Functional significance of amyloid dynamics and deposition in the AD brain

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USA

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Functional significance of amyloid dynamics and deposition in the AD brain

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Alzheimer's disease & other dementias

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Research Abstract

DESCRIPTION (provided by applicant): Alzheimer's disease is typified by the accumulation and deposition of amyloid-beta (Abeta) peptides within the brain and these processes are central to disease pathogenesis. A critical unresolved issue is how the Abeta peptides interact to form multimers, distribute into various pools and are deposited into both diffuse and compact plaques. Most importantly, it remains controversial how the diverse Abeta species act to perturb brain function. There is general agreement that soluble multimeric species subserve perturbation of synaptic function that underlies the impairment of cognition and memory. Perhaps the longest lived controversy revolves around the functional significance of amyloid plaques and whether these structures really matter. This application proposes to deploy newly discovered tools and biological assays to explore these questions. Alzheimer's disease is associated with impaired clearance of Abeta from the brain, a process normally facilitated by apolipoprotein E (ApoE). ApoE expression is transcriptionally induced through the action of the nuclear receptors peroxisome proliferator activated receptor (PPARbeta) and liver X receptors (LXR) through their interaction with retinoid X receptors (RXR). Oral administration of the RXR agonist, bexarotene, to a murine model of Alzheimer's disease resulted in enhanced clearance of soluble Abeta within hours in an apoE-dependent manner. Abeta plaque area was reduced >60% within just 72 hours through microglial-mediated phagocytosis. Furthermore, bexarotene stimulated the rapid reversal of cognitive, social, and olfactory deficits and improved neural circuit function. The discovery of the ability of RXR agonists to promote the clearance of soluble and deposited forms of Abeta through distinct mechanisms allows an unprecedented opportunity to determine how these pools are related to one another as a function of age and disease progression. Importantly, these studies are of therapeutic significance as they will inform the design of the initial clinical trials of bexarotene in AD and its prodromal states. The aims of this application are: Aim 1. To establish the dynamics of Abeta pools in the brain and their functional significance. We will explore the relationships between interstitial fluid, 'solube' Abeta levels and plaque burden in an experimental setting where either soluble Abeta or plaque clearance is stimulated and determine how these are related to deficits in neural network activity and behavior. Aim 2. To determine if age and plaque burden affect the kinetics of amyloid plaque dissolution and reformation. We will determine if age and overall plaque burden affects the susceptibility of amyloid plaques to microglial- mediated clearance. We will also determine the rate of plaque reformation following their clearance in mice of different ages and initial plaque burden. Aim 3. Determination of whether reduction in Abeta levels will prevent or delay amyloid deposition and behavioral impairment. We will test if long term enhancement of Abeta clearance will prevent the appearance of behavioral deficits and amyloid deposition. Aim 4. To ascertain if RXR activation provokes the conversion of microglia into M2 ""alternative"" activation states and restores their phagocytic competence. We propose to test the effects of bexarotene on the phenotypic polarization and phagocytic activity of microglia in vitro. These studies will be extended to the analysis APP/PS1 mice treated with bexarotene.

Lay Summary

PUBLIC HEALTH RELEVANCE: Alzheimer's disease (AD) is typified by the accumulation of b-amyloid within the brain, leading to loss of memory and cognition. We have discovered that a drug targeting the nuclear receptor, Retinoid X Receptors, very rapidly clears both soluble forms of Abeta and Abeta-containing plaques from the brain of murine models of AD. We propose to use this drug to determine which forms of Abeta are responsible for the impaired brain function in AD.

Further information available at:

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