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