Manganese-enhanced MRI of rat brain using manganese-releasing alginate beads

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Introduction

Manganese-enhanced MRI (MEMRI) is a versatile technique for imaging of the central nervous system. Tissue manganese reduces T_1 and improves tissue contrast. For detection of laminar architecture in the brain, high concentrations of manganese in tissue are needed. However, systemic administration of high doses of $MnCl_2$ is neurotoxic due to the initial high blood concentration[1]. This could be managed with slow release preparations of Mn^{2+}. A candidate for slow release is alginate beads which can be given different gelling properties by altering the composition and arrangement of the monomers in the polymer chains and by selecting different divalent ions[2]. The aim of the present study was to evaluate manganese-enhancement in brain tissue after systemic administration of manganese (Mn^{2+}) releasing alginate beads.

Materials and Methods

Alginate gel beads: Manganese Alginate gel beads (diameter ~400 microns) were formed by dripping a 1.8% (w/v) solution of high-M alginate (from Macrocystis pyrifera, 40% G) into solutions containing 100mM $MnCl_2$+10mM $CaCl_2$.

Animals: Adult Sprague-Dawley rats (~200g) were given an intraperitonal injection of either 1); Mn^{2+}-containing alginate gel beads 40mg/kg (MnAlg40; n=5) 2); Mn^{2+} -containing alginate gel beads 120mg/kg (MnAlg120; n=5) or 3); $MnCl_2$ 40mg/kg ($MnCl_2$40; n=4).

MRI: 7T Bruker Biospec 70/20 AS with BGA-12 400mT/m gradients. Coronal T_1 maps were obtained with a *Rapid Acquisition with Relaxation Enhancement with Variable Repetition Time* (RAREVTR) sequence Effective TE = 12.5ms; TR = 225/300/500/ 800/1600/3000/6000/15000ms, RARE factor = 4 and FOV = 4x3.5cm. The acquisition matrix was 200x175 giving a resolution of 200x200μm^2. T_1 maps were obtained 6 hours (h), 24h, 3 days (d), 6d and 10d after intraperitonal Mn^{2+} injection.

Data analysis: The mean relaxation ($R_1 = 1/T_1$) was calculated from manually placed ROI in the cortex, thalamus and striatum at each time point in the T_1 maps. Differences in mean R1 between groups in each region at the different time-points were tested using ANOVA with post-hoc LSD test.

Results

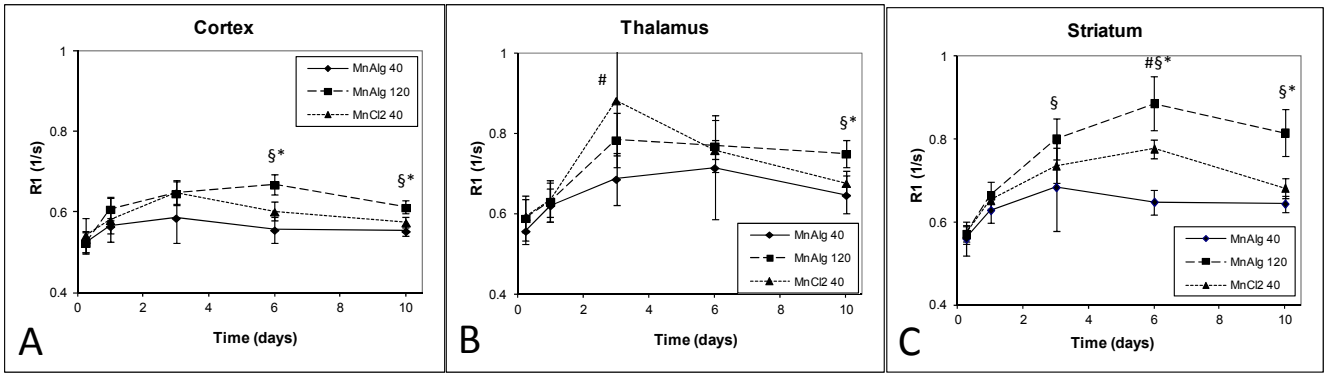

Figure 1: Figure shows the temporal development of R1 in cortex (A), thalamus (B) and Striatum (C) for rats injected with either 40mg/kg $MnCl_2$ ($MnCl_2$ 40), Manganese Alginate gel beads at a dose of 40mg/kg (MnAlg40) and 120mg/kg (MnAlg120). # $p < 0.05$ MnAlg40 vs $MnCl_2$ 40; * $p < 0.05$ MnAlg 120 vs $MnCl_2$ 40; § $p < 0.05$ MnAlg40 vs MnAlg120.

Although there was a trend towards higher R1 effect with $MnCl_2$40 than MnAlg40, no significant differences were detected in cortex. In thalamus and striatum, $MnCl_2$40 gave temporary higher R1 at day 3 and 6 than MnAlg40, but no differences were found on day 10 after injection. This effect may be related to a more continuous release of manganese from the beads, resulting in a more steady influx of manganese into the cerebral tissue.

The high dose manganese alginate beads (MnAlg120) showed a later maximum R1 and a higher maximum R1 in cortex and striatum compared to $MnCl_2$40. MnAlg120 gave consistently higher R1 on day 10 after injection in all areas compared to both $MnCl_2$40 and MnAlg40. This could be related to a higher total dose of manganese in combination with a more continuous release.

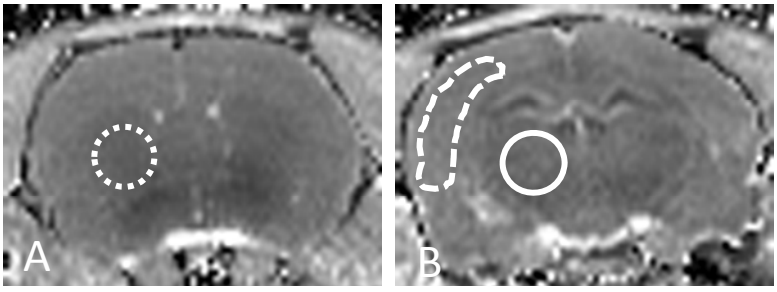

Figure 2: Figure shows T_1-maps with ROI in striatum (A; dotted line), cortex (B; dashed line) and thalamus (B; solid line)

In conclusion, manganese releasing alginate beads provide good manganese-enhancement with reduction in T_1 comparable to that of $MnCl_2$ in the rat brain. Higher manganese dose with resultant higher R1 after 10 days could be administered with alginate beads without apparent toxic effects. This may be a good alternative to repeated or continuous injections of $MnCl_2$.

References:

[1]Thuen et al. (2008), *Manganese-enhanced MRI of the rat visual pathway: Acute neural toxicity, contrast enhancement, axon resolution, axonal transport, and clearance of Mn^{2+}*. JMRI, 28: 855–865

[2] Mørch et al. (2006). *Effect of Ca^{2+}, Ba^{2+} and Sr^{2+} on alginate microbeads*. Biomacromolecules 7(5): 1471-1480