

Synthesis and Evaluation of Helical Peptide Probes for Signal Peptide Peptidase, a Homolog of Alzheimer's Disease-Related Presenilin; Evidence for a Substrate Docking Site

Abstract

Alzheimer's disease (AD) is a neurodegenerative disease characterized partly by cerebral plaques. Interneuronal cerebral plaques result mainly from the aggregation of hydrophobic, amyloid B (AB) peptides, which are ultimately formed from the cleavage of an integral membrane protein stub by an intramembrane protease called γ -secretase. Due to the significant role of γ -secretase in generating pathogenic peptides that collect in plaques and ultimately lead to AD, much research has focused on this enzyme. While it is known that presenilin functions as the catalytic component of the multiprotein γ -secretase complex and that presenilin contains a substrate docking site distinct from its active site, the exact structure of γ -secretase and the mechanism of γ -secretase-mediated generation of AB remain unknown. To better understand the initial interaction between γ -secretase substrates and the docking site of presenilin, we studied a presenilin homolog named signal peptide peptidase (SPP), which possesses many similarities to presenilin, yet is more convenient to study. Helical peptide inhibitors of SPP were synthesized manually via solid-phase peptide synthesis for use as photoactivatable molecular probes of SPP. Our results from competitive photolabeling experiments with these SPP inhibitors confirm the existence of a docking site on SPP separate from its active site and support the use of SPP as a valid model to study γ -secretase. Hopefully our results may lead to elucidation of, by analogy, the location on presenilin to which APP binds and have significant therapeutic implications for the treatment of AD.