Niebezpieczne związki białka tau z receptorami muskarynowymi – egzemplifikacja w mysich modelach chorób neurozwyrodnieniowych.

Les Liaisons dangereuses of tau protein with muscarinic receptors - exemplification in murine models of neurodegenerative disorders.

ABSTRACT

The microtubule-binding protein **tau** has numerous binding partners, including signaling molecules, cytoskeletal elements and lipids, suggesting that it is a multifunctional protein. Indeed, tau can bind to and affect cytoskeletal components and regulate signaling pathways by acting as a protein scaffold for signaling complexes; tau binding also activates or inhibits several enzymes. Tau may also exert toxic effect acting as an agonist of **cholinergic muscarinic receptors**. There are different alternatives to explain tau pathology spreading in tauopathies like AD, a disease that long time ago was associated with severe loss of cholinergic markers in the brain, and that such loss may be due to the toxic interaction of tau with muscarinic receptors. By using specific antagonists of muscarinic receptors it was found that extracellular tau binds to **M1 and M3** receptors and that it may explain the increase of intracellular calcium found in neuronal cells upon tau-binding. It is suggested that increase of calcium mediated by the interaction of tau with muscarinic receptors could result in cell death. M1 and M3 receptors are coupled with G_q/G_{11} proteins leading to activation of phospholipase C and an increase in the level of intracellular calcium. This calcium increase could activate some protein kinases, and these kinases could modify tau protein rendering the protein toxic. M1 receptors are involved in all key pathological changes found in AD - parenchymal and cerebrovascular amyloid deposition, neurofibrillary tangles, neuroinflammation, and cognitive decline studying 3xTgAD mice with the deletion of M1 receptor gene. Notably, tau over phosphorylation and potentiation of amyloidogenic processing in the mice with AD lacking M1 were attributed to changes in the GSK-3β and protein kinase C activities. Corroborating these findings, genetic deletion of M1 receptor has recently increased Aβ pathological features in $APP_{Swe/Ind}$ mice. Finally, deleting the M1 receptor increased the astrocytic and microglial response associated with Aβ plaques. These data highlight the significant effect of M1 receptors disruption in exacerbating AD-related cognitive decline and pathological features and provide critical preclinical evidence to justify further development and evaluation of selective M1 agonists for treating AD. However so far, significance of tau signaling through muscarinic receptor in solely *in vivo* tauopathic models remains uncertain.