Cadmium and its role in brain dysfunction: neuroprotective effects of Polydeoxyribonucleotide administration in a murine model of cadmium toxicity.

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Cadmium (Cd) is one of the most harmful heavy metals because it causes severe brain damage; neurotoxic effects of Cd were associated with both biochemical modifications of the cell and functional change of central nervous system. Cd-induced neurotoxicity, particularly following the long-term Cd exposure, might be also caused by impaired neurogenesis leading to massive neurodegeneration. However, the exact pathophysiological mechanism has not been completely clarified and the molecular pathways involved should be fully investigated to develop new therapeutical targets. Adenosine A2A receptor (A2AR) is believed to play a crucial role in a number of physiological responses and pathological conditions. Specifically, the activation of A2AR is essential in the context of possible neuroprotective actions including facilitated synaptic plasticity and better cognitive function. Polydeoxyribonucleotide (PDRN) is the active fraction extracted from trout spermatozoa used for tissue repair and, acting through stimulation of A2AR, is able to improve the biochemical, molecular and histological picture during different pathologic conditions, as previously shown by our research lab.

In light of this background, we aimed to investigate the possible neuroprotective effect of PDRN, in a murine model of Cd-induced brain toxicity.

Male C57 BL/6J mice (n=68), weighting 25-30 g, were randomized to one of the following i.p. treatments lasting 14 days: vehicle (0,9% NaCl solution, 1 ml/kg/day), CdCl2 (2 mg/kg/day), PDRN (8 mg/kg/day), CdCl2 + PDRN. We evaluated protein expression of mammalian target of rapamycin kinase (mTOR) and Brain-derived neurotrophic factor (BDNF) in the hippocampus samples. Moreover, in order to assess spatial memory and learning, animals were tested with Morris water maze. Finally, histological analysis were carried out.

Treatment with PDRN, an agonist of adenosine A2A receptor, significantly decreased protein expression of mTOR ($p< 0,05$ versus CdCl2 plus vehicle) and increased BDNF($p< 0,05$ versus CdCl2 plus vehicle) in hippocampus following CdCl2 administration in mice. Our results also revealed that PDRN exposure significantly reduced the escape latency compared to CdCl2-challenged animals ($p< 0,01$ versus CdCl2 plus vehicle). Finally, histological analysis showed a reduction of cell damage in animals treated with PDRN, particularly in the CA1 and CA3 hippocampal areas.

Our results shown that PDRN, an agonist of adenosine A2A receptor, displays neuroprotective effects against neurotoxicity induced by Cd in mice. Moreover, in the context of translational medicine, we suggest that the A2AR pathway stimulation could represent a valuable therapeutic

strategy to minimize the risk of adverse health effects related to Cd damage in the general population.