Improving contrast of iron oxide based cell labeling with manganese-enhanced MRI

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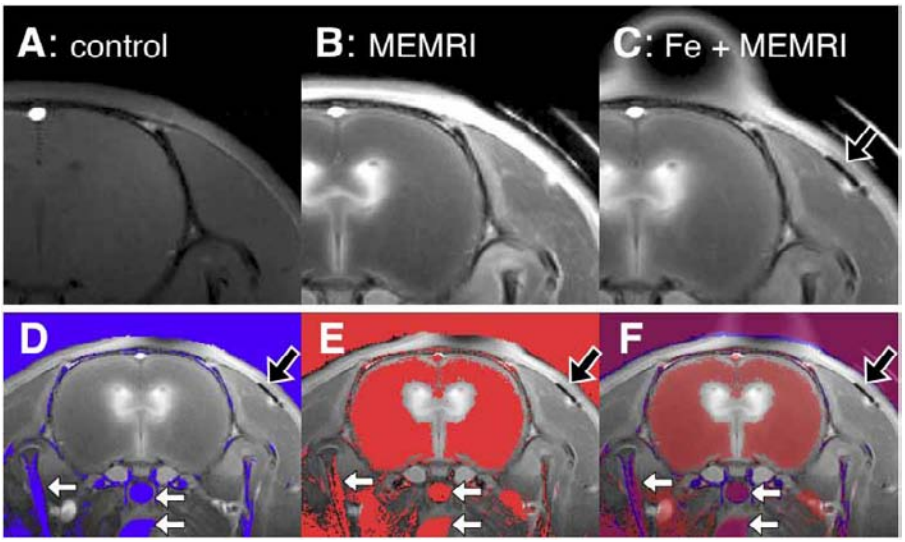
Introduction

Recently, negative MR contrast induced by iron oxide particles gaining widespread use for imaging cell migration in vivo. Iron oxide as a negative contrast agent has excellent "sensitivity" due to the large effect they have on T_2 relaxation time and large susceptibility effects on T_2* weighted MRI. Indeed, even detection of single micron sized iron oxide particles has been demonstrated (Shapiro EM, PNAS 27;101(30):10901-6, 2004). Although negative contrast agent is useful for organs which have homogeneous positive background such as liver and brain, it is difficult to distinguish iron oxide contrast agent in areas of inherently low background signal, such as abdominal organs and cavities, or areas of high susceptibility caused by air or local magnetic field inhomogeneity. The purpose of this study is to use manganese-enhanced MRI (MEMRI) to improve SNR and contrast in tissues prior to administration of iron-oxide labeled agents or cells, so that the negative contrast caused by these iron oxide-labeled agents can be better detected. Divalent manganese ion (Mn^{2+}) is known as an excellent "positive", T_1 MRI contrast agent, which has recently been used for tracing of neuronal pathways, for enhancement of brain neuroarchitecture, and for functional MRI. Mn^{2+} can rapidly enter the parenchymal of most tissue including liver, kidney, muscle, and skin after systemic administration. Thus, it is expected that Mn^{2+} can shorten the T_1 and yield better signal to noise per unit time for detecting negative contrast agents such as iron oxide particles. This information will be also useful for identifying and masking the signal voids due to local magnetic inhomogeneity or low signal areas such as air spaces and bone on T_2* weighted MRI.



Materials and Methods

Male Sprague-Dawley (SD) rats (280-300g, n = 4) were used. Rats were initially anesthetized with 4 % isoflurane and ventilated with 1.5-2.0%. Polyethylene catheter (PE-50) were placed in the femoral vein and subcutaneous for drug administration. Rats were placed in a 4.7-T magnet (Biospec, Bruker) after the preparation. First, control MRI was acquired without any contrast agent. Second, $MnCl_2$ solution (50 mM, 150 mg/kg, 2 ml/hour) was slowly administrated through femoral vein, and then MRI was obtained (MEMRI). Third, iron oxide-labeled lymphocytes were subcutaneously injected in the scalp or body, and then MRI was obtained (Fe-MEMRI). Three types of MRI were obtained consisting of spin-echo for T_1-weighted MRI (TR = 250 ms, TE = 9.6 ms, FOV = 32 mm, matrix size = 256 × 256, slice thickness = 1.2 mm, number of acquisition = 12, acquisition time = 12.8 minutes), stimulated-echo for T_2 relaxation time calculation (TR = 3000 ms, TE = 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 ms, number of acquisition = 1, acquisition time for a set = 12.8 minutes), and gradient echo MRI (TR = 250 ms, TE = 5 ms, number of acquisition = 8, acquisition time for a set = 8.5 minutes). For generation of a "parenchymal tissue map", the MEMRI was subtracted from the control. Threshold values were set using 2 times the standard deviation (2SD) of the background signal on the subtracted image and proton density-weighted MRI. Rat lymphocytes (1×10^5 cells) were labeled by incubation with iron oxide particles coated with a cationized polysaccharide for 1.5 hour.

Results and Discussion

Signals in the skin and muscle were enhanced by MEMRI (Fig. B) 30 minutes after manganese administration in comparison with the control (Fig. A). Layered structures of the skin were observed indicating that MEMRI may be useful for delineating the anatomy of the skin. In addition, paraventricular regions and the surface of cortex were also enhanced in MEMRI (Fig. B) consistent with previous reports for signal changes at this time after systemic administration of $MnCl_2$ (Aoki I et al, NeuroImage 22(3) 1046-59, 2004). Signal reduction was observed in the subcutaneous region after administration of oxide-labeled lymphocytes (Fig. C, black arrow). To eliminate "black region" related air, bone, and RF/magnetic inhomogeneity, masking maps were generated using proton density-weighted MRI (Fid. D, blue region) and MEMRI images subtracted from control (Fig. E, red region). The blue area indicates low proton density areas, and serves as a mask for inherently low signal areas, such as air and bone The red area in E means that manganese did not enhance a region within 30 minutes. Thus, most of brain region were masked due to the presence of the BBB in addition to the air, and bone. The trachea, esophagus, and bone were masked in both methods (white arrows and purple regions in Fig. F). However, regions were the signal was attenuated due to migration of the iron oxide-labeled lymphocytes were not covered by the masked-map in either method. Thus, Manganese-enhanced MRI can contribute to contrast enhancement and can provide a robust masking algorithm for low signal regions that complicate cellular imaging using negative contrast agents, such as iron oxide.