OMICS Group Conferences
Accelerating Scientific Discovery

2nd International Conference on
Alzheimer's Disease and Dementia
September 23-25, 2014 Valencia Convention Centre, Spain

Novel antidiabetic compounds improve hippocampal insulin sensitivity and attenuate tau hyperphosphorylation in model of diabetic mice

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Recently, a close relationship between Alzheimer's disease (AD) and metabolic syndrome resulting from obesity and type 2 diabetes mellitus (T2DM) which is characterized by insulin resistance was suggested. Downregulation of insulin signaling cascade in brain leads to activation of glycogen synthase kinase - 3β (GSK-3β) resulting from decreased phosphorylation on Ser9. GSK-3β is one of the most important kinases implicated in tau protein hyperphosphorylation. Hyperphosphorylated tau forms intracellular neurofibrillary tangles (NFT) which are the hallmark of AD. Drugs used for T2DM treatment could enhance central insulin signaling pathway and attenuate tau hyperphosphorylation consequently. In the study, mice with monosodium glutamate-induced obesity (MSG mice) that had significantly impaired spatial memory compared to age-matched controls were used. Compared to 2 months old animals, MSG mice at the age of 6 months had significantly lowered phosphorylation of GSK-3β on Ser9 and significantly increased phosphorylation of Tau protein on epitopes Ser396 and Thr231. Six month's old MSG mice were treated 14 days either with liraglutide, the most used anti-T2DM drug, or novel peptidic analog with potential antidiabetic effect. 14-day treatment with liraglutide or novel peptidic analog resulted in increased phosphorylation of GSK-3β on Ser9 and attenuated phosphorylation of Tau protein on epitopes Thr212, Thr231 and Ser396. These results demonstrate the potential implication of anti-T2DM drugs, both an established and a novel one, in attenuation of hyperphosphorylation of Tau protein.

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