Molecular Neuropathology and Mechanisms of BACE1 Elevation in Alzheimers Disease

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Molecular Neuropathology and Mechanisms of BACE1 Elevation in Alzheimers Disease

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Alzheimer's disease & other dementias

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Research Abstract

? DESCRIPTION (provided by applicant): BACE1 is the ß-secretase enzyme that initiates Aß production and is a prime therapeutic target for AD. Drugs that inhibit BACE1 enzyme activity are in clinical trials for AD, however the safety and efficacy of these agents are unknown. Recent studies suggest that BACE1 inhibition may cause multiple neurological side effects. Thus, it is crucial to develop alternative therapeutic strategies that reduce BACE1 cleavage of APP without impairing essential BACE1 functions. We have shown that global BACE1 protein levels are markedly elevated in APP transgenic mouse and AD brains. Elevated BACE1 is concentrated within dystrophic axons and terminals surrounding amyloid plaques and is associated with increased generation of BACE1- cleaved APP fragments and Aß42. We also find that Aß42 causes increased resting [Ca2+]i and microtubule disruption in neurons. We hypothesize a feed-forward mechanism in which plaque-associated Aß causes axonal dystrophy, BACE1 accumulation, and accelerated Aß generation that drives AD progression. Elucidating the molecular and cellular mechanisms of dystrophic BACE1 elevation could lead to novel AD therapeutic strategies to normalize BACE1 levels and reduce peri-plaque Aß production, yet preserve BACE1 activity for essential functions and side effect mitigation. We hypothesize that Aß-induced Ca2+ influx into peri-plaque axons causes microtubule disruption, impaired axon transport, BACE1 accumulation, axonal dystrophy, and accelerated Aß generation and amyloid load. Our preliminary data show that Aß elevates resting [Ca2+]i in primary neurons via Ca2+-selective channels. Moreover, axons of Aß-treated primary neurons exhibit disrupted microtubules and impaired BACE1 axon transport. Peri-plaque dystrophic axons in 5XFAD mice also show elevated resting [Ca2+]i and disrupted microtubules. Using Ca2+ channel inhibitors or shRNA-AAVs, we will identify the channel(s) that mediates Aß-induced Ca2+ influx in neurons in vitro and in vivo (Aim 1). Additionally, using Ca2+ channel inhibitors or shRNA-AAVs, we will decrease Aß-induced elevated resting [Ca2+]i, block microtubule and motor protein disruption, improve axon transport, and reduce BACE1 elevation (Aim 2). We will also rescue BACE1 elevation and axon transport by exposing Aß-treated primary neurons and 5XFAD mice to the microtubule stabilizing agent Epothilone D and determine whether Aß-induced BACE1 elevation is tau-independent (Aim 2). Finally, we will determine whether BACE1 elevation accelerates Aß generation and amyloid progression by performing 1) 35S-metabolic labeling of Aß-treated primary neurons to measure de novo Aß production, 2) in vivo Aß microdialysis to analyze Aß production in peri-plaque regions, 3) multicolor Aß time-stamp labeling to analyze the rate of individual plaque growth and dystrophic neurite formation in 5XFAD mice (Aim 3). These experiments will provide proof of concept for therapeutic strategies to reduce peri-plaque BACE1 elevation as a safer alternative to direct inhibition of BACE1 enzyme activity.

Lay Summary

PUBLIC HEALTH RELEVANCE: BACE1 inhibitors are currently in clinical trials for Alzheimer’s disease (AD), an intractable neurodegenerative disorder with no disease-modifying therapy, but the safety and efficacy of these agents are unknown. We have discovered that BACE1 levels are increased around amyloid plaques in AD brain, which could accelerate the progression of the disease. This application will determine the mechanism of the BACE1 increase and whether reducing it will slow the progression of the disease, thus providing proof of concept for AD therapeutic strategies to block the BACE1 increase in AD.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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