INHIBITORS OF BACE1 REDUCE BETA AMYLOID PRODUCTION IN GUINEA PIGS: DOSE-DEPENDENT EFFECTS IN CEREBROSPINAL FLUID AND BRAIN

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Introduction: Inhibiting beta amyloid (Aβ) production by targeting the beta-site amyloid precursor protein (APP)-cleaving enzyme 1 (BACE1) that cleaves APP to generate Aβ is an approach for disease modification in Alzheimer's disease (AD). Small molecule BACE1 inhibitors are expected to decrease Aβ-peptide generation and thereby reduce amyloid plaque formation in the brain, a hallmark neuropathological lesion in AD.

Aims: In the present study, the effects of potent small molecule BACE1 inhibitors on amyloid levels in plasma, cerebrospinal fluid (CSF) and brain were evaluated in guinea pig. Understanding the relationship between Aβ40 levels in brain and CSF of guinea pigs treated with BACE1 inhibitors will aid dose setting in man where Aβ levels can be analyzed in CSF.

Methods: Male Dunkin Hartley guinea pigs received vehicle or a small molecule AZ BACE1 inhibitor as a single dose via oral gavage. Plasma and CSF samples were collected and brain dissected at different time points after dose to measure Aβ40 levels and drug exposure.

Results: The AZ BACE1 inhibitor caused a dose-dependent reduction of Aβ40 in plasma, CSF and brain. The reduction of Aβ40 was time-dependent, tending towards a small delay in CSF versus brain.

Conclusions: These results demonstrate that an oral small molecule AZ BACE1 inhibitor reduces the levels of Aβ in brain, CSF and plasma, thereby supporting BACE1 inhibition as a feasible approach for disease modification in AD.