NeuroToxicology 64 (2018) 1–4

Contents lists available at ScienceDirect

NeuroToxicology

Editorial

Neurotoxicity of manganese: Indications for future research and public health intervention from the Manganese 2016 conference

ARTICLE INFO

Keywords:
Manganese
Neurotoxicity
Brain imaging
Occupational environmental exposure
Neurodevelopmental effects
Developmental origins of adult disease
Neurodegenerative effects

ABSTRACT

Manganese is an essential trace element, but also at high levels a neurotoxicant. Manganese neurotoxicity has been extensively studied since its discovery in highly exposed workers. The International conference MANGANESE2016 held at the Icahn School of Medicine at Mount Sinai in New York provided relevant updates on manganese research in relation to both occupational and environmental exposures. Epidemiological, toxicological and cellular studies reported at the conference have yielded new insights on mechanisms of manganese toxicity and on opportunities for preventive intervention. Strong evidence now exists for causal associations between manganese and both neurodevelopmental and neurodegenerative disorders. The neurodevelopmental effects of early life exposures are an example of the developmental origin of health and disease (DOHAD) concept. Brain imaging has rapidly become an important tool for examining brain areas impacted by manganese at various life stages. Candidate biomarkers of exposure are being identified in hair, nails, and teeth and reflect different exposure windows and relate to different health outcomes. Sex differences were reported in several studies, suggesting that women are more susceptible. New evidence indicates that the transporter genes SLC30A10 and SLC39A8 influence both manganese homeostasis and toxicity. New potential chelation modalities are being developed.

1. The Manganese 2016 international conference

On September 25–28, 2016, the Icahn School of Medicine at Mount Sinai convened the 28th International Neurotoxicology Conference – Manganese Health Effects on Neurodevelopment and Neurodegenerative Diseases – in New York City. More than 150 scientists and physicians attended the conference and additionally more than 250 viewers from 20 countries, including Sri Lanka, Egypt, and Peru watched the conference in real time via webcast. The conference was also the Second International Conference on the neurotoxicity and prevention of adverse manganese health effects, after the previous conference that took place in Little Rock, AR on October 26–29, 1997 (for selected papers see JM Cranmer et al. (Cranmer et al., 1999)). Manganese is an essential trace element that is abundantly present in the brain. Despite its importance in normal brain functions, excess manganese is neurotoxic and causes neurodegeneration and neurodevelopmental effects. One of the most used metals in many industrial, agricultural applications, and in transportation as gasoline additive, manganese is increasingly present in the environment, due to anthropogenic sources (Herndon et al., 2011). This special volume of NeuroToxicology includes original research articles, perspectives and reviews on various aspects of manganese neurotoxicity from academic and governmental scientists who are leading experts in the field. The papers deal with molecular, cellular, genetic and epidemiological data, the latter focusing predominantly on recent advances in occupational exposures and environmental exposures, both in adults and children. The articles span a range of mechanisms, stretching from the effects of manganese on transcription factors, inflammatory processes and energy generation, to its neurodevelopmental effects in children and motor deficits among workers and the general population.

The newly compiled volume attests to the tremendous strides in the understanding of the essentiality and neurotoxic effects of manganese, imparting new information on relationships between exposure and causality and mechanistic events leading to clinical disease.

We assembled a series of papers/reviews that advance the latest developments and scientific breakthroughs in this fast-paced research area, and provide information that should be of interest to risk assessors, neurobiologists, clinicians and neurotoxicologists. We are hopeful that this volume of NeuroToxicology will offer the reader appreciation and renewed sense on contemporary issues in this topic. We are also truly indebted to the authors for their contributions, and hope that as a reader, whether you are novice or a seasoned expert in the topic, the knowledge amassed herein will stimulate and transform your thinking on this contemporary health issue.

https://doi.org/10.1016/j.neuro.2018.01.002
0161-813X/

2. Scientific advances reported at the conference

New data were presented at the conference on various topics including: i) the environmental and occupational sources of manganese; ii) routes of human exposure; iii) developmental neurotoxicity; iv) the contribution of manganese to neurodegenerative diseases; v) biochemical and genetic mechanisms of toxicity and susceptibility; vi) risk assessment and protective standards as opportunities for disease prevention; vii) chelation modalities for Mn. Ongoing prospective epidemiologic studies and new toxicological investigations were reviewed. It was noted that much progress had been made in understanding the toxicology and epidemiology of manganese since the last international conference on manganese convened at the University of Brescia in Italy in 2006 (Landrigan et al., 2007), and earlier, since the first International Conference on Manganese in Little Rock, USA, in 1997. Prospective epidemiological studies that follow exposed persons longitudinally over many years and cross-disciplinary investigations that combine epidemiology, toxicology, genetics and epigenetics were particularly important drivers of this scientific progress.

2.1. Occupational exposure

Paul Blanc presented an accurate historical reconstruction of the biomedical recognition of manganese-caused neurotoxicity as mirroring changing technologies throughout the world, and starting from the initial reports in the 19th century. Despite the scientific evidence on Mn intoxication, exposure remained uncontrolled for more than a century (Blanc, 2017). Still today, data from OSHA's inspections in the US presented at the conference showed a 3.3% of air measurements higher than 1 mg/m^3, and 0.4% even higher than the current PEL of 5 mg/m^3. According to a WHO document, clinical intoxication has been described starting from the concentration of 1 mg/m^3 (WHO, 1981). The Unified Parkinson Disease Rating Scale motor subsection part 3 (UPDRS3) was identified by Racette et al. (Racette et al., 2018) as a simple test to help non-neurologists identify workers with clinical Mn neurotoxicity. The same group has shown also that cumulative exposure to Mn-containing welding fume may cause a dose-dependent progression of parkinsonism as measured with UPDRS3, especially upper limb bradykinesia, limb rigidity, and impairment of speech and facial expression (Racette et al., 2017).

2.2. Brain imaging studies

Several imaging studies focused on occupationally exposed workers, crossing observations with UPDRS scale and exposure assessment. Criswell et al. (Criswell et al., 2018) used 6-[18F] fluoro-L-DOPA PET on Mn-exposed welders and workers and demonstrated lower caudate FDOPA uptake, indicating pre synaptic dopaminergic dysfunction in Mn-exposed subjects that was not associated with clinical parkinsonism. Magnetic Resonance Spectroscopy (MRS) was used to measure γ-amminobutyric acid (GABA), and thalamic GABA levels and motor function displayed a non-linear pattern of response to Mn exposure among welders, suggesting a threshold effect (Ma et al., 2018). Striatal and thalamic GABA did not differ between Mn-exposed workers, Parkinsonian patients or hemochromatosis patients, and controls (Casjens et al., 2018). This may be due to the low exposure levels of the Mn-exposed workers and the challenges to detect small changes in GABA. Blood Mn and serum ferritin were observed as significant predictors of R1 relaxation rate at MRU, indicative of metal accumulation, especially in the globus pallidus (Casjens et al., 2018). Presynaptic dopamine transporter (DAT) positron emission tomography (PET) used in cirrhotic patients with concurrent parkinsonism showed different imaging patterns indicating cirrhosis-related parkinsonism as a heterogeneous disorder (Yang et al., 2018). In a resting state functional magnetic resonance imaging (fMRI) study the right globus pallidus showed reduced intrinsic functional connectivity with the dorsal anterior cingulate cortex and lateral prefrontal cortex, in children who were exposed to higher prenatal Mn levels (de Water et al., 2018).

2.3. Developmental neurotoxicity

In children, evidence from recent epidemiological studies suggests that exposure to manganese in early life causes subclinical developmental neurotoxicity. A community study showed impairment of full scale IQ associated with hair Mn in children residing in the vicinity of a ferroalloy plant in the USA (Haynes et al., 2018). In the same community, tremor and motor symptoms and executive dysfunctions were presented among adult residents (Kornblith et al., 2018). Manganese in hair and toenails reflected Mn exposure from drinking water in southeastern New Brunswick, Canada (Ntihabose et al., 2018). In a longitudinal assessment in this area, higher levels of Mn in drinking water, but not hair Mn, were associated with lower Performance IQ in girls, whereas the opposite was observed in boys (Dion et al., 2018). Evidence of sex-specific neurodevelopmental effects of Mn were presented at the conference also for motor functions (Chiu et al., 2017), visuospatial ability (Bauer et al., 2017). Teeth Mn reflecting early life exposure resulted a significant predictor for the same motor functions (Chiu et al., 2017) and visuospatial ability (Bauer et al., 2017), and Mn concentrations in dentine was influenced by common SNPs of Mn transporter genes SLC30A10 and SLC39A8, with sex differences (Wahlberg et al., 2018). Finally, coexposure to Mn and depression during pregnancy was shown as having an impact on developmental Bayley scores among the children at 24 months of age (Munoz-Rocha et al., 2018).

2.4. Experimental studies

The MANGANESE2016 addresses several novel findings on the pathophysiology of Mn, focusing on its mechanisms of neurotoxicity. Several studies addressed signaling pathways that modulate Mn-homeostasis and the resultant neuroinflammatory response. Bryan and colleagues established a role for phosphatidylinositol 3 kinase (PI3K) in modulating Mn homeostasis in a striatal cell line (Bryan et al., 2018), while Yin et al. suggested Mn triggers the microglial JAK2-STAT3 pathway, in turn, leading to neuroinflammatory responses (Yin et al., 2018). That Mn causes proinflammatory events was also established in astrocytes, concomitant with altered mitochondrial bioenergetics (Sarkar et al., 2018). Li et al. corroborated increased inflammatory cytokines and COX-2 transcription levels concomitant with increased MAPK signaling and COX-2 in response to *in vivo* rodent model with sub-chronic Mn exposure, further suggesting (sodium P-aminosalicylic acid) PAS-Na treatment may reverse these effects along with the Mn-induced learning and memory deficits (Li et al., 2018). Another potential treatment for excessive Mn exposure was discussed by Johnson et al., suggesting valproate and sodium butyrate reverses Mn-induced dysfunction of astrocytic glutamate transporter GLT-1 expression and locomotor deficiencies in mice (Johnson et al., 2018). The role of mitochondria in Mn-induced neurotoxicity was also advanced by Langley and collaborators. Taking advantage of a newly available mitochondrially defective transgenic mouse model of Parkinson's disease (PD), the MitoPark mouse, this group corroborates gene environment interactions associated with mitochondrial defects in the nigral dopaminergic system (Langley

et al., 2018). Loss of ATP13A2 function in ATP13A2-deficient mice is also shown as a risk factor for increased sensitivity to Mn *in vivo* (Fleming et al., 2018). Harischandra et al. addressed the role of Mn in modulating extracellular miRNA content through exosomal release from dopaminergic neurons, establishing that Mn treatment in α-synuclein-expressing cells increases the protein Rab27a, the latter regulating exosome release from cells (Harischandra et al., 2018). Additional genetic factors that contribute to manganism were highlighted, alluding to the role of mutations in SLC30A10 and SLC39A14 in maintaining Mn homeostasis (Mukhopadhyay, 2018). And finally, Foster et al. described a nasal instillation model that is useful in assessing Mn-induced olfactory deficits (Foster et al., 2018).

2.5. Risk assessment and intervention

The need to revise both the OSHA and NIOSH standards in the USA was indicated as an urgent necessity for a more adequate protection of workers' health especially in a lifetime perspective. Par and Berg presented a preliminary risk assessment by US-NIOSH indicating exposures causing 1% increase of neurological impairment over five years, corresponding to 10 $\mu g/m^3$ $\mu g/m^3$ for Mn fumes (<0.1 μm in diameter) and 25 $\mu g/m^3$ for Mn in larger particles (>0.1 μm) (Park and Berg, 2018). An alternative analysis was presented, showing a possible Occupational Exposure Levels for welders of 100–140 $\mu g/m^3$ (Bailey et al., 2018). An overview of the scientific data and models for Mn risk assessment was presented as generated by EPA with the Clean Air Act, section 211 (b) testing rule, in response to the concern cause by the proposed use of methylcyclopentadienyl Mn tricarbonyl (MMT) as an octane-enhancing gasoline fuel additive (Smith et al., 2018). Results of an Environmental Management program in the large Mn deposit of Hidalgo, Mexico were presented, showing a reduction of Mn concentration in PM10 and PM2.5 by 92% and 85% respectively (Cortez-Lugo et al., 2018).

3. Emerging needs for future research

Despite these important advances in scientific knowledge, it was noted in the conference that serious overexposures to manganese continue to occur in many countries and that there are large gaps in strategies for prevention of manganese toxicity. Prevention has lagged behind science. Particularly important gaps in prevention identified by conference participants are the following:

- There is no established health-based global standard for the level of manganese permitted in drinking water, despite the fact that water is the principal route of manganese exposure for pregnant women and young children.
- Occupational exposure standards for manganese in many countries do not fully reflect current scientific knowledge of manganese toxicity, and are not sufficiently stringent to protect the health of adult workers or the neurobehavioral development of the unborn children of pregnant women workers.
- Despite grave concerns expressed ten years ago at the Brescia conference about health hazards resulting from the addition of organic manganese compounds such as MMT to gasoline, these highly neurotoxic compounds continue today to be added to gasoline in a number of countries.

In response to the new scientific findings on manganese presented at the conference and to address the gaps identified in public health protection, we have developed the following recommendations to advance manganese research and to strengthen public health protection.

1. Welders need adequate protection against potential neurodegenerative effects of long term and cumulative Mn exposure. Imaging research combined with neuropsychological assessment, accurate environmental exposure metrics, and biomarkers is keen to understanding mechanisms of toxicity and to allow identification of dose-response relationship suitable for risk assessment. Further validation studies are needed to verify whether nails can be a reliable biomarker for this type of exposure.
2. Research on Mn biomarkers needs to be enhanced, to understand what type of exposure and what exposure window can be better reflected by each candidate biomarkers, including hair, nails, saliva, blood and urine. Studies in children and adults suggest that some specificity of biomarkers also for different neuropsychological functions, at different developmental and age stages.
3. Genetic studies on the manganese transporters such as SLC30A10 and SLC39A8 need further extension to elucidate the mechanisms of potential influence on both neurodevelopmental and neurodegenerative effects. Common SNPs from these genes should be included in the studies at higher exposure, targeting occupational settings like welding.
4. Studies on Mn research need to include sex-based analysis, and new in-depth studies are needed to further explore the gender differences observed in humans. Further protections may be needed for women both in the general environment and in the workplace.
5. Co-exposure of Mn with other elements and pollutants requires a mixed-exposure approach both in the study design and analysis. Different statistical models should be compared for a more accurate assessment of health impacts and risk assessment based on multiple hazards and stressors.
6. The toxicodynamics of this essential element include a slow excretion rate from the brain and the body, and potential long-term accumulation. This is why Mn can link neurodevelopmental and neurodegenerative impacts as a prototype pollutant for the developmental origins of health and diseases (Heindel et al., 2015). Therefore, studies on lifetime approach to cumulative Mn exposure should integrate early and adult life, community and workplace exposure, within an exposomic conceptual approach.

Acknowledgments

Financial support for the Manganese 2016 Conference was provided by the Department of Environmental Medicine and Public Health at the Icahn School of Medicine at Mount Sinai, the National Institute of Environmental Health Sciences (R13ES027342), the U.S. Environmental Protection Agency (X3-83678101-0), the National Institute of Neurological Disorders and Stroke (R13ES027342), the International Manganese Institute, Charles River Laboratories, the International Commission on Occupational Health, the Society of Toxicology, Elsevier, and Drs. Morris and Joan Cranmer. In-kind support was provided by the Centre national du cinema (Paris) and the Royal Society of Chemistry.

The conference was convened at the Icahn School of Medicine at Mount Sinai with organizing support from the Department of Environmental Medicine and Public Health, Division of Occupational and Environmental Medicine, and Selikoff Centers for Occupational Health.

Special thanks to the International Advisory Committee: Roberto Lucchini, MD, Icahn School of Medicine at Mount Sinai, USA (Chair); Joan M. Cranmer, PhD, ATS, University of Arkansas for Medical Sciences, USA (Co-Chair); Kent Anger, PhD, Oregon

Institute of Occupational Health Services, USA; Michael Aschner, PhD, Albert Einstein College of Medicine, USA; Paul Blanc, MD, MSPH, University of California San Francisco, USA; Rosemarie M. Bowler, PhD, MPH, San Francisco State University, USA; William Boyes, PhD, Environmental Protection Agency, USA; Karin Broberg, PhD; Karolinska Institutet, Sweden; Lucio G. Costa, PharmD, University of Washington, USA; Dag Ellingsen, PhD, National Institute of Occupational Health, Norway; Tomás R. Guilarte, PhD, Florida International University, USA; Erin N. Haynes, DrPH, MS, University of Cincinnati, USA; Yangho Kim, MD, PhD, MPH, Ulsan University Hospital, South Korea; Philip J. Landrigan, MD, MSc, Icahn School of Medicine at Mount Sinai, USA; Ana Maria Mora, MD, PhD, Universidad Nacional, Costa Rica; José Antonio Menezes Filho, PhD, Universidade Federal da Bahia, Brazil; Donna Mergler, PhD, Université du Québec à Montréal, Canada; Gill Nelson, PhD, University of Witwatersrand, South Africa; Brad Racette, MD, Washington University in St. Louis, USA; Harry A. Roels, PhD, MSc, Université catholique de Louvain, Belgium; Donald Smith, PhD, University of California Santa Cruz, USA; Anne Tremblay, ABD, International Manganese Institute, France; Christoph van Thriel, PhD, Leibniz Research Centre for Working Environment, Germany; and Robert O. Wright, MD, MPH, Icahn School of Medicine at Mount Sinai, USA.

Special thanks also to the Carla Azar and Renu Nadkarni, MPH for their organizing support.

References

Bailey, L.A., Kerper, L.E., Goodman, J.E., 2018. Derivation of an occupational exposure level for manganese in welding fumes. Neurotoxicology 64, 166–176.
Bauer, J.A., et al., 2017. Manganese in teeth and neurobehavior: sex-specific windows of susceptibility. Environ. Int. 108, 299–308.
Blanc, P.D., 2017. The early history of manganese and the recognition of its neurotoxicity, 1837–1936. Neurotoxicology .
Bryan, M.R., et al., 2018. Phosphatidylinositol 3 kinase (PI3K) modulates manganese homeostasis and manganese-induced cell signaling in a murine striatal cell line. Neurotoxicology 64, 185–194.
Casjens, S., et al., 2018. Association of exposure to manganese and iron with striatal and thalamic GABA and other neurometabolites – neuroimaging results from the WELDOX II study. Neurotoxicology 64, 60–67.
Chiu, Y.H., et al., 2017. Sex differences in sensitivity to prenatal and early childhood manganese exposure on neuromotor function in adolescents. Environ. Res. 159, 458–465.
Cortez-Lugo, M., et al., 2018. Evaluation of the effect of an environmental management program on exposure to manganese in a mining zone in Mexico. Neurotoxicology 64, 142–151.
Cranmer, J., Mergler, D., Williams-Johnson, M., 1999. Manganese. Neurotoxicology 20 (2–3) .
Criswell, S.R., et al., 2018. [18F]FDOPA positron emission tomography in manganese-exposed workers. Neurotoxicology 64, 43–49.
de Water, E., et al., 2018. Prenatal manganese exposure and intrinsic functional connectivity of emotional brain areas in children. Neurotoxicology 64, 85–93.
Dion, L.A., et al., 2018. Changes in water manganese levels and longitudinal assessment of intellectual function in children exposed through drinking water. Neurotoxicology 64, 118–125.
Fleming, S.M., et al., 2018. The effect of manganese exposure in Atp13a2-deficient mice. Neurotoxicology 64, 256–266.
Foster, M.L., et al., 2018. Olfactory toxicity in rats following manganese chloride nasal instillation: a pilot study. Neurotoxicology 64, 284–290.
Harischandra, D.S., et al., 2018. Environmental neurotoxicant manganese regulates exosome-mediated extracellular miRNAs in cell culture model of Parkinson's disease: relevance to alpha-synuclein misfolding in metal neurotoxicity. Neurotoxicology 64, 267–277.
Haynes, E.N., et al., 2018. Impact of air manganese on child neurodevelopment in East Liverpool, Ohio. Neurotoxicology 64, 94–102.
Heindel, J.J., et al., 2015. Developmental origins of health and disease: integrating environmental influences. Endocrinology 156 (10), 3416–3421.
Herndon, E.M., Jin, L., Brantley, S.L., 2011. Soils reveal widespread manganese enrichment from industrial inputs. Environ. Sci. Technol. 45 (1), 241–247.
Johnson Jr., J., et al., 2018. Valproate and sodium butyrate attenuate manganese-decreased locomotor activity and astrocytic glutamate transporters expression in mice. Neurotoxicology 64, 230–239.
Kornblith, E.S., et al., 2018. Environmental exposure to manganese in air: tremor, motor and cognitive symptom profiles. Neurotoxicology 64, 152–158.
Landrigan, P., et al., 2007. The Declaration of Brescia on prevention of the neurotoxicity of metals June 18, 2006. Am. J. Ind. Med. 50 (10), 709–711.
Langley, M.R., et al., 2018. Manganese exposure exacerbates progressive motor deficits and neurodegeneration in the MitoPark mouse model of Parkinson's disease: relevance to gene and environment interactions in metal neurotoxicity. Neurotoxicology 64, 240–255.
Li, S.J., et al., 2018. Sodium *P*-aminosalicylic acid inhibits sub-chronic manganese-induced neuroinflammation in rats by modulating MAPK and COX-2. Neurotoxicology 64, 219–229.
Ma, R.E., et al., 2018. Thalamic GABA: levels and occupational manganese neurotoxicity: association with exposure levels and brain MRI. Neurotoxicology 64, 30–42.
Mukhopadhyay, S., 2018. Familial manganese-induced neurotoxicity due to mutations in SLC30A10 or SLC39A14. Neurotoxicology 64, 278–283.
Munoz-Rocha, T.V., et al., 2018. Prenatal co-exposure to manganese and depression and 24-months neurodevelopment. Neurotoxicology 64, 134–141.
Ntihabose, R., et al., 2018. Assessment of saliva, hair and toenails as biomarkers of low level exposure to manganese from drinking water in children. Neurotoxicology 64, 126–133.
Park, R.M., Berg, S.L., 2018. Manganese and neurobehavioral impairment. A preliminary risk assessment. Neurotoxicology 64, 159–165.
Racette, B.A., et al., 2017. Dose-dependent progression of Parkinsonism in manganese-exposed welders. Neurology 88 (4), 344–351.
Racette, B.A., et al., 2018. A screening tool to detect clinical manganese neurotoxicity. Neurotoxicology 64, 12–18.
Sarkar, S., et al., 2018. Manganese exposure induces neuroinflammation by impairing mitochondrial dynamics in astrocytes. Neurotoxicology 64, 204–218.
Smith, D., et al., 2018. Manganese testing under a clean air act test rule and the application of resultant data in risk assessments. Neurotoxicology 64, 177–184.
WHO, 1981. Geneva: World Health OrganizationManganese. IPCS International Programme on Chemical Safety, Vol. Environmental Health Criteria 17. .
Wahlberg, K., et al., 2018. Polymorphisms in manganese transporters show developmental stage and sex specific associations with manganese concentrations in primary teeth. Neurotoxicology 64, 103–109.
Yang, H.J., et al., 2018. 18F-FP-CIT dopamine transporter PET findings in cirrhotic patients with Parkinsonism. Neurotoxicology 64, 78–84.
Yin, L., et al., 2018. Manganese exposure facilitates microglial JAK2-STAT3 signaling and consequent secretion of TNF-a and IL-1beta to promote neuronal death. Neurotoxicology 64, 195–203.

Roberto G. Lucchini[a,b]
[a]*Icahn School of Medicine at Mount Sinai, New York, USA*

[b]*University of Brescia, Italy*

Michael Aschner
Albert Einstein College of Medicine, Bronx, New York, USA

Philip J. Landrigan
Icahn School of Medicine at Mount Sinai, New York, USA

Joan M. Cranmer
University of Arkansas for Medical Sciences, Little Rock, AR, USA