Perspectives in Science (2015) 3, 57–58

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/pisc

EXTENDED ABSTRACT

Interactions of PD-related genes and Mn-induced neurotoxicity in *C. elegans* ☆

Julia Bornhorst[a,b,*], Sudipta Chakraborty[b,c], Sören Meyer[a], Hanna Lohren[a], Sigrid Große Brinkhaus[d], Uwe Karst[d], Tanja Schwerdtle[a], Michael Aschner[b,e]

[a]*Institute of Food Chemistry, University of Münster, Münster, Germany*
[b]*Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN, USA*
[c]*Neuroscience Graduate Program, Vanderbilt University Medical Center, Nashville, TN, USA*
[d]*Institute of Inorganic and Analytical Chemistry, University of Münster, Münster, Germany*
[e]*Department of Pharmacology, the Kennedy Center for Research on Human Development, and the Center for Molecular Toxicology, Vanderbilt University Medical Center, Nashville, TN, USA*

Received 30 July 2014; accepted 31 August 2014
Available online 3 December 2014

Although manganese (Mn) is an essential trace element, concerns are rising about the neurotoxic effects of elevated Mn exposure (environmental and occupational) in humans. Mn overexposure promotes a neuropathy resembling Parkinson's disease (PD). While only 10–20% of PD cases are documented as having genetic causes, growing evidence implicates an environmental/occupational contribution. Therefore, by using the genetically amenable *Caenorhabditis elegans* (*C. elegans*) model system, interactions between Mn and the two PD associated genes (*dj-1.1* and *pink1*) were studied to address the question: is Mn toxicity and dopaminergic (DA) neurodegeneration exacerbated in *djr-1.1* or *pink1* deletion mutants? Worms with a *djr-1.1* deletion (tm918) or *pink1* deletion (tm1779), genes that both regulate oxidative stress pathways, were utilised. The genetic deletion of either gene did not increase mortality in L1 worms acutely exposed to Mn, with an LD50 indistinguishable from wildtype (WT) worms. However, *djr-1.1* and *pink1* deletion mutants exhibited altered oxidative defence responses compared to WT worms, as confirmed by inherently decreased total glutathione (GSH) levels and increased Mn-induced reactive oxygen/nitrogen species (RONS) induction. Interestingly, the *djr-1.1* deletion mutants showed a quicker and more robust increase in RONS induction compared to WT and *pink1* deletion mutants upon exposure to Mn. This effect correlated with increased Mn bioavailability in the *djr-1.1* deletion mutants compared to WT and *pink1* worms, as confirmed by ICP-MS/MS and LA-ICP-MS.

Prominent theories on PD-associated neurodegeneration implicate changes in the expression and aggregation of α-synuclein. While *C. elegans* do not express α-synuclein, strains containing the *djr-1.1* or *pink1* deletion and transfected with the WT human α-synuclein were utilised to study the second question raised in this study: is α-synuclein expression ameliorating or exacerbating the effect of Mn toxicity and DA neurodegeneration in the respective α-synuclein (wt) containing deletion mutants? Loss of *djr-1.1* or *pink1* in these α-synuclein-containing worms resulted in a modest increase in lethality compared to worms containing α-synuclein alone. Interestingly, the loss of *djr-1.1* in these α-synuclein-containing worms resulted in reduced

☆This article is part of a special issue entitled "Tracing the elements – Diagnostic and medical importance of trace elements".

*Corresponing author at: Institute of Food Chemistry, University of Münster, Münster, Germany.
E-mail address: j_born02@uni-muenster.de (J. Bornhorst).

http://dx.doi.org/10.1016/j.pisc.2014.11.019

Mn-induced RONS induction and Mn uptake compared to worms containing the *djr-1.1* deletion alone. However, *pink1* mutants showed increased neurodegeneration that was further attenuated by α-synuclein expression, whereas *djr1.1* mutants expressing α-synuclein showed severe neurodegeneration compared to *djr1.1* mutants alone. The neuroprotective or neurotoxic role of α-synuclein seems to depend on its expression level, which has to be elucidated in further studies. Identifying the role of α-synuclein will provide novel insights into the mechanisms of Mn-induced neurotoxicity and gene by environment interactions in PD.

Conflict of interest

The authors declare that there is no conflict of interest.