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Combinational Effects of Type 2 Diabetes and Protein Post translationally Modification in the Pathophysiology and Progression of Alzheimer s disease

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Alzheimer s disease (AD) is a multi-factorial degenerative disease of the brain with an estimated prevalence of 1 in 9 age 65 and older and a global population burden projected to triple by 2050. Main pathological hallmarks of this disease are abnormal aggregation and misfolding of the amyloid beta peptide as well as tau protein. These are accompanied by pathophysiological events such as leaky blood brain barrier (BBB), synaptic degeneration, neuro-inflammation and neuronal degeneration. Main risk factor of this disease is aging, but obesity, Type 2 Diabetes, sleep disorders and stress also contribute to the progression of this neurodegenerative disorder. A? peptides are commonly subjected to post-translational modifications, including truncation and phosphorylation, which are shown to play a pivotal role in A? plaque aggregation. N-terminally truncated A? peptides containing pyroglutamatic acid (pGlu) catalyzed by glutaminyl cyclase (QC) e.g., pGlu3-A? (3-40/42) are the major A? peptide fragments within the core of the neuritic plaques and are shown to correlate with disease severity and progression. Type 2 diabetes (T2D) is one of the major risk factors associated with AD and compelling evidence supports the notion that insulin resistance, a key feature of T2D, is involved in AD-type neurodegeneration. Using APPxhQC transgenic mice expressing N-terminal modified pGlu A? peptides, we aim to understand what adding another risk factor (T2D besides hQC) could mean for the AD pathology in this model and if this could give a hint that more than one risk factor might affect AD in humans more significantly.