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IMPLICATION OF EPIGENETIC MECHANISM IN MANGANESE INDUCED PARKINSONISM

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Manganese (Mn) is an essential trace element required for optimal functioning of cellular biochemical pathways in the central nervous system. Elevated exposure to Mn through environmental and occupational exposure can cause neurotoxic effects resulting in manganism, a condition with clinical symptoms identical to idiopathic Parkinson's disease. Epigenetics is now recognized as a biological mechanism involved in the etiology of various diseases. Here, we investigated DNA methylation alterations and miRNA profiling upon chronic Mn (100 µM) exposure in human neuroblastoma (SH-SY5Y).Whole-genome bisulfate conversion and sequencing indicate epigenetic perturbation of key genes involved in biological processes associated with neuronal cell health. Integration of DNA methylation data with gene expression reveals epigenetic alterations to *PINK1, PARK2* and TH genes that play critical roles in the onset of Parkinsonism. Mn induced alteration of DNA methylation of *PINK1–PARK2* may influence mitochondrial function and promote Parkinsonism.The miRNA PCR array results reveal alterations in expression levels of miRNAs, which have previously been associated with the regulation of synaptic transmission and apoptosis. The expressions of miR-7 and miR-433 significantly reduced upon manganese exposure. By in silico homology analysis we identified SNCA and FGF-20 as targets of miR-7 and miR-433. We demonstrate an inverse correlation in expression levels where reduction in these two miRNAs causes increases in SNCA and FGF-20. Transient transfection of SH-SY5Y cells with miR-7 and miR-433 mimics resulted in down regulation of SNCA and FGF-20 mRNA levels. Our study is the first to uncover the potential link between manganese exposure, altered miRNA expression and parkinsonism: manganese exposure causes overexpression of SNCA and FGF-20 by diminishing miR-7 and miR-433 levels. These miRNAs may be considered critical for protection from manganese induced neurotoxic mechanism and hence as potential therapeutic targets. Our findings provide a basis to further explore and validate the epigenetic basis of Mn-induced neurotoxicity.

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