

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/pisc

EXTENDED ABSTRACT

Exploring the mechanism of Mn-induced dopaminergic injury^{☆, ☆ ☆}

Katharina Fernsebner^{a,*}, Julia Zorn^b, Basem Kanawati^a,
Alesia Walker^a, Philippe Schmitt-Kopplin^{a,c}, Bernhard Michalke^a

^aHelmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Analytical Biogeochemistry, Ingolstädter Landstraße 1, D-85764 Neuherberg, Germany

^bHelmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Comparative Medicine, Ingolstädter Landstraße 1, D-85764 Neuherberg, Germany

^cTechnische Universität München, Chair of Analytical Food Chemistry, Freising-Weihenstephan, Germany

Received 30 July 2014; accepted 31 August 2014

Manganese (Mn) is an essential trace element contributing to various physiological processes like brain development, diverse metabolisms and proper function of antioxidative enzymes like Acetylcholinesterase (AChE) (Erikson et al., 2005). On the downside, overexposure to Mn can lead to the degeneration of dopaminergic neurons inducing a Parkinson-like complaint called manganism. Extensive studies have been carried out to decipher transport routes into the brain and to detect cellular mechanisms of oxidative injury in the affected brain areas (Crossgrove et al., 2003; Yokel,

2009; Yokel and Crossgrove, 2004; Aschner et al., 2007). Nevertheless, the correlation between the active Mn-species and the occurring conceivable causes of oxidative injury has not been drawn so far. The aim of this study is therefore, to elucidate the predominant Mn-species in the exposed brain and link it to levels of glutamate or GABA, AChE activity, Fe(II)/(III) status and levels of other trace elements like Cu, Fe or Zn (Figure 1).

The applied model was a feeding trial of rats, where Mn levels were elevated (500 mg/kg) in a non-toxic manner in the test group and which lasted for 53 days.

After removal of the brain, it was deep frozen and roughly homogenized. Levels of Mn, Cu, Fe and Zn were determined in the whole brain by ICP-OES or -MS. Mn levels were significantly higher in Mn-exposed (test) rats compared to normal exposed (control) rats, which was interestingly also true for Cu levels. Furthermore an aqueous extraction of the brain served as matrix for determination of AChE activity as well as glutamate and GABA levels by commercial available kits. Test rats showed significantly elevated AChE activity as well as increased glutamate levels, indicating oxidative stress in the affected brain tissue (Erikson and Aschner, 2003; Melo et al., 2003). The same brain extracts were applied for determination of the Fe(II)/(III) status by IC-ICP-OES. Interestingly, a significant shift of the Fe(II)/(III) ratio in favor of Fe(II) was observed in Mn-exposed rat brain

Abbreviations: GABA, gamma-aminobutyric acid; ICP-OES/-MS, inductively coupled plasma - optical emission spectrometry/- mass spectrometry; IC, ion chromatography; FT-ICR-MS, fourier transformed ion cyclotron resonance mass spectrometry; GSSG, glutathione disulfide; PGB1/PGH2, prostaglandins B1 and H2; 15(S)-HETE, 15S-hydroxy-5Z,8Z,11Z,13E-eicosatetraenoic acid; SEC, size exclusion chromatography; LA, laser ablation

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

^{☆☆}Part of the data have already been published in *Metallomics*, 2014. DOI: 10.1039/C4MT00022F: Manganese leads to an increase in markers of oxidative stress as well as to a shift in the ratio of Fe(II)/(III) in rat brain tissue.

*Corresponding author.

E-mail address: Katharina.Fernsebner@helmholtz-muenchen.de (K. Fernsebner).

<http://dx.doi.org/10.1016/j.pisc.2014.11.023>

2213-0209/© 2014 Published by Elsevier GmbH. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/3.0/>).

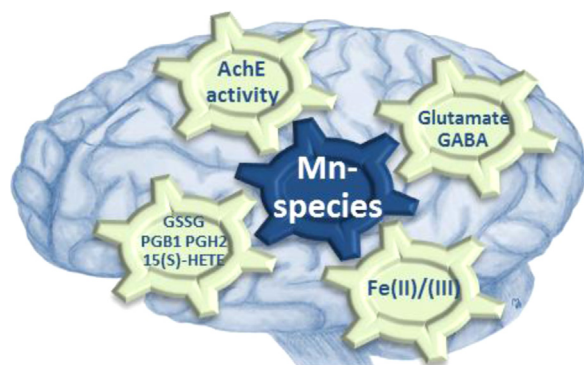


Figure 1 Aim of the study: Correlation of active Mn-species with levels of AchE activity and glutamate, with Fe(II)/(III) ratios as well as markers of oxidative stress due to Mn exposure in rats.

extracts. The increase in highly reactive Fe(II) might therefore contribute to Mn-induced neurotoxicity by facilitating oxidative stress via the Fenton reaction (Sadrzadeh and Saffari, 2004). In addition, a MeOH extraction of the brain served for FT-ICR-MS measurement for targeted analysis of markers for oxidative stress. Main differences could be observed for levels of GSSG, PGB1 and PGH2 as well as 15(S)-HETE, a marker of lipid peroxidation. These metabolites were significantly increased in test samples due to oxidative stress and inflammation in the brain.

The next step will be the correlation of these findings to the active Mn-species in the brain, which is still in progress by SEC-ICP-MS. Future work will include local distribution of Mn in the brain by LA-ICP-MS of brain sections as well as the comparison of this oral with an i.v. injected exposure to Mn.

Conflict of interest

The authors declare that there is no conflict of interest.

References

- Aschner, M., Guilarte, T.R., Schneider, J.S., Zheng, W., 2007. Manganese: recent advances in understanding its transport and neurotoxicity. *Toxicol. Appl. Pharmacol.* 221 (2), 131-147.
- Crossgrove, J.S., Allen, D.D., Bukaveckas, B.L., Rhineheimer, S.S., Yokel, R.A., 2003. Manganese distribution across the blood-brain barrier. I. Evidence for carrier-mediated influx of manganese citrate as well as manganese and manganese transferrin. *Neurotoxicology* 24 (1), 3-13.
- Erikson, K.M., Aschner, M., 2003. Manganese neurotoxicity and glutamate-GABA interaction. *Neurochem. Int.* 43 (4-5), 475-480.
- Erikson, K.M., Syversen, T., Aschner, J.L., Aschner, M., 2005. Interactions between excessive manganese exposures and dietary iron-deficiency in neurodegeneration. *Environ. Toxicol. Pharmacol.* 19 (3), 415-421.
- Melo, J.B., Agostinho, P., Oliveira, C.R., 2003. Involvement of oxidative stress in the enhancement of acetylcholinesterase activity induced by amyloid beta-peptide. *Neurosci. Res.* 45 (1), 117-127.
- Sadrzadeh, S.M., Saffari, Y., 2004. Iron and brain disorders. *Am. J. Clin. Pathol.* 121 (Suppl.), S64-S70.
- Yokel, R.A., 2009. Manganese flux across the blood-brain barrier. *Neuromol. Med.* 11 (4), 297-310.
- Yokel, R.A., Crossgrove, J.S., 2004. Manganese toxicokinetics at the blood-brain barrier. *Res. Rep. Health Eff. Inst.* 119, 7-58 (discussion 59-73).