

**P014** Analysis of  $\beta$ -secretase kinetics and the protein levels of BACE1 and BACE2 in human control and Alzheimer's disease brain.

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$\beta$ -secretase (also known as BACE1) is the rate limiting step in the proteolytic production of  $A\beta$  from the amyloid precursor protein (APP). BACE2 is a homolog of BACE1 and competes with BACE1 for cleavage of APP in a manner that precludes  $A\beta$  formation. This is the first study of  $\beta$ -secretase kinetics with respect to BACE1 and BACE2 protein levels in control ( $n = 7$ ) and AD ( $n = 9$ ) temporal cortex brains, which have been staged for the severity of the disease as measured by neurofibrillary tangle (NFT) pathology (I – VI). Using a substrate based on the  $\beta$ -secretase cleavage site of APP we detected significantly increased  $V_{max}$  of  $\beta$ -secretase in AD cases ( $5.8 \pm 0.66$  nM/min) compared to controls ( $3.5 \pm 0.41$  nM/min), and no significant changes in the  $K_m$  of  $\beta$ -secretase. However, we detected BACE1 protein levels to be significantly decreased (34%,  $p < 0.05$ ) in AD cases. There was no direct relationship between  $\beta$ -secretase kinetics and BACE1 levels, but the decreased BACE1 levels correlated significantly with disease staging and synaptic loss. Examination of BACE2 protein levels also decreased significantly (32%,  $p < 0.05$ ) in AD cases compared to controls and in a manner correlating with the disease progression and synaptic loss. We also did not detect significant changes in the levels of APP between cases. These results show that increased  $V_{max}$  for  $\beta$ -secretase is a feature of AD pathogenesis and that this increase does not directly correlate with reduced levels of BACE1 and BACE2 proteins.