The Antioxidant Role of the JAK2/STAT3 Signaling Pathway on Methylmercury-Induced Toxicity in a Mouse Astrocyte Neuronal C8-D1A Cell Line

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Toxic methylmercury (MeHg) readily crosses the blood brain and placental barriers, leading to developmental delays and neurological issues particularly with in utero exposure. Upon exposure, MeHg reaches the brain and selectively accumulates in astrocytes, disrupting glutamate and calcium homeostasis and increasing oxidative stress. Nuclear factor erythroid 2-related factor 2 (Nrf2) may be a therapeutic target against MeHg toxicity. However, recent studies indicate the Nrf2 signaling pathway alone is insufficient to mitigate MeHg-induced damage, suggesting the existence of other protective mechanisms. The signal transducer and activator of transcription 3 (STAT3) plays a significant role in cell growth and survival. STAT3 involvement in redox regulation is well documented, preventing oxidative stress through modulation of nuclear genes that encode electron transport complexes and antioxidant enzymes. These characteristics suggest that STAT3 could serve as a key mechanism to mitigate MeHg toxicity. To elucidate the role of the STAT3 signaling pathway in MeHg neurotoxicity, STAT3 was pharmacologically inhibited using C188-9 and AG490 inhibitors in an astrocytic cell line exposed to 10 μM MeHg.?? Cells were treated with two antioxidant treatments, N-acetyl-cysteine and Trolox, to determine whether MeHg-induced ROS production activates STAT3. Utilization of MTT/LDH, ROS, western blot, qPCR, and glutathione assays demonstrated that inhibition of STAT3 phosphorylation exacerbates MeHg-induced mortality, antioxidant responses, and ROS production. STAT3 may contribute to neuroprotection against MeHg exposure in astrocytes. Further research is warranted to evaluate the defense response of the JAK2/STAT3 signaling pathway against MeHg toxicity on other neuronal cell models.

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