Cadmium exacerbates the Warburg effect in neuronal cells, but not in microglia

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Abstract:
The heavy metal cadmium is a widespread toxic pollutant, released into the environment mainly by anthropogenic activities at a rate of 30,000 tons/year. Human exposure can occur through inhalation of polluted air, cigarette smoking or ingestion of contaminated food and water, as well as by occupational exposure. It mainly enters the human body through the respiratory and the gastrointestinal tract, accumulating in liver and kidneys with an estimated half-life of 25-30 years. Once inside the body, cadmium exerts a plethora of toxic effects: from interfering with essential bio-elements, altering their homeostasis and biological functions, to weakening the antioxidant enzymatic and non-enzymatic defence systems, resulting in the damage of key macromolecules, intracellular organelles, and cellular membranes.

Brain is also a target of cadmium toxicity since this toxicant may enter the central nervous system through the olfactory nerves or by increasing blood brain barrier permeability. In fact, cadmium exposure has been related to impaired functions of the nervous system and recent data suggest a role for heavy metals in many neurodegenerative diseases. However, the role and the exact mechanisms of cadmium neurotoxicity are still to be elucidated.

Our work aims to investigate cadmium toxicity towards not only neuronal cells, but glial ones too, focusing on cellular metabolism, mitochondrial functionality, and antioxidant defense mechanisms.

On neuronal cells cadmium exacerbates the Warburg effect, causing an increase in glycolysis and in glycolytic ATP production, paralleled by a decrease in ATP production by oxidative phosphorylation, due to an impairment of mitochondrial respiration. Moreover, following cadmium administration, mitochondria increased their dependency on glutamine, as a substrate for lipid biosynthesis.

On the other hand on microglia, cadmium induces the release of proinflammatory cytokines, without markedly switching to M1 phenotype, and the alterations of cell morphology and metabolism leading to a mitochondrial impairment, but not to a Warburg effect.