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Netrin-4 Mitigates Tau Pathology in Alzheimer's Disease Across Hippocampal and Myenteric Neurons via UNC5A

Alzheimer's disease (AD) neuropathological hallmarks include senile plaques with aggregated amyloid beta as a major component, neurofibrillary tangles (NFTs) containing truncated and hyperphosphorylated tau, significant neuronal loss, and chronic neuroinflammation. However, molecules associated with Tau and early Alzheimer's disease pathology remain largely unexplored. Notably, netrin-4 (NTN-4) is highly expressed in the healthy adult subiculum, a region located at the base of the hippocampus between the hippocampus proper and the entorhinal cortex. Protein-protein interactions between NTN-4 and Tau (4R2N) using ClusPro 2.0 revealed multiple interaction sites between the Tau N1 and NTN-4 NTR protein domains. This observation prompted us to investigate a role of the NTN-4/ UNC5 pair in hippocampal neurons by assessing the expression levels of NTN-4 and Tau in human AD patients, cellular models, and mouse models of AD. We infected Tau (4R2N) virus at primary hippocampal neurons and HT-22 cell line, and performed stereotaxic injection of Tau virus into the mouse hippocampus region to observe differences in NTN-4, UNC5A-D, DCC, and DSCAM expression levels with tauopathy compared to control group. Surprisingly, the overexpression of Tau led to NTN-4 depletion in hippocampal neurons, which subsequently induced apoptosis in myenteric neurons. In addition, chronic dextran sulfate sodium (DSS)-induced gut inflammation further reduced Netrin-4 expression and exacerbated Tau pathology in MAPT mice, leading to hippocampal structural damage and cognitive impairments. Furthermore, we observed NTN-4 depletion in brain samples from AD patients but not in those from healthy controls. These results highlight the critical role of NTN-4 in inhibiting Tau pathology during Alzheimer's disease progression and reveal a mechanistic link between gut inflammation and neurodegeneration through the modulation of NTN-4 and Tau, underscoring the therapeutic potential of targeting NTN-4/UNC5A signaling in AD.

Keywords: NTN4, neurofibrillary tangles, Alzheimer's disease, Tau, amyloid beta, UNC5A, hippocampal neuron

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Biography

I am an undergraduate student in the Department of Biomedical Sciences at Hallym University, where I began my studies in 2022. Since 2023, I have been conducting research in the Department of Physiology at Hallym University College of Medicine under the supervision of Prof. Ahn. Currently in my second year of research, I focus on neurodegenerative diseases, particularly Alzheimer's and Parkinson's disease. My research aims to uncover the underlying mechanisms of these disorders and explore potential therapeutic approaches. Through my work, I strive to contribute to advancements in neuroscience and the development of improved treatments for neurodegenerative diseases.

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