THE SULFONAMIDE INHIBITOR MRK-560 DISPLAYS A PREFERENCE FOR PS1 MEDIATED PROCESSING OF BOTH APP AND NOTCH IN VITRO

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Introduction: g-secretase is a well established target for treating Alzheimer's Disease, because of its role in amyloid precursor protein (APP) processing and Abeta peptides generation. g-Secretase also catalyzes processing of other substrates, including Notch, which plays a pivotal role in cell fate determination processes. This variety of substrates complicates the development of g-secretase inhibitors for AD as exemplified by the benzodiazepine LY-411575, which causes mechanism based toxicity in animal models, probably due to impaired Notch signaling. However, other g-secretase inhibitors exist, such as the sulfonamide MRK-560 which exhibits an impressive therapeutic window in the mouse albeit it was shown to be equipotent in inhibiting APP and Notch processing in HEK293 cells.

Aim: Explore and compare the mode of action of in-vivo tolerable and intolerable g-secretase inhibitors.

Methods: Radioligand binding and g-secretase activity assays.

Results and conclusions: Herein we report that MRK-560 has a much higher potency in inhibiting Presenilin 1 (PS1) - vs PS2-expressing g-secretases regarding both APP and Notch processing. Furthermore, by competition binding experiments, we show that MRK-560 is 44-fold more potent in competing binding of [3H]-LY-411575 in PS1- vs PS2-overexpressing membranes, providing a molecular mechanism for the differential inhibitory effect on cellular PS1 and PS2 expressing g-secretases, respectively. Interestingly, MRK-560 only partially displaces the binding of [3H]-LY-411575 in both tissue sections and membrane preparations, suggesting that the interaction of MRK-560 and LY-411575 with g-secretase differs. Combined these data suggests the importance of exploring g-secretase subcomplex specific signaling in vivo for the development of tolerable g-secretase inhibitors.