Fractionated Manganese-Enhanced MRI

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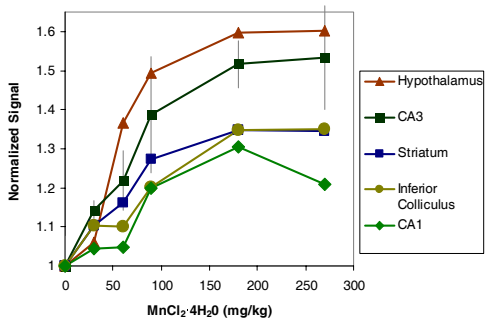
Introduction: In manganese-enhanced MRI (MEMRI), manganese can be administered systemically to improve contrast in the neuroarchitecture[1] and to probe neuronal function[2]. To maximize contrast, a large dose is administered at the risk of eliciting acute toxic side-effects and limiting data acquisition to an optimal time period following injection. In the present work, we investigate administering manganese in small, fractionated doses over time to *1* lessen the acute toxicity of the Mn^{2+} for susceptible organs like the liver and heart, and *2* provide multiple periods of Mn^{2+} exposure in an animal to perform functional stimulations or pharmacological challenges.

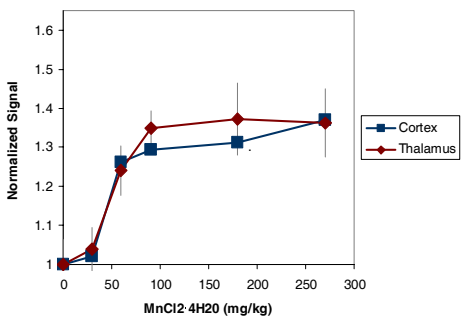
Methods: Twenty male Sprague-Dawley rats (222-286 g) were used under the guidelines of the NINDS/NEI, NIH ACUC. For single-dose studies, animals received a tail-vein injection of 180 mg/kg $MnCl_2{\cdot}4H_2O$ as a 100mM solution pH-buffered in bicine and infused at 1.25 ml/h[3]. The other rats received fractionated intraperitoneal doses of 30 mg/kg $MnCl_2{\cdot}4H_2O$ as a 25 mM solution every 48 hours to allow the Mn^{2+} to clear the heart and liver[4] before the next dose. Animals were imaged live at 48 hours post-injection on a 7T Bruker animal MRI with a T_1-weighted 3D sequence (FSE, rare factor = 2, TE = 12.3 ms, TR=150 ms, isotropic resolution = 167 μm). B_1 inhomogeneity in the surface coil images was corrected using a transmit coil reference image, and the signals from various regions in the brain were measured and normalized to the signal from muscle in the head for inter-animal comparisons.

Results: Figures 1 and 2 show signal enhancement curves (mean normalized to pre-injection values ± std. dev., n=4 at each point) in brain regions over nine injections of 30 mg/kg $MnCl_2{\cdot}4H_2O$. The signal in brain regions saturated around a total cumulative dose of 180 mg/kg (Fig. 1) or at a lower dose of around 90 mg/kg (Fig. 2). Figure 3 shows representative images at various fractions (top) and for the single 180 mg/kg dose (bottom). Both the contrast and SNR are better in the single-dose image and fine details of the neuroarchitecture, such as cortical lamination, are better visible. Figure 4 shows a comparison of signal (mean ± std. dev., n=4 for each group) in the brains of rats receiving a cumulative dose of 180 mg/kg in fractions, or as a single dose. Regions that significantly enhanced at the p=0.05 level are denoted with an asterix.

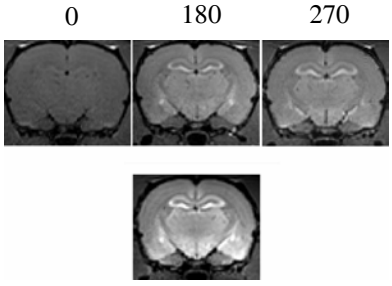
1



2

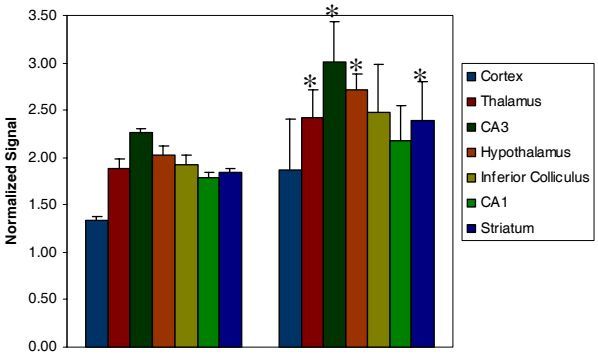


3 Total Fractionated Dose (mg/kg)



Single 180 mg/kg Dose

4



Discussion and Conclusion: Fractionating the Mn^{2+} dose greatly lessened the toxic burden; all fractionated rats appeared healthy after 18 days of injections, while the single-dose rats were euthanized after imaging because of necrosis in their tails and lethargic behaviour. Fractionation at 30 mg/kg every 48 h produced progressive enhancement of brain regions closest to the ventricles. However, the earlier signal saturation in the cortex and the thalamus implies reduced Mn^{2+} available for uptake and suggests they receive Mn^{2+} via anterograde transport from other regions closer to the ventricles. Finally, the lower final signal in the fractionated rat images suggests that the cumulative manganese uptake is affected by a lower driving gradient following the 30 mg/kg versus the 180 mg/kg dose. Overall, fractionated MEMRI produced good images with a healthier outcome for the animals.

References: 1) Lin YJ et. al. Magn. Reson. Med., 38 p 378-388 (1997)
2) Yu X et. al. Nat. Neurosci., 8 p 961-968 (2005)
3) Lee JH et. al. Magn. Reson. Med., 53 p 640-648 (2005)
4) Ni Y et. al. Acta Radiol., 38 p 623-625 (1997)