Contrast Enhancement as a Function of Time and Dose after Intraveneous MnCl2 Administration using High Resolution Manganese Enhanced MRI (MEMRI) of Mouse Brain

J. H. Lee[1], A. C. Silva[1], H. Merkle[1], A. P. Koretsky[1]

[1]Laboratory of Functional and Molecular Imaging, National Institute of Neurological Disorders and Strokes, NIH, Bethesda, Maryland, United States

Introduction

Manganese enhanced MRI (MEMRI) has been increasingly acknowledged for its potentially powerful applications for imaging biological processes in living substances. MEMRI allows us to measure synaptic activity [1, 2], neural architecture [3, 4], trace neural connections [5]. Combining all these properties of Mn^{2+}, MEMRI can be a new method for molecular imaging using Mn^{2+} as a smart contrast agent to visualize *in vivo* functional neural circuits and activities. Understanding of the mechanism of distribution and accumulation of Mn^{2+} in the brain upon systemic injection will be important to further develop MEMRI as a robust tool to image biological events occurring in living systems. The exact knowledge of selective uptake of Mn^{2+} to the various regions of the brain, and distribution of Mn^{2+} throughout the brain as a function of time in conjunction with dose dependent MRI enhancement pattern, needs to be investigated for future applications of MEMRI in molecular imaging. In this study, we evaluated the relationship between the dose of Mn^{2+} administered and both contrast enhancement and T_1 values in MEMRI in various regions of the mouse brain. We also investigated the time course of Mn^{2+} uptake and distribution, and subsequently the distribution pathways throughout the brain with systemic injection.

Methods

Animal Preparation: Experiments were carried on 36 adult FVB mice weighting 25-28g. An isotonic solution of $MnCl_2$ was prepared at a concentration of 120 mM, which was administered through a tail vein line at 6 different doses (4 animals per each dose), 175, 131, 88, 44, 18, and 9 mg/kg at a rate of 250 µL/hr 20-24 hours prior to MRI. Nine animals were infused with 88 mg/kg of $MnCl_2$ systemically 0 (during infusion), 1, 2, 4, 6, 8, 10, 14, 24 hours prior to MRI. The animals were anesthetized by breathing 2 % isoflurane into oxygen-enriched air while rectal temperature was carefully monitored and maintained at 36±1°C during MRI acquisition. Three animals were used as control without Mn^{2+} administered.

MEMRI: All MRI experiments were performed on a horizontal 11.7T/31 cm magnet (Magnex Scientific, Ltd., Abbingdon, UK) interfaced to a Bruker Avance MRI console (Bruker-Biospin, Billerica, MA) equipped with a 9 cm gradient set capable of supplying up to 30 G/cm in 65 msec rise-time. A homebuilt birdcage coil for transmitting and a saddle typed surface coil for receiving the signal were used. Multi-slice T_1-weighted spin-echo sequence (TR/TE=300/6.6 ms, in-plane resolution: 100x100µm, slice thickness: 500µm, FOV=1.92x1.92 cm, matrix size=192x192) and 3D spin echo T_1 weighted MRI (TR/TE=400/6.6 ms, 100µm isotropic resolution, FOV=2.56x1.28x1.28 cm, matrix size=256x128x128) were used to evaluate the contrast in MEMRI. Absolute T_1 measurements were performed by using 10 different inversion times in standard inversion-recovery, multi-slice T_1-weighted spin-echo sequence (TR/TE/TI=10000/7.68/10 – 2000 ms, in-plane resolution: 200x200µm, slice thickness: 500µm). T_1 values were computed in different regions of the brain, including pituitary gland (PIT), periventricular tissue (PVT), hippocampus (Hippo), cortex, olfactory bulb (OB), cerebellum (CEB) and interpeduncular nucleus (IPN). High resolution 3D MEMRI, fast spin echo T_1-weighted (TR/TE=300/6.6 ms, 100 µm isotropic resolution, echo train length=2) was acquired to evaluate the distribution of Mn^{2+} as a function of time. The SNR was measured using the standard deviation of the air signal as a reference.

Results and Discussion

Figure 1 shows T1 weighted MRI of a slice through the hipocampus as a function of $MnCl_2$ dose. Enhancement occurred throughout the brain, although in a heterogeneous manner. After systemic Mn^{2+} administration, T_1 values decreased as the Mn^{2+} doses increased, and varied significantly among regions (Figure 2). The T_1 values in various regions of the brain ranged from 1.167±0.026 to 1.760 ± 0.011sec without Mn^{2+} administered. A significant decrease in T_1 was evident throughout the brain with as little as 9 mg/kg of Mn^{2+} administered. The shortest T_1 values were observed in the pituitary gland that ranged from 231.0 ± 39.0 ms at the lowest dose of Mn^{2+} to 142.6 ± 12.5 ms at the highest dose (Figure 2). The longest T_1 values were observed in the cortex, and ranged from 1059.7 ± 31.0 ms at the lowest dose of Mn^{2+} to 637.0 ± 31.6 ms at the highest dose. The optimal dose of Mn^{2+} to enhance the whole brain seems to be in the range of 18-44 mg/kg. The regional variation of Mn^{2+} uptake, distribution, and accumulation in the brain as a function of time was observed. Upon systemic administration of Mn^{2+}, solutes of Mn^{2+} in CSF are transported to extracellular spaces and intracellular spaces throughout the CNS *via* paravascular pathways by diffusion process [6], which may explain the distribution mechanisms in olfactory bulb and cerebellum (Figure 3). The accumulation profile in a variety of brain substructures was shown. Figure 4 shows the course of enhancement in the hippocampus, Mn^{2+} which accumulates in periventricular region by I hour, enters the hippocampus directly at the CA1-CA2 boundary and then spreads throughout the hippocampus.

Conclusion

The results of the current study suggest that the optimal dose of Mn^{2+} and the MRI time should be determined depending on the target region of investigation. The MEMRI method with the results of the current study has opened the door for a number of future studies of various parts of the brain involved in neurological diseases. Also, these properties of Mn^{2+} in MRI can be potentially combined with molecular strategies to explore the use of Mn^{2+} as a contrast agent in MR molecular imaging.

References

1. Lin YJ, *et al. Magn. Reson. Med. 1997;38:378-388*; **2.** Duong TQ, *et al. Magn Reson Med*, 2000;43:383-392; **3.** Watanabe T, *et al. Magn Reson Med*, 2001;46:424-429; **4.** Aoki I, *et al. Proc. Intl. Soc. Mag. Reson*, 2002;10; **5.** Paulter RG, *et al*. 1998;40:740-748; 6. Rennels ML, *et al., Adv. Neurol* 1990;52:431-439.

Figure 1. Manganese dose dependent contrast in MEMRI (Doses in mg/kg).

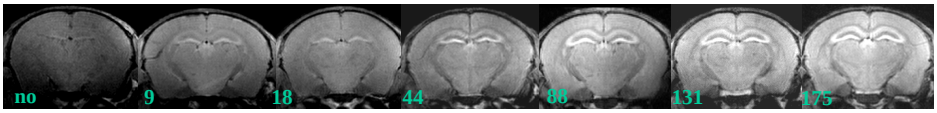


Figure 2. Manganese dose dependent T_1 values.

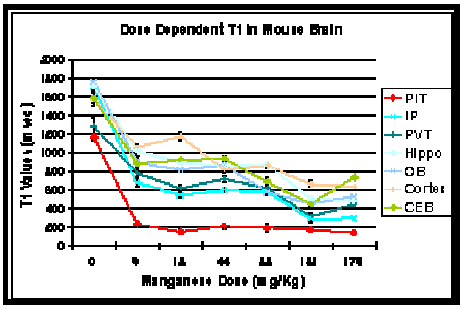


Figure 3. The distribution of Mn^{2+} as a function of time in cerebellum.

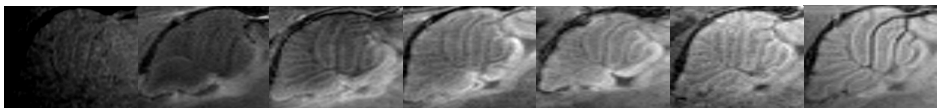
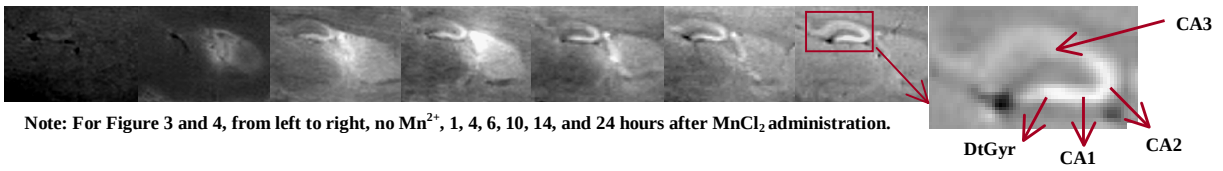


Figure 4. The distribution of Mn^{2+} as a function of time in hippocampus.



Note: For Figure 3 and 4, from left to right, no Mn^{2+}, 1, 4, 6, 10, 14, and 24 hours after $MnCl_2$ administration.