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Chronic vanadium neurotoxicity: synthetic and natural product iron chelator protection in vitro

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Introduction: High concentrations of reactive iron can increase oxidative stress-induced neuronal vulnerability, and iron accumulation may exacerbate the toxicity elicited by environmental or endogenous toxins. Vanadium (an exogenous heavy metal) toxicity has been shown to be exacerbated in the presence of iron in oligodendrocyte progenitor cells [1]. It has been used at low doses in different therapeutic formulations. Environmental exposure to fumes and effluents of vanadium is very common in industries, such as metallurgical and petrochemical plants, which can have deleterious effects on human health over a long period. This study is designed to investigate the interplay/interaction of vanadium with iron in neurons and how these effects can be ameliorated using a natural plant product.We have recently shown that the plant natural product, *Aloysia citrodora palau* essential oil is a potent iron-chelator [2].

Methods: Cathecholaminergic a-differentiated (CAD) neuronal cells provides a useful tool for studying the effect of vanadium salts (in the form of sodium metavanadate) on early development using differentiated cells (6 days post serum removal). Initially, a dose-dependent effect (1-500 µM of vanadium on the viability of CAD cells was investigated for 24h or 6 days. All values are mean ± SD (4-6 replicates, n = 3 experiments).

Results: Both undifferentiated and differentiated CAD cells was insensitive to vanadium following a 24h exposure. Interestingly, at 1000 µM, while undifferentiated CAD cells shows no change in cell viability to vanadium treatments, differentiated CAD cells displayed an apparent increase in cell viability (175±24 %)**.**. In contrast, a six day exposure to vanadium elicited a profound delayed toxicity (15±5 % and 76±9 % at 200 µM and 500 µM, respectively) in differentiating neurons. The association between iron and vanadium was investigated using the synthetic iron chelator (Deferoxamine (DFO), 25, 50 and 100 µM). DFO was non-toxic over this concentration range and time-frame. DFO (10µM) significantly protected the neurons from 200 µM vanadium. This correlates with [1], but on this occasion in differentiated neurons. Treatment of differentiating CADs with *A. citrodora* (0.1mg/ml) elicited a complete neuroprotective effect against vanadium (200 µM) toxicity over a 6 day period**.**

Conclusions: These findings present a new therapeutic option for combating chronic exposure to vanadium accumulation in the body in polluted regions of the world.

1. Todorich, B. et al (2011); *Neurotoxicity research*, *19*: 361-373.

2. Abuhamdah, S. et al (2015); *J Pharm Pharmacol*, *67*:1306-1315.

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