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Neuropathology

**BACE1 – Dependent APP Signaling Is Required For Learning And Memory**

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We have established previously that BACE1 is required for the generation of  $\beta$ -amyloid peptides (A $\beta$ ) that are implicated in the pathogenesis of Alzheimer's disease (AD) and have suggested that the activity of this aspartyl protease is a major determinant of the vulnerability of the brain to the deposition of A $\beta$ . To determine whether the deletion of BACE1 restores the cognitive deficits observed in APP<sup>swe</sup>/PS1<sup>? E9</sup> mice, we generated and analyzed APP<sup>swe</sup>/PS1<sup>? E9</sup> mice lacking BACE1 in a series of water maze tasks that assess reference and episodic-like memories. Our results show that ablation of BACE1 abolished A $\beta$  deposition and rescued age-associated memory deficits occurring in APP<sup>swe</sup>/PS1<sup>? E9</sup> mice. While BACE1 deficient mice show no overt developmental abnormalities or adult onset neuropathology, they exhibit cognitive and emotional deficits. Importantly, memory impairments occurring in mice lacking BACE1 are rescued by increased expression of APP and PS1. These findings establish a role for BACE1-dependent APP signaling in cognition and have important implications for the development of potential therapies designed to inhibit BACE1 in the treatment of AD.