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Importance of Mitochondria in Manganese-Induced Cellular Toxicity:

Response to Letter by Gunter et al., The Case for Manganese Interaction with Mitochondria, *NeuroToxicology*

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Dear Editor:

Gunter et al. may have mixed the concepts of the subcellular distribution with the end point of cellular toxicity. In our discussion, we have explicitly pointed out that “a relatively small amount of Mn in the mitochondrial fraction as demonstrated by this and Morello’s work should not rule out the importance of mitochondria in Mn-induced cytotoxicity, as the structural and functional integrity of mitochondria is pivotal to the cell survival.” In fact, our own studies have found that Mn exposure inhibits mitochondrial [Fe-S] containing enzymes including aconitase and Complex-I (Zheng et al., 1998; Chen et al., 2001). Detrimental effect of Mn on mitochondria notwithstanding, our finding on less than 0.5% of cellular ⁵⁴Mn recovered from the mitochondrial fraction is indeed surprising, yet reflecting the experimental outcomes.

As to the “high concentration” of Mn (100 μM) used in our study, we had read, prior to our experimentation, the comment made by Gunter et al., 2006, quoted as “Based on published data from tissue Mn measurements and observation of symptoms in monkeys, taken after weekly injections of Mn at a range of doses over a period of months, the threshold for clinical signs of toxicity was around 100 μM in globus pallidus and stratum and increase in both severity and frequency with concentration above that level” (page 1824). The Mn concentration in our report was so justified as taking into consideration this and other reports.

We wish to point out that the presence of suggested “redistribution of Mn²⁺” in the fractionation study bespeaks the fact that Mn ions may in fact loosely bind to the mitochondrial components. Hence, the minuscule amount of Mn in mitochondria is deemed to be insignificant with regards to the overall subcellular storage of Mn.

Respectfully,

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