

Mechanistic insights into MARK4 inhibition by galantamine toward therapeutic targeting of Alzheimer's disease

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Motivation and Aim: Hyperphosphorylation of tau is an important event in Alzheimer's disease (AD) pathogenesis, leading to the generation of "neurofibrillary tangles," a histopathological hallmark associated with the onset of AD and related tauopathies. Microtubule-affinity regulating kinase 4 (MARK4) is an evolutionarily conserved Ser-Thr (S/T) kinase that phosphorylates tau and microtubule-associated proteins, thus playing a critical role in AD pathology. The uncontrolled neuronal migration is attributed to overexpressed MARK4, leading to disruption in microtubule dynamics. Inhibiting MARK4 is an attractive strategy in AD therapeutics.

Methods and Algorithms: Molecular docking was performed to see the interactions between MARK4 and galantamine (GLT). Furthermore, 250 ns molecular dynamic studies were performed to investigate the stability and conformational dynamics of the MARK4–GLT complex. We performed fluorescence binding and isothermal titration calorimetry studies to measure the binding affinity between GLT and MARK4. Finally, an enzyme inhibition assay was performed to measure the MARK4 activity in the presence and absence of GLT.

Results: We showed that GLT, an acetylcholinesterase inhibitor, binds to the active site cavity of MARK4 with an appreciable binding affinity. Molecular dynamic simulation for 250 ns demonstrated the stability and conformational dynamics of the MARK4–GLT complex. Fluorescence binding and isothermal titration calorimetry studies suggested a strong binding affinity. We further show that GLT inhibits the kinase activity of MARK4 significantly ($IC_{50} = 5.87 \mu M$).

Conclusion: These results suggest that GLT is a potential inhibitor of MARK4 and could be a promising therapeutic target for AD. GLT's inhibition of MARK4 provides newer insights into the mechanism of GLT's action, which is already used to improve cognition in AD patients.

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