Approach to Molecular MR Imaging using RGB-composite Manganese-enhanced MRI (MEMRI)

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Introduction

Noninvasive investigation of cellular and molecular events is important for understanding of biology and medicine. Visualization methods are required to represent various kinds of cellular, molecular, and physiological information simultaneously. The divalent manganese ion (Mn^{2+}) is known as an excellent MRI contrast agent, which has recently been applied for many kinds of modalities such as for tracing of neuronal pathways, enhancement of brain neuroarchitecture (1), and for functional MRI (fMRI) (2). Activity-Induced Manganese-dependent (AIM) MRI was introduced in fMRI as method independent of hemodynamic changes (2). In addition, we recently improved AIM for pharmacological application to detect neurotransmitter-induced neural activation, a technique named Pharmacological AIM (PhAIM) MRI (3). These manganese-enhanced MRI (MEMRI) methods which use manganese contrast agent rely on many kinds of molecular and physiologic functions such as voltage-gated calcium channel opening, chemical-induced neural activation, neuroarchitecture, and transport in the brain. The purpose of this study was to reveal morphological and functional architecture of the hippocampus (CA) and develop new visualization methods that combine the use of the different modalities of manganese, simultaneously using data from AIM (2), PhAIM (3), and neuroarchitectural MEMRI (1).

Materials and Methods

Twenty male Sprague-Dawley (SD) rats (200-250g) were divided into 4 groups; neuroarchitectural MEMRI group (n=5), AIM MRI with stimulation group (n=5), AIM MRI without stimulation group (n=5), and PhAIM MRI group (n=5).

Three types of MEMRI experiments were performed. *1) Neuroarchitectural MEMRI*: Rats were initially anesthetized with 4.0% isoflurane, orally intubated, and then ventilated with 1.5-2.0 % isoflurane. 75 mg/kg $MnCl_2$ (50 mM) was administrated by infusing at a rate of 2.0 ml/hour through the tail vein. MRI measurement was performed 2 days after the $MnCl_2$ administration. *2) AIM MRI with or without whisker stimulation*: Rats were initially anesthetized with 4.0 % isoflurane and ventilated with 2.5%. Polyethylene catheters (PE-50) were placed in the femoral artery and vein. The right external carotid artery was also cannulated for drug administration. The blood brain barrier (BBB) was broken by 25 % D-mannitol under mixed anesthesia with isoflurane and propofol. $MnCl_2$ solution (25 mM) was infused for three minutes from the right external carotid artery. Whiskers were stimulated with approximately 2Hz frequency during the $MnCl_2$ infusion only for the "with stimulation group". *3) PhAIM MRI for glutamate-induced activation*: Rats were prepared the same manner as the AIM MRI. The experiment was performed according to previously described methods (4). Ten percent D-mannitol was slowly infused to prevent brain swelling due to BBB disruption. The BBB was disrupted using 25 % D-mannitol injection. $MnCl_2$ solution (25 or 50 mM, 0.3 ml) and glutamate (10 mg/ml, 0.3 ml) mixture were administrated through the external carotid artery.

MRI measurements and post-processing: T1-weighted coronal and horizontal images were acquired on 4.7T MRI (Bruker, Germany) using a spin-echo sequence with following parameters; TR = 182 ms, TE = 9.6 ms, FOV = 32 mm, matrix size = 256 × 256, slice thickness = 1.2 mm, number of acquisition = 8 or 16, acquisition time for a set = 6.2 or 12.4 minutes. Each MEMRIs were adjusted the locations and figuration manually and composed to RGB map using IDL (Research Systems, Inc., CO), Image-J (NIH, MD), and Adobe Photoshop (Adobe, Inc., CA).

Results and Discussion

The RGB-composite MEMRI was produced that consisted of AIM (whisker stimulation), PhAIM (glutamate administration), and neuroarchitectural MEMRI (Fig. 1). This map contains multiple molecular-physiologic information; calcium channel related neural activity (green), glutamate induced neural activity (blue), and neuroarchitectural data (red). Figure 2A shows T_1 weighted MRI from the hippocampal CA1-3 of a rat 2 days after $MnCl_2$ administration illustrating neuroarchitectural MEMRI. The hippocampal CA1-3 and DG area were detected and is in excellent agreement with the rat brain atlas and previous report (1). Signal enhancement was observed in the pyramidal cell layer (Py) of the Ammon's horn region of the CA and DG. Figure 2B shows images from AIM MRI induced by whisker stimulation. Signal enhancement in the pyramidal cell layer (Py) was narrow and sharp in comparison with the neuroarchitectural MEMRI (Fig. 1, 2A, 2B, and 2C; arrows). CA enhancement was not observed in the AIM MRI in the "without stimulation group". The venticular region also enhanced in both AIM MRI groups. Figure 2D shows PhAIM MRI induced by glutamate administration. Signal enhancement was observed in the entire hemisphere especially in the caudate-putamen, CA, and DG area. It is known that the density of glutamate receptors is high in CA region. The enhanced region may reflect distribution of glutamate receptor. The RGB-composite MEMRI is useful for comparison and evaluation between different kinds of molecular specific imaging such as MEMRI.

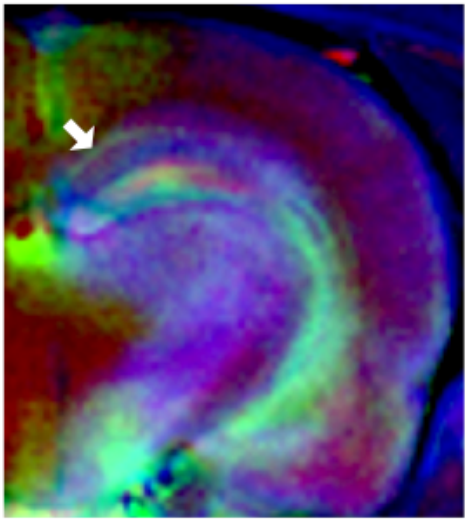

Figure 1. RGB-composite MEMRI. It was produced from AIM MRI (Green), PhAIM MRI (blue), and neuroarchitectural MEMRI (red).

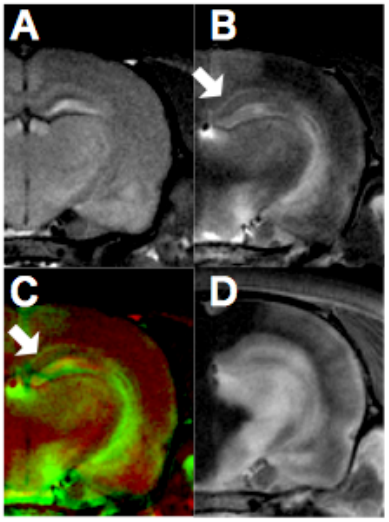

Figure 2. MEMRIs. (A) MEMRI, (B) AIM MRI induced by whisker stimulation, (C) composite image between A and B, and (D) PhAIM MRI induced by glutamate.

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