

Impaired cognitive function and Alzheimer's Disease related pathology associate with reduced O-GlcNAc transferase expression in a mouse model of metabolic syndrome

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Objective: To examine the link between cognitive performance, AD-related pathology and O-GlcNAc signaling in MetS KKAY mice

Risks of Alzheimer's disease (AD) is increased >1.5 times in metabolic syndrome (MetS) patients. Hyperphosphorylated tau (pTau), is an important hallmark of AD pathology. Recent studies in AD patients and AD mouse models suggest a putative link between tau pathology and cerebral glucose hypometabolism, characterized by reduced O-linked N-acetylglucosamine protein levels. However, the role of O-GlcNAc signaling in etiology of AD in MetS is poorly understood. The goal of the present study was to investigate the link between AD-related pathology and cognitive function and O-GlcNAc transferase (OGT), a key regulator of O-GlcNAc signaling, in a mouse model of MetS (KKAY^{+/-}). Obese diabetic (KKAY^{+/-}), lean prediabetic (KKAY^{-/-}), and normal C57BL/6 control mice weaned at 4 weeks of age underwent periodic body weight testing, random blood glucose monitoring, and behavior testing at 12+ months of age followed by plasma and brain tissue (frontal cortex and hippocampus) harvest. Obese diabetic KKAY^{+/-} mice exhibited significant impairments in novel object recognition and spontaneous activity vs. KKAY^{-/-} and C57BL/6J mice, indicative of cognitive deficits. Immunoblotting of brain tissue lysates revealed increased ptau expression coupled with reduced pGSK3 β and pERK expression in MetS KKAY^{+/-} compared to non-MetS KKAY^{-/-} mice. Notably, enhanced ptau level was accompanied with attenuated OGT expression in brain tissue lysates of MetS KKAY^{+/-} mice vs. non-MetS KKAY^{-/-}. Together, these data demonstrate a direct link between cognitive dysfunction, hyperphosphorylated tau and OGT expression in MetS mice. Overall, our study suggests a novel role of OGT in AD etiology associated with MetS.