Developmental Manganese Neurotoxicity Is Reversed by the Antioxidant Trolox

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While manganese (Mn) is essential for proper central nervous system (CNS) development, excessive Mn exposure may lead to neurotoxicity. Younger individuals accumulate greater Mn levels in the CNS, and are more vulnerable to its toxicity. Moreover, the mechanisms mediating developmental Mn-induced neurotoxicity are not completely understood. The present study investigated the developmental neurotoxicity elicited by Mn exposure (5, 10 and 20 mg/kg; i.p.) from postnatal day 8 (PN8) to PN27 in rats. Neurochemical analyses were carried out on the striatum at PN29. Intracellular signaling pathways (MAPKs, Akt and DARPP-32) were evaluated by western blotting, F2-isoprostanones were determined by gas chromatography/mass spectrometry and caspase activity was measured fluorimetrically. Motor alterations were evaluated later in life at 3, 4- or 5-weeks-of-age by the rotarod test. Mn exposure (20 mg/kg) increased caspase activity, F2-isoprostanone production, p38MAPK and Akt phosphorylation, but decreased DARPP-32-Thr-34 phosphorylation. Paralleling the changes in striatal biochemical parameters, Mn also caused motor impairment, evidenced by increased falling latency in the rotarod test. Notably, the antioxidant Trolox reversed the Mn-dependent augmentation in p38MAPK phosphorylation, reduced the Mn-induced caspase activity and F2-isoprostanone production. Moreover, Trolox reversed the Mn-induced motor coordination deficits. These findings show that long-term exposure to Mn during a critical period of neurodevelopment causes motor coordination dysfunction with parallel neurochemical alterations in the striatum. Moreover, we establish Trolox as a potential neuroprotective agent given its efficacy in reversing the Mn-induced neurodevelopmental effects.

Key words: developing brain, manganese, neurotoxicity, neuroprotection

Supported by: CNPq, CAPES, FAPESC-PRONEX