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Cadmium induced cell death of SN56 basal forebrain cholinergic neurons mediated by oxidative stress generation

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Cadmium is a toxic compound reported to produce cognitive dysfunctions, though the mechanisms involved are unknown. In a previous work we described how cadmium blocks cholinergic transmission and induces a greater cell death in primary cholinergic neurons from the basal forebrain. It also induces cell death in SN56 cholinergic neurons from the basal forebrain partially through muscarinic 1 receptor (M1R) blockage, alterations in the expression of acetylcholinesterase (AChE) variants and glycogen synthase kinase 3 (GSK-3β), and an increase in amyloid beta (Aβ) and total and phosphorylated Tau protein levels. Moreover, all previously described mechanisms for blocking cholinergic transmission and inducing cell death on SN56 cells after cadmium exposure are partially mediated by M1R through the alteration of AChE expression suggesting other mechanism are involved. In this regard, cadmium also is able to induce reactive oxygen species (ROS) formation, which have been related with the alteration of AChE splice variants and GSK-3β gene expression, Aβ production and Tau abnormal phosphorylation that could also contribute to explain the effect observed. Accordingly, we hypothesized that cadmium induced cell death on basal forebrain cholinergic neurons is mediated by the ROS generation. To prove this hypothesis, we evaluated, in SN56 cholinergic neurons from basal forebrain region, whether cadmium induces ROS and whether this effect mediated the induced cell death observed after cadmium exposure. Our results prove that cadmium induce ROS formation and this effect leads to lipid peroxidation and finally to cell death. Thus, our results help to explain the mechanism by which cadmium induces cell death in basal forebrain cholinergic neurons and may explain cognitive dysfunctions observed in cadmium toxicity.

Recent Publications:

1. Del Pino J et al. (2016) SN56 basal forebrain cholinergic neuronal loss after acute and long-term chlorpyrifos exposure through oxidative stress generation: P75(NTR) and α7-nAChRs alterations mediated partially by AChE variants disruption. Toxicology. 353-354:48-57.
2. Del Pino J et al. (2016) Muscarinic M1 receptor partially modulates higher sensitivity to cadmium induced cell death in primary basal forebrain cholinergic neurons: a cholinesterase variants dependent mechanism. Toxicology. 361-361:1-11.
3. Del Pino J, Clements KJ, Suvorov A, Krishnan S, Adams HL, Petersen SL (2016) Developmental exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin may alter LH release patterns by abolishing sex differences in GABA/glutamate cell number and modifying the transcriptome of the male anteroventral periventricular nucleus. Neuroscience. 329:239-253.
4. Moyano P et al. (2017) Toxicogenomic profile of apoptotic and necrotic SN56 basal forebrain cholinergic neuronal loss after acute and long-term chlorpyrifos exposure. Neurotoxicology and Teratology. 59:68-73.
5. Del Pino J et al. (2017) Amitraz changes NE, DA and 5-HT biosynthesis and metabolism mediated by alterations in estradiol content in CNS of male rats. Chemosphere. 181:518-529.

Biography

Javier Del Pino received his PharmD Degree at the Complutense University of Madrid, Spain in 2004. He has two Master of Science Degrees (2009 and 2010 respectively). He has specialized in neurotoxicology and neurodevelopmental toxicology and received his PhD in Toxicology in 2009. He was an Associated Researcher at the University of Massachusetts (UMASS) working in Sandra Petersen´s Lab at National Institute of Health (NIH) project on developmental effects of TCDD endocrine disruptor on sexual differentiation for the period 2010 to 2012. In 2010 he worked at the Institute of Health Carlos III in the National Center of Environmental Health. In 2016 he got a position as Associated Professor of Toxicology at the Complutense University of Madrid, Spain.

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