ANTI-ADDL ANTIBODIES ACT IN THE BRAIN TO SEQUESTER ADDLS AND ATTENUATE THEIR DEPOSITION INTO GROWING PLAQUES IN A MOUSE MODEL OF ALZHEIMER´S DISEASE

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Accumulating evidence suggests that neuronal binding of diffusible oligomers of Aβ (ADDLs) leads to neuronal disfunction and the dementia associated with Alzheimer´s disease (AD). One therapeutic approach for the treatment of AD is development of anti-ADDL antibodies. To this end, a panel of anti-ADDL antibodies was characterized using cell-based endpoints. The results of this screen revealed several antibodies of interest, antibodies that preferentially bind ADDLs and abate ADDL-induced neuronal dysfunction. An in vivo study in 12-month-old hAPP over-expressing mice revealed that ¹²⁵I-labeled anti-ADDL or m266 antibody penetrated the blood-brain-barrier and enters the CSF and brain. Interestingly, while the anti-ADDL antibody bound oligomers around the periphery of growing plaques, no m266 immunoreactivity was detected. To investigate the ability of antibodies to abate ADDL levels in brain, biotin-labeled ADDLs were infused into the hippocampus of transgenic mice to label existing plaques. The animals were then treated weekly, for 4 weeks with an anti-ADDL antibody, m266 or vehicle (8mpk; IV injection) and the deposition of endogenous ADDLs into labeled plaque assessed with immunocytochemistry. Evaluation of growing plaques with confocal microscopy revealed that treatment with an anti-ADDL antibody significantly reduced the deposition of new thioflavin S-positive material into plaques, when compared with m266 and vehicle treated mice. The results suggest that anti-ADDL antibodies can cross the blood-brain-barrier, sequester ADDLs and block their deposition into growing plaques. The treatment of patients with an anti-ADDL antibody might facilitate the removal of ADDLs from the brain; and thereby alleviates some of the pathological outcomes associated with AD.