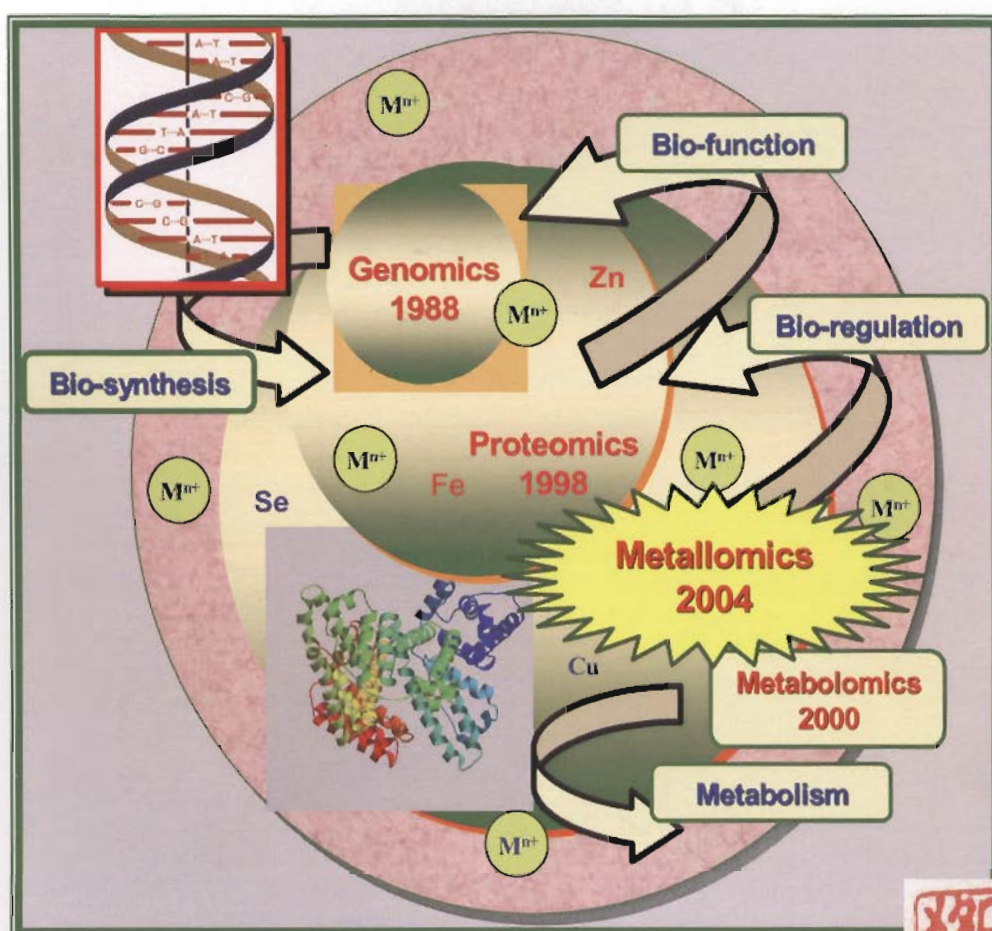


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**IS LIFETIME EXPOSURE TO MANGANESE
A DETERMINANT OF PARKINSON'S DISEASE?
POSSIBLE APPLICATION OF METALLOMICS APPROACH**

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Background: Manganese, Mn, can cause Parkinsonian disturbances in humans. Experimental studies have shown that Mn is an effective inhibitor of mitochondrial function, cellular iron homeostasis, and an inducer of oxidative stress. However, the outcomes of many of these studies are qualified by the relatively large Mn dosing regimens and acute exposure durations that they employed. Instead, effects in humans are likely to occur after prolonged exposures to much lower doses.

Methods: A cross sectional study was conducted on Parkinsonian patients resident in Valcamonica, a valley of the Italian pre-Alps where ferroalloy plants operated for about a century causing environmental contamination with Mn, iron, lead and other metals. Patients from this area were examined with various neurological, neuropsychological assessment, tremorimetric and MRI measures. Various biomarkers were used including metal concentrations in biological fluids, and also genetic polymorphism for genes involved in dopamine metabolism. Results were compared with those of patients resident in non polluted areas, and with sex- and aged-matched healthy controls. To elucidate the molecular mechanisms of low level Mn neurotoxicity on the basal ganglia, a 2-D DIGE proteomic experiments was also conducted in PC12 cells and in GABA producing M213 cells, exposed to 100µM Mn for 24 hours (n=5/treatment). Cells were processed for protein expression profiling and protein spots were analyzed on the MALDI-TOF mass spectrometer for protein identification.

Results: Exposed patients presented a more severe phenotype as assessed with UPDRS, MMSE, Token and Trail Making Tests, and higher levels of blood and urinary Mn levels, and lead levels. Familiarity for Parkinsonian disturbances and different allelic distribution of DRD4 gene were observed among non exposed patients. The 2-D DIGE assessment for the PC12 cell identified 30 proteins of altered expression due to Mn exposure, including down regulation of secretogranin II, and upregulation of the dopamine degrading enzyme catecholamine-O-methyltransferase methyltransferase and the proteasome pathway enzyme ubiquitin carboxy hydrolase L1.

Conclusions: These data further our understanding of how Mn exposure may reduce cellular dopaminergic function, and lead to the identification of protein targets of Mn. This may represent the underlying mechanism of Mn-induced Parkinsonian damage.