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学位論文の題名	Insulin Deficiency Increases Sirt2 Level in Streptozotocin-Treated Alzheimer's Disease-Like Mouse Model: Increased Sirt2 Induces Tau Phosphorylation Through ERK Activation （ストレプトゾトシン投与によるインスリン欠乏はアルツハイマー病モデルマウス脳内のSirt2発現を増加させる。Sirt2の増加はERKの活性化を介してタウのリン酸化を誘導する） Molecular Neurobiology, 59 (9):5408-5425, 2022
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Abstract

(Background)

Alzheimer's disease (AD) is a major neurodegenerative disease characterized by the presence of extracellular senile plaques, intraneuronal neurofibrillary tangles, neuroinflammation, and neuronal loss. Amyloid-β (Aβ) is generated from the Aβ precursor protein (APP) by β- and γ-secretases, resulting in the subsequent formation of Aβ plaques. Intraneuronal neurofibrillary tangles are composed of aggregated hyperphosphorylated tau proteins. Diabetes is a risk factor for AD, and insulin deficiency affects AD pathologies. However, the underlying molecular mechanisms are not entirely understood. Here, we investigated the effects of insulin deficiency on AD-like pathologies using an insulin-deficient AD mouse model (Tg2576 mice).

(Methods)

Three-month-old Tg2576 mice were injected intraperitoneally with streptozotocin (STZ) to induce insulin deficiency, and their body weight, serum glucose levels, and serum insulin levels were evaluated. The deposition and levels of Aβ and the expression of AD pathology-related proteins in the brain were evaluated using immunohistochemistry, enzyme-linked immunosorbent assay (ELISA), and western blot analysis. To identify the proteins affecting AD pathologies, cortical proteins from vehicle- and STZ-treated mice brains were separated by two-dimensional gel electrophoresis and analyzed using liquid chromatography-tandem mass spectrometry. The role of sirtuin 2 (Sirt2) in tau phosphorylation in neuronal cells was assessed using both loss- and gain-of-function approaches.

(Results)

Compared with vehicle-treated mice, STZ-treated mice showed lower body weight, serum insulin level, and insulin receptor phosphorylation, but higher blood glucose level. STZ treatment exacerbated Aβ accumulation, tau hyperphosphorylation, glial activation, and neuroinflammation. Increased Sirt2 protein levels were observed in the brain of STZ-treated mice. Furthermore, *in vitro* experiments revealed that insulin depletion or interleukin-6 treatment increased Sirt2 protein levels. The overexpression of Sirt2 induced tau hyperphosphorylation through extracellular signal-regulated kinase (ERK) activation. Conversely, Sirt2 knockdown reversed tau hyperphosphorylation.

(Conclusion)

We showed for the first time that Sirt2 is upregulated in the brains of STZ-treated Tg2576 mice and is involved in tau phosphorylation through ERK activation. Our findings suggest that Sirt2 may be a promising therapeutic target for AD.