Controlling the dissolution of MnO nanocrystals for time-dependent T_1 MRI contrast agents

Y-C. Lee[1], D-Y. Chen[2], S. J. Dodd[2], N. Bouraoud[2], A. P. Koretsky[2], and K. M. Krishnan[1]

[1]MSE, University of Washington, Seattle, Washington, United States, [2]NINDS, National Institutes of Health, Bethesda, Maryland, United States

Introduction: Nanostructured inorganic nanoparticles and core-shell structures can be used as MRI contrast agents with the advantages of flexible surface modification characteristics [1]. Manganese based nanoparticles have potential as agents that can be "activated" when taken into cells. For example, Mn oxides or Mn carbonates are insoluble at pH 7 but dissolve to release Mn^{2+} at the lower pH found in the endosome-lysosome pathway. The dissolution of Mn based particles in an acidic environment leads to large enhancement of the T_1 relaxation rate [2]. In addition, Mn^{2+} can leave the endosome-lysosome pathway to fill the entire cell leading to a much larger volume distribution of the contrast agent [2]. It would be advantageous to be able to control the rate of dissolution of Mn based nanoparticles to control T_1 contrast signals, *in vivo* with time. To this end, five different coatings on MnO nanocrystals have been tested to study the release rate of the Mn^{2+} ions and change in relaxivity at pH 7 compared to pH 5.

Experiments: Highly monodisperse, single-phase, MnO nanocrystals (NCs), ~10 nm in diameter, were prepared by chemical routes and their magnetic properties were extensively characterized [3]. Mercaptosuccinic acid (MSA), poly(maleic anhydride-alt-1-octadecene) (PMAO), Pluronic F-127 (PF127), PMAO-PEG and SiO_2 were then used, respectively, to transfer native hydrophobic particles to aqueous solutions for biocompatible applications. T_1 relaxivities of these particles coated with five different molecules were determined by phantom experiments. In addition, particles were injected into the brain in the region of the thalamus [4], in order to test the rate of dissolution and subsequent neuronal tracing of the released Mn^{2+}. Five rats received 100 nL of 16.8 mM $MnCl_2$ solution into the left hemisphere and MnO@SiO_2 solution into the right hemisphere. Images were acquired with an 11.7 T/31 cm horizontal bore magnet (Magnex Scientific Ltd., Abingdon, UK), which was interfaced to a Bruker Avance console (Bruker Biospin, Billerica, MA, USA). A Magnetization Prepared Rapid Gradient Echo (MP-RAGE) sequence was used. Sixteen coronal slices with FOV=2.56×2.56 cm, matrix 256×256, thickness=0.5 mm (TR=4000 ms, Echo TR/TE= 15/5 ms, TI=1000 ms, number of segments=4, Averages=8) were used to cover the area of interest at 100 μm in-plane resolution in 34 min.

Results: MSA-, PMAO-, PF127- , and PMAO-PEG- coated nanoparticles had relatively high relaxivities in PBS buffer solutions at pH 7 (1.8-2.5 $s^{-1}mM^{-1}$) and dissolved very quickly at pH 5. For example, it took ~20 min to reach relaxivity of 6.94 for MSA coated particles at pH 5. SiO_2 coated particles showed the smallest relaxivity (0.29 $s^{-1}mM^{-1}$) at neutral pH, which was stable over time. The MnO@SiO_2 nanoparticles had the best dynamic range for contrast change when the pH was lowered. Time dependent relaxivity measurements (Fig 1), at pH ~5.0 in acetate buffer solution of MnO@SiO_2 nanoparticles showed values increasing to 2.44 $s^{-1}mM^{-1}$ by 53 min to 6.1 $s^{-1}mM^{-1}$ after 75 hours. This final relaxivity is equivalent to $MnCl_2$ indicating that the particles had completely dissolved. The release rate of Mn^{2+} ions was faster for the first 5 hrs, subsequently slowing down after 10 hrs. MP-RAGE images of the rat brain (Fig 2) showed that the signal intensity at the injection site of MnO@SiO_2 particles (left sides in images) increased with time consistent with the slow dissolution rate measured in vitro. The signal at the site of $MnCl_2$ injection (right sides of images) was elevated at the first image after injection and began to decrease slightly due to tracing of the Mn^{2+} ions to different parts of the brain.

Conclusions: Different coating for MnO nanoparticles can affect the T_1 relaxivity at pH 7 and the rate of dissolution at pH 5. MnO@SiO_2 particles had the lowest pH 7 relaxivity and the slowest dissolution rate at pH 5 in vitro. *In vivo* MRI of MnO@SiO_2 particles injected into the brain showed time-dependent signal changes consistent with the in vitro rates. The MnO@SiO_2 particles show the best potential for delaying the release of MRI contrast until specific biological processes have occurred, such as endocytosis.

References: [1] Na et al, Adv. Mater. 21: 2133-2148 (2009). [2] Shapiro et al, Mag. Res. Med. 60: 265-269 (2008). [3] Lee et al, J Appl. Phys. Submitted (2009). [4] Tucciarone et al, NeuroImage 44: 923-931 (2009).

Fig 1. (left) Time-dependent relaxivity of MnO@SiO_2 nanopaticles soaking in pH 5.0 buffer solutions.

Fig 2. (right) MP-RAGE images of injected $MnCl_2$ and MnO@SiO_2 solutions: (a) 1 hour, (b) 2 hours, (c) 4 hours, and (d) 6 hours post injection.