Chronic cadmium exposure disrupts zinc and iron homeostasis in human neural cells

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Keywords: cadmium, neurotoxicity, metal ions, ZnT, DMT1, HMOX1

Abstract: The heavy metal cadmium, a natural element in the Earth's crust, is released in the environment at a rate of 30000 tons/year, by both natural and anthropogenic activities due to its extensive use in industry and agriculture. Cadmium slow excretion from the human body as well as a very long biological half-life (10-30 years) cause its heavily accumulation in organisms, making it an environmental pollutant of global concern. Exposure to cadmium may lead to kidneys, liver, skeletal and cardiovascular system damage, and more recently, it has been associated to neurodegenerative disorders such as amyotrophic lateral sclerosis and Parkinson's disease. In fact, due to inhalation, cadmium can be uptaken from the nasal mucosa and transported along the primary olfactory neurons in the brain, bypassing the intact blood brain barrier. In the nervous system, cadmium tends to accumulate in the choroids plexus at concentrations much greater than those found in other brain areas and it exerts its toxicity with multiple mechanisms, such as oxidative stress, interference with essential metals and epigenetic effects.

Our previous toxicogenomic studies on human neuroblastoma SH-SY5Y cell line, a widely used *in vitro* model for neurotoxicity and neurodegenerative diseases studies, showed a significant perturbation on the mineral absorption pathway following acute cadmium treatment, with up-regulated genes linked to zinc and iron homeostasis. These results lead us to investigate zinc and iron homeostasis in SH-SY5Y cells exposed for a maximum of 6 days to low cadmium doses.

A chronic exposure cause cadmium accumulation inside the cells in a time and dose dependent manner with dysregulation of both zinc and iron homeostasis. An increased in both zinc and iron intracellular content is detected in neural cells treated with 5 µM $CdCl_2$ at all time points analysed; however, if zinc transporters ZnT1 and ZnT2 resulted upregulated, the iron transporter DMT1 is downregulated. Finally, the higher iron content found after a 5 µM $CdCl_2$ treatment could correlate with the induction of heme oxygenase 1 expression. In conclusion a chronic cadmium exposure lead to a general metal ions dyshomeostasis in neural cells.