Cadmium affects mitochondrial functionality and induces mitochondrial fission in differentiated neural cells

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Abstract: Cadmium is a non-essential environmental pollutant, able to accumulate inside human body with a long biological half-life of about 30 years, that has been associated to neurodegeneration. It may enter the central nervous system through the olfactory nerves or by increasing blood brain barrier permeability and it can exert its neurotoxicity through the impairment of mitochondrial function.

In this study, differentiated human neuroblastoma SH-SY5Y cells were used as an *in vitro* model, to better investigate the molecular mechanisms underlying cadmium neurotoxic effects on mitochondria. First of all, cadmium cytotoxicity was assessed by MTT assay, identifying an EC_{50} of 11.93 ± 0.46 µM and, based on this data, all the following experiments were performed using 10 µM $CdCl_2$ for 24h and 48h.

Seahorse analyses showed a decrease in mitochondrial respiration and ATP production with a complementary increase in the glycolytic ATP, starting from the 24h treatment, indicating a shift towards a more glycolytic metabolism in cadmium treated cells. Moreover, mitochondrial membrane potential was reduced already at 24h.

At the molecular level, cadmium induced an increase in MFF, indicative of enhanced mitochondrial fission, instead the expression of mitochondrial fusion marker OPA1 remained unchanged.

Overall, these results show that cadmium compromises mitochondrial functionality in neural differentiated cells through a combination of bioenergetic dysfunction, loss of membrane potential, and alterations in mitochondrial dynamics, highlighting the central role of mitochondria in cadmium-induced neurotoxicity.