Modeling an Anti-Amyloid Combination Therapy for Alzheimer’s Disease

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Abstract

As only symptomatic treatments are now available for Alzheimer’s disease (AD), safe and effective mechanism-based therapies remain a great unmet need for patients with this neurodegenerative disease. Although 

$\beta$-secretase and BACE1 [b-site $\beta$-amyloid (A$\beta$) precursor protein (APP) cleaving enzyme 1] are well-recognized therapeutic targets for AD, untoward side effects associated with strong inhibition or reductions in amounts of these aspartyl proteases have raised concerns regarding their therapeutic potential. Although moderate decreases of either $\beta$-secretase or BACE1 are not associated with mechanism-based toxicities, they provide only modest benefits in reducing A$\beta$ in the brains of APPswe/PS1DE9 mice. Because the processing of APP to generate A$\beta$ requires both $\beta$-secretase and BACE1, it is possible that moderate reductions of both enzymes would provide additive and significant protection against A$\beta$ amyloidosis. Here, we test this hypothesis and assess the value of this novel anti-amyloid combination therapy in mutant mice. We demonstrate that genetic reductions of both BACE1 and $\beta$-secretase additively attenuate the amyloid burden and ameliorate cognitive deficits occurring in aged APPswe/PS1DE9 animals. No evidence of mechanism-based toxicities was associated with such decreases in amounts of both enzymes. Thus, we propose that targeting both $\beta$-secretase and BACE1 may be an effective and safe treatment strategy for AD.

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