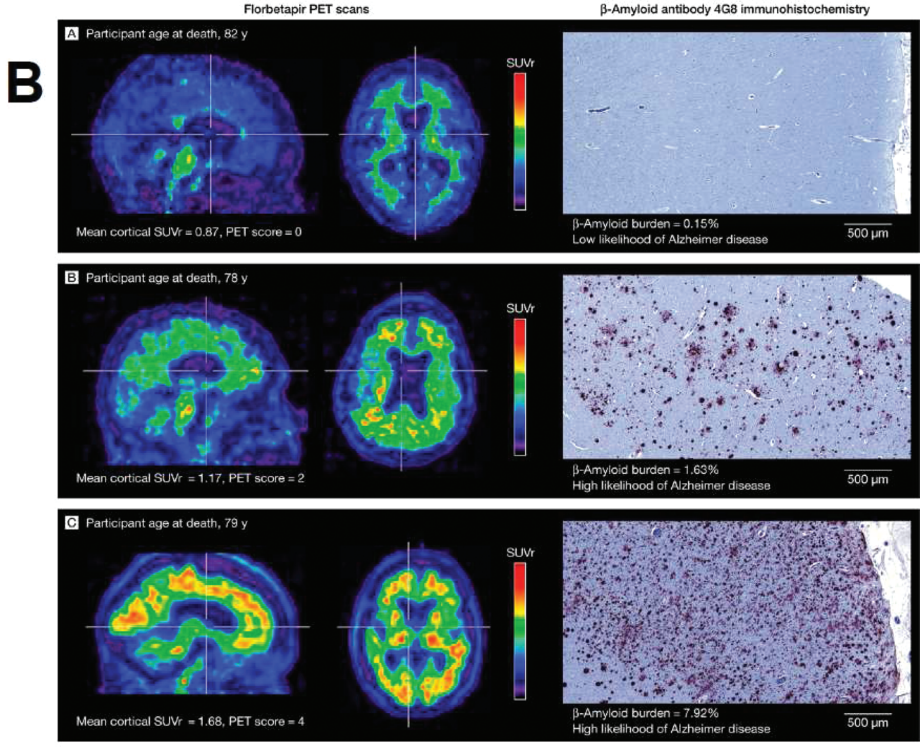

Figure 2. (A) Four Aβ imaging agents have been studied in humans. The success in using [^{11}C]PIB for imaging Aβ plaques in the brain has provided considerable impetus for further refinement of this PET imaging technique. [^{11}C]PIB ($T_{1/2}$ = 20 min) has limitations (requires an on-site cyclotron and a radiochemistry team). Additional tracers labeled with ^{18}F ($T_{1/2}$ = 110 min) for Aβ imaging were developed. Using ^{18}F PET agents, the manufacturing and distribution can be centralized, which will significantly simplify the clinical application.[4] Currently, the final FDA approval of florbetapir f18 (Amyvid) is pending; flutemetamol f18 and florbetaben f18 are under phase II clinical trials. (B) Paired representative florbetapir f18-PET scans in living human brain and Aβ antibody immunohistochemistry staining of comparable postmortem brain sections. PET scans and antibody staining of representative brain sections are shown: (A) Normal control (no Aβ plaques), (B) moderate level of Aβ plaques, and (C) high level of Aβ plaques.[3] Reproduced with permission from ref 3. Copyright 2011 American Medical Association.

prevent excess build up of Aβ peptides in the brain, including inhibition of β- and γ-secretases, Aβ peptide removal by an active or passive immunotherapy, etc. However, despite much effort and financial resources devoted to the development "anti-plaque" therapeutics, results of clinical trials in this area have been disappointing.

Aβ PLAQUE-SPECIFIC IMAGING FOR DIAGNOSIS AND DRUG DEVELOPMENT

There are four PET imaging agents that have been well-studied in humans: [^{11}C]PIB,[2] florbetapir f18 (Amyvid),[3,4] florbetaben f18,[5] and flutemetamol f18[6] (Figure 2A). Results of a phase 3

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clinical study of the leading candidate, florbetapir f18, have demonstrated a close correlation of in vivo amyloid PET imaging with florbetapir f18 with postmortem histopathological findings (Figure 2B).[3] It is now pending FDA approval for routine clinical uses. The development of diagnostic imaging agents targeting Aβ aggregates may lead to improved selection and monitoring of patients undergoing drug treatment designed to reverse the Aβ plaque buildup in the brain.

IMAGING PLAQUES IN THE BRAIN

Clinically, Aβ imaging will be important for the differential diagnosis of dementia. A negative scan will indicate that dementia is not related to AD. A positive scan will imply that there is a risk factor for AD. It is also important to detect preclinical AD and predict the progression from mild cognitive impairment (MCI) to AD; establishing a direct correlation between the Aβ imaging and the neurotoxicity in the progress of Aβ formation and deposition. Early monitoring of patients with genetic or family risk factors will also be highly desirable. One of the significant considerations is for ApoE4-positive subjects. It has been demonstrated that ApoE4 carriers will show early development of a positive scan and progression of plaque build-up. Aβ plaque-positive patients even without memory deficit are likely at risk for AD. Recent news from the 2012 Human Amyloid Imaging Conference suggests that "...the overall trend of those (PET imaging) studies appears to be that brain amyloid deposition is bad news, though it can take years until a given person suffers cognitive consequences, and the initial cognitive decrements are subtle." (by Gabrielle Strobel of Alzforum; http://www.alzforum.org/new/detail.asp?id=3074).

SUMMARY

Human amyloid imaging is now on the verge of being approved by the FDA for routine clinical use. Although this procedure may prove to be tremendously valuable once it is incorporated into the routine clinical workup of dementia patients, currently, this imaging procedure is not without its critics. The debate on the utility of human amyloid imaging may be just a part of the validation process for this new technology. Ten years ago, AD and "aging" researchers overwhelmingly celebrated the first [^{11}C]PIB human amyloid imaging that demonstrated the feasibility to "see" the Aβ plaques in the living human brain and the corroboration of the Aβ hypothesis. Now, the F-18 Aβ-specific agents will take this imaging tool to the next level, benefiting a large number of patients. This is an exciting time for clinicians and scientists who may further examine or clarify the Aβ hypothesis and correlate its relationship to AD by "peeking" into the living human brain from various angels. The amyloid-specific imaging will also provide a renewed scientific vigor in selecting and monitoring patients enrolled in clinical trials for AD drugs specifically targeting Aβ deposition in the brain.

AUTHOR INFORMATION

Corresponding Author

*Tel: 215-662-3096. Fax: 215-349-5035. E-mail: kunghf@sunmac.spect.upenn.edu.

Notes

The authors declare the following competing financial interest(s): University of Pennsylvania owns the intellectual properties for florbetapir f18a.

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