PHARMACOLOGY AND MECHANISM OF ACTION OF A NOVEL GAMMA-SECRETASE MODULATOR


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Introduction and aims: Amyloid-beta (Aβ) accumulation is a major hallmark of Alzheimer's disease. Formation of Aβ is catalyzed by beta- and gamma-secretases. Gamma-secretase is also responsible for the cleavage of Notch among other substrates. Gamma-secretase inhibitors (GSI) reduce Aβ, but produce undesirable adverse events by interfering with Notch processing. A novel gamma-secretase modulator (GSM), E2012, has been designed to reduce Aβ levels without affecting Notch cleavage.

Methods: The effect of E2012 on production of Aβ isoforms was assessed in vitro and in rat CSF, brain, and plasma, using ELISA. Notch intracellular domain (NICD) production after E2012 treatment was assayed in vitro. Photo-affinity labeled compound, L-852,505, was used to compare the binding of GSIs and E2012 to gamma-secretase complex.

Results: E2012 reduced the production of Aβ40 and Aβ42 and increased Aβ38 in vitro without affecting total Aβ levels. Aβ40 and Aβ42 levels in rat CSF, brain and plasma were decreased by E2012 in a dose-dependent manner. E2012 did not induce APP-CTF accumulation, suggesting that E2012 modulates, but does not inhibit, the cleavage of APP by gamma-secretase. Production of NICD was not inhibited by E2012. Chemical photoprobe of a classical GSI, L-852,505, labeled both PS1-NTF and -CTF. E2012 did not affect the labeling by L-852,505, suggesting that the binding site of E2012 is different from that of GSIs.

Conclusions: GSMs, such as E2012, can achieve substantial reductions in toxic Aβ species without the deleterious effects of Notch inhibition. This unique mechanism of action imports further development for the treatment of Alzheimer's disease.