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NOVEL UPSTREAM MARKERS OF AMYLOID PRECURSOR PROTEIN PROCESSING IN THE DIAGNOSIS AND PROGNOSIS OF ALZHEIMER'S DISEASE

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Objective: To assess cerebrospinal fluid (CSF) β-site amyloid precursor protein (APP)-cleaving enzyme 1 (BACE1) activity in relation to Alzheimer's disease (AD) and to correlate the enzyme activity with protein markers of APP metabolism and axonal degeneration.
Methods: BACE1 activity and protein concentrations were measured and analysed in 342 participants of the AD Neuroimaging Initiative, including 99 normal controls, 75 stable mild cognitive impairment (MCI), 87 progressive MCI and 79 AD dementia cases. All statistical analyses were Bonferroni corrected for multiple comparisons.
Results: No significant differences between controls and any of the three patient groups were detected for BACE1 activity and soluble APP (sAPP)β concentrations in CSF. Significant correlations with BACE1 activity were found for CSF APPβ and total tau in all four groups; and for CSF phosphorylated tau_{181} in all groups but the progressive MCI group. There were no correlations for CSF amyloid β $(Aβ)_{1-42}$ nor for plasma $Aβ_{1-42}$ and $Aβ_{1-40}$.
Conclusions: The consistent correlation between BACE1 activity and sAPPβ supports their role as biomarkers of target engagement in clinical trials on BACE1 inhibition.

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