THE CELLULAR NUCLEIC ACID BINDING PROTEIN REGULATES BACE1 IN VIVO

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Introduction: The ZNF9 gene on chromosome 3 encodes the Cellular Nucleic Acid Binding Protein (CNBP), a primarily cytoplasmic zinc finger protein that interacts with single-stranded nucleic acids. CNBP is a ubiquitously expressed protein that is highly conserved among vertebrates. We have recently discovered a role for CNBP in regulation of β-secretase (BACE), the rate-limiting enzyme in the formation of Aβ peptide, which is thought to play a causal role in Alzheimer's disease pathogenesis.

Aims: Using Adeno-associated virus (AAV) to overexpress CNBP, we tested the hypothesis that CNBP regulates BACE and this interaction has consequences for Aβ-related pathology.

Methods: AAV2 was used to overexpress CNBP in cell culture and in genetically modified (APP/PS1 or APP overexpressing) mice. Both tissue and cultured cells were evaluated by ELISA (Aβ), western blot (CNBP and BACE1), and RT-PCR (CNBP and BACE1).

Results: CNBP AAV2 treatment resulted in 3 fold overexpression of CNBP in vivo after 1 month, leading to an increase in BACE1 protein (p< 0.01) and subsequent increase in Aβ (p< 0.01). In culture, increased BACE1 was detectable after 24 hours. The steady state amount of BACE1 mRNA did not change in vivo or in vitro after CNBP AAV2 treatment, although in culture the half-life of the message was shorter, indicating that CNBP may have broad roles in BACE1 regulation.

Conclusions: These data support the hypothesis that CNBP regulates BACE1, and that this effect is largely post-transcriptional or translational. Future studies will elucidate the effect of CNBP knockdown on BACE1 and Aβ related pathology.