Alzheimer's disease (AD) is the most common neurodegenerative disorder leading to dementia. Neuritic plaques, neurofibrillary tangles, and neuronal loss represent the main histological hallmarks observed in AD brains. Particularly, Amyloid b-protein (Ab) accumulation, which is the central component of neuritic plaques, appears to play a critical role in AD pathogenesis. Ab is generated from sequential cleavages of the b-amylloid precursor protein (APP) by the b- and γ-secretases. Therefore, inhibition of the pathways that lead to Ab generation will have therapeutic implications for the treatment of AD. Previous studies indicated that glycogen synthase kinase 3 (GSK3) facilitates Ab production by positively modulating γ-secretase activity. Lithium chloride (LiCl) and valproic acid (VPA) are well known inhibitors of GSK3. We found that LiCl and VPA treatment lead to an accumulation of APP C-terminal fragments (CTF) in vitro and in vivo, indicating inhibition of γ-secretase activity. Although LiCl and VPA are GSK3 inhibitors, these compounds also activate a plethora of signaling cascades that may differentially regulate APP processing. Using a GSK3 specific inhibitor, we observed reduced CTF levels in a dose-dependent manner. This indicated that GSK3 inhibition by ARA014418 inhibited APP processing via a γ-secretase-independent mechanism. We also found that ARA014418 treatment to a mouse model of Alzheimer's disease reduced plaque formation and rescued cognitive deficits. Our work suggests that GSK3 regulates APP processing at different levels and that GSK3 remains a valid target for treating AD pathology.