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Review about the manganese speciation project related to neurodegeneration: An analytical chemistry approach to increase the knowledge about manganese related parkinsonian symptoms

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ABSTRACT

Neurodegenerative diseases get a growing relevance for societies. But yet the complex multi-factorial mechanisms of these diseases are not fully understood, although it is well accepted that metal ions may play a crucial role. Manganese (Mn) is a transition metal which has essential biochemical functions but from occupational exposure scenarios it appeared that Mn can cause severe neurological damage. This "two-faces"-nature of manganese initiated us to start a project on Mn-speciation, since different element species are known to exhibit different impacts on health. A summary about the step-wise developments and findings from our working group was presented during the annual conference of the German trace element society in 2015.

This paper summarizes now the contribution to this conference. It is intended to provide a complete picture of the so far evolved puzzle from our studies regarding manganese, manganese speciation and metabolomics as well as Mn-related mechanisms of neural damage. Doing so, the results of the single studies are now summarized in a connected way and thus their interrelationships are demonstrated. In short terms, we found that Mn-exposure leads to an increase of low molecular weight Mn compounds, above all Mn-citrate complex, which gets even enriched across neural barriers (NB). At a Mn serum concentration between 1.5 and 1.9 μg/L a carrier switch from Mn-transferrin to Mn-citrate was observed. We concluded that the Mn-citrate complex is *that* important Mn-carrier to NB which can be found also beyond NB in human cerebrospinal fluid (CSF) or brain of exposed rats. In brain of Mn-exposed rats manganese leads to a decreased iron (Fe) concentration, to a shift from Fe(III) to Fe(II) after long term exposure and thus to a shift toward oxidative stress. This was additionally supported by an increase of markers for oxidative stress, inflammation or lipid peroxidation at increased Mn concentration in brain extracts. Furthermore, glutamate and acetylcholineesterase were elevated and many metabolite concentrations were significantly changed.

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Abbreviations: AD, Alzheimer disease; CSF, cerebrospinal fluid; CE, capillary electrophoresis; CZE, capillary zone electrophoresis; DMT-1, divalent metal transporter 1; DRC, dynamic reaction cell; ESI-FT-ICR-MS, electrospray ionization—Fourier transform ion cyclotron resonance—mass spectrometry; Fe(S), total Fe in serum; Fe-Tf(S), Fe-transferrin in serum; Fe-Cit(S), Fe-citrate in serum; GPx, glutathione peroxidase; IC, ion chromatography; ICP-MS, inductively coupled plasma mass spectrometry; ICP-OES, inductively coupled plasma optical emission spectrometry; IEC, ion exchange chromatography; MMT, methylcyclopentadienyl-manganese-tricarbonyle; HMM, high molecular mass; LMM, low molecular mass; MCT, monocarboxylate transporter; Mn(C), total Mn concentration in cerebrospinal fluid; Mn-Cit(S), Mn-citrate in serum; MRI, magnetic resonance imaging; Mn(S), total Mn concentration in serum; Mn-Tf(S), Mn-transferrin in serum; NB, neural barriers; PD, Parkinson disease; ROS, reactive oxygen species; SEC, size exclusion chromatography; SOD, superoxide dismutase; Tf, transferrin; Tf-R, transferrin-receptor.

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1. Introduction—background of the Mn speciation project

Today, neurodegenerative diseases like Alzheimer's disease (AD) and Parkinson's disease (PD) are gaining increasing relevance in our aging society. However, the complex multi-factorial mechanisms of these diseases are yet not sufficiently understood [1–3]. Metal ions, specifically chronic or excessive Manganese (Mn) exposure is a cause of severe neurological dysfunction although Mn is an element of janiform nature: It is an essential micronutrient required for normal physiological processes in mammals. Particularly, it plays important roles as a cofactor for a series of enzymes including Mn-dependent superoxide dismutase [2], which are crucial for antioxidant defence, energy metabolism, immune function, reproduction, brain function, or DNA repair [4–6]. However, already since 1837 toxic neurological health effects of Mn are known. The most severe one is called manganism and was first described by James Couper in 1837. He observed paraplegia in the lower extremities of Scottish MnO_2-ore grinding workers [7]. Since then it has been explored that elevated levels of Mn may cause damage of the central nervous system with symptoms such as adynamia/fatigability, sialorrhea, cephalalgia, sleep disturbances, muscular pain and hypertonia, masklike face, gait changes, reduced coordination, hallucinations, and mental irritability [8]. These detrimental health effects are presumably induced by oxidative stress, with inhalation being the primary route of concern for occupational health effects. Several of the above mentioned health effects are similar to symptoms of Parkinsonism (PD).

Exposure scenarios from occupational health are known for miners, industrial steel workers or welders. Symptoms of manganism were found for *some* of the exposed individuals, but even more alarming, for the *whole group* an increased prevalence for PD was reported. First concern about additional manifestation of Mn neurotoxicity other than manganism was raised by a study from Racette et al. [9], reporting that in 953 cases the age at PD diagnosis was 17 years earlier in career welders than in non-welders. Nowadays, Mn neurotoxicity is becoming of great public health concern due to diverse factors affecting even a broader range of population [10].

For example it is reported that population living in the surroundings of big industrial vicinities or living close to highly-frequented traffic routes with Mn containing car exhaust from methylcyclopentadienyl-manganese-tricarbonyle (MMT) charged fuel probably is at risk [11,12]. The group around Lucchini had extensively studied the population and PD prevalence around the big ferroalloy plant in the province of Brescia, Italy, which were operating until 2001 [13]. Their results showed that an environmental exposure to Mn was associated with an increased prevalence of PD disturbances. Such chronic exposures may progressively extend the site of Mn deposition and toxicity from the globus pallidus to the entire area of the basal ganglia, including the substantia nigra pars compacta, involved in PD [14].

Based on these recent epidemiologic studies, Lucchini et al. developed the concept of lifetime Mn exposure with the hypothesis of an increased risk of Parkinsonian disturbances, where lifetime exposure to low Mn levels, starting from prenatal to older age, may be a risk factor for Parkinsonism.

Another epidemiological study investigated associations between PD and exposure to industrial emissions of Mn as well as vehicle exhaust due to the use of MMT added to gasoline since 1976 [11]. From these findings Finkelstein et al. [11] concluded that ambient Mn exposure lowers the age of PD diagnosis, suggesting that Mn exposure amplifies the natural loss of neurons caused by aging process. Overall, Finkelstein et al. [11] conclusions were in line with Lucchiniís hypothesis [14] of an increased risk of Parkinsonian disturbances after lifetime Mn exposure.

The janiform nature of manganese—its' essential or potentially detrimental role—prompted us to investigate Mn speciation in human serum, CSF and rat brain extracts after exposure, since different Mn compounds might be metabolized or transported by different pathways, and by that way causing opposing health effects.

The absorption of inhaled Mn is high and it is well accepted that Mn is transported to the liver, where it is metabolized and the newly formed Mn species get transported with blood to brain. In literature transferrin (Tf) was supposed to be a plasma Mn-carrier for physiological condition, and a well-controlled transferrin-receptor (Tf-R) mediated Mn transport across the NB is known. However, under Mn exposure, different Mn species seem to cross the NB independently from Tf-R. These different Mn compounds appear in CSF. The first question in our project therefore related to Mn-speciation at NB, because these Mn-compounds are key-metabolites which had to be addressed according to differences in transport of Mn to the brain under varying conditions [15].

The second question relates to the neurotoxic mechanism of Mn on the cellular level, which is still unclear. Common explanations comprise reactive oxygen species (ROS) generation: Reasons for ROS production were discussed regarding the various oxidation states of Mn, or its affinity to mitochondria connected to energy supply depletion in neurons, or by disturbance of cellular iron and calcium homeostasis [16]. But also Mn-related DNA damage in neurons may cause neurodegenerative effects, since Mn(II) has been reported to substantially decrease the fidelity of DNA replication and it has been shown that in intact human cells Mn(II) reduces the extent of poly(ADP-ribosyl) ation stimulated by H_2O_2 at low, non-cytotoxic concentrations. It is important to know that poly(ADP-ribosyl) ation is considered as a DNA-repair system which occurs as one of the first nuclear events shortly after

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