Jochen Herms
Director of the Institute of Neuropathology
Ludwig-Maximilians-University Munich
Germany

BACE1 Inhibition in AD Therapy and its Potential Side Effects

As the key protease of Aβ production, Beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) is a promising drug target for the treatment of Alzheimer's disease (AD). However, we have recently shown that prolonged inhibition of BACE1 interfers with structural and functional synaptic plasticity (Filser et al. Biol. Psych 2015), most likely due to the diminished processing of physiological BACE1 substrates. Seizure protein 6 (Sez6) is exclusively processed by BACE1 and it is required for normal dendritic arborization and spine maintenance. Interestingly, the side effect of BACE1 inhibitor was not observed in chronically treated Sez6 knockout mice, suggesting that Sez6 is critically involved in these BACE1 inhibitor-mediated synaptic alterations. Encouragingly, we also observed that BACE1 inhibitor treatment in a transgenic AD mouse model (APPPS1) reduced amyloid plaque formation as well as growth, and ameliorated the plaque associated synaptic and axonal pathology. In conclusion, our results suggest that an adequate inhibitor dosage for the treatment of AD might be identified to balances both clinical safety and efficacy.