TRANSLATIONAL REGULATION OF ß-AMYLOID (Aß) PRECURSOR PROTEIN (APP): A NEW DRUG DISCOVERY APPROACH FOR ALZHEIMER DISEASE (AD)

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Our studies are focused on discovering small molecules that regulate gene expression post-transcriptionally. We previously showed that the acetylcholinesterase inhibitor (AChEI), phenserine (PHEN), significantly inhibits translation of APP without changing mRNA levels in neuronal cells. Herein, PHEN reduced extra- and intracellular APP levels, resulting in reduced Aß secretion. The PHEN chiral isomer that lacks AChEI action significantly reduced the levels of newly synthesized APP (pulse labeling), confirming that translation of APP mRNA is specifically inhibited, independent of AChEI action. To discover more potent molecules that translationally regulate APP, we screened similar small molecules and measured APP secretion in cultured media by sandwich. Several of these molecules significantly reduced extracellular APP levels. Many of these molecules also reduced steady state intracellular APP levels, although a few compounds caused a decrease in secreted APP without reducing intracellular APP. Consistent with a specific translational inhibitor, several compounds that decreased steady state APP levels significantly decreased levels of newly synthesized APP without changing either total protein synthesis or APP mRNA levels. Thus, we have identified small molecules that selectively regulate APP mRNA translation, providing a novel and specific mechanism to lower Aß, a widely accepted therapeutic goal in AD. *Supported by AG14936-03.*