Caspase-1 inhibition improves cognition without significantly altering amyloid and inflammation in aged Alzheimer disease mice

Joseph Flores, Marie-Lyne Fillion, and Andréa C. LeBlanc.

Human genetic and animal model studies indicate that brain microglial inflammation is a primary driver of cognitive impairment in Alzheimer Disease (AD). Inflammasome-activated Caspase-1 (Casp1) enzyme is associated with both AD microglial inflammation and neuronal degeneration. In mice, Casp1 genetic ablation or VX-765 (Belnacasan) small molecule inhibition of Casp1 given at onset of cognitive deficits strongly supports the association between microglial inflammation and cognitive impairment. Here, VX-765 significantly improved episodic and spatial memory impairment eight months after the onset of cognitive impairment in aged AD mice with significant amyloid beta peptide (Aβ) accumulation and microglial inflammation. Unexpectedly, while cognitive improvement was associated with dendritic spine density and hippocampal synaptophysin level recovery, VX-765 only slightly decreased Aβ deposition and did not alter biochemically-measured Aβ levels. Furthermore, increased hippocampal Iba1+-microglia, GFAP+-astrocytes, IL-1β, and TNF-α levels were unaltered by VX-765. These results support the hypothesis that neuronal degeneration, not Aβ or microglial inflammation, drives cognitive impairment in AD.

Our work indicates that inflammation and amyloid accumulation are not drivers of episodic or spatial memory deficits in J20 mice, although these pathologies may exacerbate cognitive deficits. Therefore, directly targeting neuronal degeneration pathways, rather than targeting AD-related pathologies, may provide more efficient treatments against age-dependent and AD-related memory impairment.

https://doi.org/10.1038/s41419-022-05290-x