Reviewer’s report

Title: Role of astrocytes in manganese mediated neurotoxicity

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Reviewer: Claudia Zwingmann

Reviewer’s report:

This is an excellent review on the role of astrocytes in Mn neurotoxicity. It is very well and in a rational manner written, and an extensive list of literature is given. I have a few comments, and some very important issues are missing in the review.

Introduction and Chapter 2.1

Among different effects of Mn in the CNS, it should be discussed better why it can cause an oxidative stress. This in particular as to the depletion of glutathione. In this regard, it could have an effect in the liver as well, which might result in a compromised hepatocellular function with consequent secondary effects on the brain. Furthermore, astrocytes contain might amounts of hypotaurine, and its possible role as an antioxidant (oxidation to taurine in the neurons) might be interesting to include.

Chapter 2.1

It is not true that neurons lack the capacity to synthesize glutamate from glucose. There is a huge controversy as to the relative contribution of glial and neuronal oxidative metabolism, but it is clear now that neurons can oxidize glucose in the Krebs cycle. What is true is that pyruvate carboxylase is an astrocyte-specific enzyme and contributes to the replenishment of Krebs cycle intermediates. Because of the involvement of Mn to the activity of PC and its important role for anaplerosis and glutamate replenishment, a paragraph discussing PC should be essential in Chapter 2.1, e.g. when discussing the synthesis of glutamine. In general, the role of Mn for PC and glutamine synthetase, and the consequences for neurotransmission, should be discussed in much more detail.

The effect of Mn on astrocytic pathology should also be discussed as this is an important point. This includes the relative effect on astrocyte swelling and the appearance of Alzheimer type II astrocytosis, which are observed in patients, animal models and cell culture.

Both pathological changes in astrocytes by Mn may represent an important aspect of manganese neurotoxicity. In this regard it also may be a factor in low-grade brain edema associated with chronic hepatic encephalopathy (HE), in addition to ammonia. Astrocyte swelling and Alzheimer type II astrocytosis are also observed in HE. It will be important to include the role of Mn in HE, also considering the effects of ammonia on neuron-glia metabolic shuttles and neurotransmission.
Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I have no competing interests.