

[3P]Alzheimer's Disease and Dementia

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Videos are available throughout the meeting period.*[3P-212]Cannabinoid receptor type II in microglia as a therapeutic target for Alzheimer's disease**

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Alzheimer's disease (AD) is the most common form of dementia, characterized by accumulation of amyloid β (A β) and phosphorylated Tau. Current therapies for AD are aimed to correct synaptic malfunction of neurons based on the cholinergic hypothesis. These therapies treat the symptoms but do not modify the progression of the disease. On the other hand, neuroinflammation, mediated by activation of glial cells such as astrocytes and microglia, is considered to play an important role in the progression of AD. However, the extent to which these events contribute to the A β pathologies remains to be determined. In this study, we performed next-generation sequence analysis using RNAs derived from the precuneus of patients with AD, which is selectively vulnerable to amyloid deposition at the early stage, and RNAs derived from microglia isolated from cerebral cortices of 4, 8 and 12-month-old *App*^{NL-G-F} mice by using magnetic-activated cell sorting. The expression of cannabinoid receptor type II (CB2) gene was commonly altered in these samples. CB2, mainly expressed in peripheral immune cells and CNS microglia, contributes to modulate inflammation. To elucidate the role of CB2 in the CNS, we analyzed the primary microglia and *App*^{NL-G-F} mice using JWH133, a selective CB2 agonist. JWH133 negatively regulated the RNA expression levels of inflammatory cytokines such as TNF- α and CXCL10 in IFN- γ -stimulated microglia in vitro. In addition, chronic oral administration of JWH133 significantly ameliorated the cognitive impairments of *App*^{NL-G-F} mice in the novel object recognition test. JWH133-treated *App*^{NL-G-F} mice also showed significant decrease of activated (A1) astrocyte's markers and microglial *C1q*, one of inducers for the A1 astrocyte, compared to vehicle-treated *App*^{NL-G-F} mice. These results suggest that stimulating microglial CB2 ameliorates cognitive dysfunction in *App*^{NL-G-F} mice through controlling astrocyte activation and inducing beneficial neuroinflammation.