

Abstract No. Chan0220

Neuronal Studies of Manganese Toxicity

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Beamline(s): X9B

The toxicological effects of Mn are primarily caused by damage to the striatum and to the globus pallidus. This damage has been hypothesized to be caused by oxidation of dopamine by Mn^{3+} , produced by oxidation of Mn^{2+} by superoxide radical; however, the amount of Mn^{3+} in the neurons of striatum and globus pallidus have never been determined. In addition, there are alternative hypotheses describing how damage could be caused by Mn^{2+} . Once inside neurons within these brain areas, most of the Mn is sequestered by mitochondria. By comparing the XANES spectra of intramitochondrial manganese and intraneuronal manganese with spectra of specific manganese model compounds, we are currently studying the speciation of manganese within these biological systems. XANES has the sensitivity to study concentrations of pathological interest within the cells and concentrations of both physiological and pathological interest in the mitochondria. We have used curve fitting techniques to show that: 1) In brain, heart, and liver mitochondria all of the intramitochondrial Mn is in the 2+ form except perhaps for a small fraction of the endogenous Mn. 2) Almost all of the Mn present in mitochondria can be accounted for by Mn(II) ATP and Mn(II) Hpi complexes. 3) A small fraction of the endogenous Mn may be in the 3+ form and is probably in the Mn superoxide dismutase complex. 4) There is no difference between the XANES spectra of Mn in brain, heart, and liver mitochondria.

We are currently working on Mn in PC12 cells, PC12 cells induced to become more neuron-like by nerve growth factor, NT2 cells, a stable neuronal cell line, and cultured astrocytes. The Mn complexes in these cells do not seem to be greatly different from those observed in the mitochondria. No spectra identifiable as Mn^{3+} have been observed in the cells studied. Our work clearly shows that Mn^{3+} is not stabilized within complexes in either mitochondria, neuron-like cells, or astrocytes and consequently any cellular damage caused by Mn^{3+} must occur within the short interval between its formation by superoxide oxidation of Mn^{2+} and its breakdown.