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Glial-neuronal signaling mechanisms underlying the neuroinflammatory effects of manganese.

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Abstract

BACKGROUND: Exposure to increased **manganese** (Mn) causes inflammation and neuronal injury in the cortex and basal ganglia, resulting in neurological symptoms resembling Parkinson's disease. The mechanisms underlying neuronal death from exposure to Mn are not well understood but involve inflammatory activation of microglia and astrocytes. Expression of neurotoxic inflammatory genes in glia is highly regulated through the NF-κB pathway, but factors modulating neurotoxic glial-glial and glial-neuronal signaling by Mn are not well understood.

METHODS: We examined the role of NF-κB in Mn-induced **neurotoxicity** by exposing purified microglia, astrocytes (from wild-type and astrocyte-specific IKK knockout mice), and mixed glial cultures to varying Mn concentrations and then treating neurons with the conditioned media (GCM) of each cell type. We hypothesized that mixed glial cultures exposed to Mn (0-100 μM) would enhance glial activation and neuronal death compared to microglia, wild-type astrocytes, or IKK-knockout astrocytes alone or in mixed cultures.

RESULTS: Mixed glial cultures treated with 0-100 μM Mn for 24 h showed the most pronounced effect of increased expression of inflammatory genes including inducible nitric oxide synthase (Nos2), Tnf, Ccl5, Il6, Ccr2, Il1b, and the astrocyte-specific genes, C3 and Ccl2. Gene deletion of

IKK2 in astrocytes dramatically reduced cytokine release in Mn-treated mixed glial cultures. Measurement of neuronal viability and apoptosis following exposure to Mn-GCM demonstrated that mixed glial cultures induced greater neuronal death than either cell type alone. Loss of IKK in astrocytes also decreased neuronal death compared to microglia alone, wild-type astrocytes, or mixed glia.

CONCLUSIONS: This suggests that astrocytes are a critical mediator of Mn **neurotoxicity** through enhanced expression of inflammatory cytokines and chemokines, including those most associated with a reactive phenotype such as CCL2 but not C3.

KEYWORDS: Astrocyte; CCL2; Glial-glial communication; Glial-neuronal communication; Manganism; NF-κB; Neuroinflammation

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