IN VITRO CHARACTERIZATION OF NOVEL AΒ42-LOWERING Γ-SECRETASE MODULATORS

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Introduction: Generation of the neurotoxic 42-amino acid variant of the amyloid β-peptide (Aβ) by β- and γ-secretase cleavage of the β-amyloid precursor protein (APP) is believed to cause Alzheimer disease (AD). Lowering of Aβ42 generation is a hopeful approach towards AD treatment. In this regard, γ-secretase modulators (GSMs), which reduce the generation of Aβ42 and concomitantly increase the levels of short Aβ species, are preferred over γ-secretase inhibitors, because they do not inhibit the processing of other γ-secretase substrates such as Notch1, which has a crucial signaling function. A subset of non-steroidal anti-inflammatory drugs (NSAIDs) were the first described γ-secretase modulators, but these compounds show low activity on γ-secretase, poor brain permeability and side effects related to inhibition of cyclooxygenases.

Aims: We characterized novel non-NSAID type GSMs to understand their mode of action, to identify their molecular target, and to get further insight into the catalytic mechanism of γ-secretase.

Methods: Cell-free assays using purified γ-secretase were employed to investigate the activity and potency of these GSMs.

Results and conclusions: The investigated compounds show IC50 values for Aβ42 in the nano to low micromolar range on purified γ-secretase. Further biochemical analyses show that these compounds are active on all six human γ-secretase complexes. The analysis of their activity on familial AD mutations in presenilin and APP is ongoing and the progress of these studies will be presented. We conclude that these novel GSMs are potent second generation Aβ42-lowering compounds with the potential of future therapeutics for the treatment of AD.