Selective modulation of neuroinflammation by targeting p38α MAPK with a novel, isoform-specific inhibitor, MW150, in an Alzheimer's disease mouse mode

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Background: P38α mitogen-activated protein kinase (MAPK) is a key regulator of stressor-induced neuroinflammatory responses, especially the overproduction of proinflammatory cytokines from microglia. The cytokine release, in turn, can lead to synaptic and neuronal damage. As a result, inhibitors of p38α MAPK have become an attractive target for new therapies against CNS diseases or injuries that involve overproduction of inflammatory responses.

Methods: In this study, we aimed to determine the extent and specificity of p38α MAPK modulated neuroinflammatory responses, by using our recently developed p38α MAPK inhibitor, MW150. MW150 is a novel, chemically stable, orally bioavailable, CNS-penetrant, small molecule that is highly selective for the p38α MAPK isoform. We have previously shown that MW150 is effective in suppression of hippocampal-dependent associative and spatial memory deficits in APP/PS1 knock-in mice, a model of Alzheimer's disease (AD) pathology progression. To determine the effects of MW150 on proinflammatory cytokines, we measured levels of IL-1β, TNFα and IL-6 in the cortex of these mice using ELISA. Glial markers CD45, CD68 and GFAP were assessed by immunohistochemistry. Microglia and amyloid plaques were quantified by immunofluorescence staining followed by confocal imaging. We further extended our study by comparing proliferation, migration and phagocytosis activities in a murine microglia BV2 cell line with and without MW150 treatment using live cell imaging techniques.

Results: MW150 attenuated the increased levels of IL-1β and TNFα but not IL-6 in the APP/PS1 knock-in mice. The compound also increased the Iba1+ microglia within a 15 μm radius of the amyloid plaques, without affecting overall microglia or plaque volume. MW150 did not alter levels of the glial markers CD45, CD68 and GFAP, and also did not affect microglial migration, proliferation or phagocytosis.

Conclusion: Our study demonstrates that MW150 has a selective role in modulation of neuroinflammatory responses without pan-suppression of normal physiological functions of microglia. These results further document the utility of MW150 to probe the role of p38α MAPK in CNS disorders that include dysregulated neuroinflammation as part of the disease mechanism.