BACE inhibition-dependent repair of Alzheimer's pathophysiology.

Abstract:
Amyloid-β (Aβ) is thought to play an essential pathogenic role in Alzheimer’s disease (AD). A key enzyme involved in the generation of Aβ is the β-secretase BACE, for which powerful inhibitors have been developed and are currently in use in human clinical trials. However, although BACE inhibition can reduce cerebral Aβ levels, whether it also can ameliorate neural circuit and memory impairments remains unclear. Using histochemistry, in vivo Ca imaging, and behavioral analyses in a mouse model of AD, we demonstrate that along with reducing prefibrillary Aβ surrounding plaques, the inhibition of BACE activity can rescue neuronal hyperactivity, impaired long-range circuit function, and memory defects. The functional neuronal impairments reappeared after infusion of soluble Aβ, mechanistically linking Aβ pathology to neuronal and cognitive dysfunction. These data highlight the potential benefits of BACE inhibition for the effective treatment of a wide range of AD-like pathophysiological and cognitive impairments.