LRP4 Deficiency in Astrocytes Exacerbates Alzheimer's-Associated Pathology and Cognitive Dysfunction

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Objective

To understand how astrocytic low-density lipoprotein receptor-related protein 4 (LRP4) mediates Alzheimer's associated pathology and cognitive function in 5xFAD mice.

Background

Alzheimer's disease (AD) is the most common neurodegenerative disorder and cause of dementia worldwide and characterized by the accumulation of amyloid plaques, tau tangle formation, neuron loss, glial activation, and memory loss. Astrocytes are essential for brain health, regulating homeostasis, metabolism, and synaptic transmission. Growing evidence supports a fundamental and active role of astrocytes in AD etiology and progression. LRP4 mainly expressed by astrocytes and facilitates glutamatergic transmission by controlling ATP release. However, whether and how astrocytic LRP4 contributes to AD pathogenesis is unknown.

Methods

LRP4 expression pattern and cell type specificity were indicated by Lrp4-CreER cross with Ai9 reporter mice. LRP4 deficiency in the whole brain and astrocyte by cross Lrp4f/f mice in the 5XFAD

background with GFAP-Cre and GFAP-CreER, respectively. Aβ plaque deposition, Aβ level, and neuronal inflammation were examined by immunohistochemistry, ELISA and immunofluorescence. Synaptic dysfunctions were analyzed by morphological analysis and electrophysiological recording. Cognitive function was evaluated by Y maze and Morris water maze. The Aβ uptake and degradation were investigated in cultured primary astrocyte and analyzed by imaging, flow cytometry, and ELISA.

Results

We found that LRP4 protein level was reduced in AD patients and LRP4 specifically expressed in astrocytes. On the phenotype, we found LRP4 deficiency in astrocytes increased Aβ deposition, exacerbated neuronal inflammation, synaptic dysfunction, and cognitive deficits in 5xFAD mice. However, LRP4 deficiency did not affect Aβ production or blood-brain barrier (BBB) integrity. On the mechanism, we found LRP4 deficiency in astrocytes impaired Aβ degradation caused by impairing receptor-mediated cellular uptake. Increased A2AR and P2X7 expression in LRP4 deficiency mice may due to increasing ATP released from astrocyte.

Conclusion

Our findings reveal a critical role for astrocytic LRP4 in Aβ metabolism, neuroinflammation, and synaptic transmission in AD mice and a potential pathological mechanism of AD development.