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Oral Presentation

Therapeutic Potential of a Novel NMDA Receptor Subunit 2B Antagonist in a Mouse Model of Autoimmune Neuroinflammation

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Abstract

Glutamate-mediated excitotoxicity and neurodegeneration have been shown as pathophysiological hallmarks of multiple sclerosis (MS) and other autoimmune inflammatory CNS disorders. NMethylDAspartate (NMDA) receptors play a pivotal role in the mediation of neuronal glutamate excitotoxicity leading to cellular damage and apoptotic cell death. Current treatment approaches targeting glutamate excitotoxicity are unspecific and associated with severe adverse events due to the broad and important functions of NMDA receptors in the CNS. Hence, the present study investigates the neuroprotective potential of a novel specific NMDA receptor 2B (GluN2B) subunit antagonist. Prophylactic and therapeutic treatment with the GluN2B antagonist WMS14-10 (WMS) significantly ameliorated the disease course in myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis (MOG-EAE), a murine model of MS. At disease maximum microglia from WMS treated mice showed decreased CD86 expression indicating reduced microglial activation. In agreement, activated microglia expressed GluN2B. Under restimulation with MOG splenocytes from WMS treated mice demonstrated decreased secretion of TNFα, INFγ and IL-17. In vitro WMS showed no significant effects on the function of T cells and macrophages/monocytes. However, incubation with WMS reduced lipopolysaccharide (LPS)-mediated secretion of cytokines like GM-CSF, IL-1α and TNFα by microglia. In conclusion, our results indicate that specific inhibition of GluN2B in microglia cells displays a newly identified pathway in neuroinflammatory degeneration. Ongoing studies aim at dissecting the underlying mechanisms and a putative additional effect on neuronal glutamate excitotoxicity.

Keywords: Therapeutic, Inflammatory, Mice

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