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HY2109 ameliorates brain inflammation and improves memory impairments in Alzheimer's disease mice model

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Alzheimer's disease (AD) is the most common cause of dementia. Neuro-inflammation and neuronal apoptosis due to progressive deposition of amyloid beta (Aβ) in the brain incur defects in cognition and memory. In this study, we showed that HY2109 could improve memory deficits in AD mice model (5XFAD). As a vehicle group, the 5XFAD mice were given with PBS. HY2109 significantly reduced the time to find platform, increased platform crosses and quadrant occupancy in water maze test, suggesting improvement in learning and memory of 5XFAD mice after treatment with HY2109 compared with control group. Furthermore HY2109 treatment significantly decreased the number of amyloid plaque, the number of astrocyte and microglia in the frontal cortex. The number of astrocyte was also decreased by HY2109 treatment in hippocampus. iNOS expression of astrocyte in the frontal cortex was drastically reduced by HY2109 treatment. TUNEL (+) apoptotic cells in the frontal cortex were significantly lower in HY2109-group of mice. Interestingly, $CD11b^{+}Gr1^{-}F4/80^{+}$ myeloid cells were significantly increased in the spleen and brain of 5XFAD mice that were treated with HY2109. Blood CCL3 was significantly lower in HY2109 group of mice. These findings suggest that HY2109 might be a new molecular entity that can control pathogenesis of Alzheimer disease.

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Neutrophils induce Alzheimer's disease-like pathology and cognitive decline via a mechanism dependent on LFA-1 integrin

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Inflammation is a pathological hallmark of Alzheimer's disease and understanding the underlying mechanisms may facilitate the development of new treatments. Using mice with five familial Alzheimer's disease (5xFAD) mutations presenting amyloid pathology, and 3xTg-AD mice with both amyloid and tau pathology, we found increased expression of vascular adhesion molecules and increased accumulation of neutrophils in the brain. Neutrophils extravasated in areas with amyloid beta (Abeta) deposits, releasing neutrophil extracellular traps (NETs) and producing IL-17. Abeta1-42 peptide triggered the LFA-1 integrin high-affinity state and rapid neutrophil adhesion. Two-photon laser-scanning microscopy experiments showed that LFA-1 integrin controls neutrophil extravasation and intraparenchymal motility. Neutrophil depletion or the inhibition of neutrophil trafficking using LFA-1 genetic ablation or an anti-LFA-1 antibody dramatically rescued memory loss in 5xFAD and 3xTg-AD mice. Interfering with neutrophil activity also reduced microglial density and activation, amyloid deposition, tau phosphorylation and restored synaptic protein loss. Importantly, restoration of cognitive function in mice with temporary inhibition of neutrophil function during early disease was maintained also at later time points in aged animals. To understand the relevance of our data in humans, we analyzed human cortical brain samples from subjects with Alzheimer's disease. Our results showed that neutrophils adhered and spread inside brain venules or migrated into the parenchyma in high numbers and release NETs in Alzheimer's brains compared to control subjects. In conclusion, our data demonstrate that neutrophils induce cognitive impairment and neuropathological changes suggesting that the inhibition of neutrophil trafficking may represent a new therapeutic strategy to address Alzheimer's disease.