Methodological Issues and the Solutions for Activity-induced Manganese-dependent contrast (AIM) MRI

I. Aoki[1], Y. Kawai[2], Y. Mori[2], Y. Shimizu[2], M. Umeda[1], T. Higuchi[2], S. Naruse[3], A. C. Silva[4], C. Tanaka[1,2]

[1]Department of Medical Informatics, Meiji University of Oriental Medicine, Kyoto, Japan, [2]Department of Neurosurgery, Meiji University of Oriental Medicine, Kyoto, Japan, [3]Department of Radiology, Kyoto Prefectural University of Medicine, Kyoto, Japan, [4]Cerebral Microcirculation Unit, Laboratory of Functional and Molecular Imaging, NINDS, NIH, Bethesda, MD, United States

Introduction

The divalent manganese ion (Mn^{2+}) is known as an excellent MRI contrast agent, which has recently been used for tracing of neuronal pathways, for enhancement of brain neuroarchitecture, and for functional MRI (fMRI). Activity-Induced Manganese-dependent (AIM) MRI was introduced in fMRI as method independent of hemodynamic changes. There are many advantages to AIM in the performance of fMRI experiments. First, AIM has extremely high sensitivity and signal-to-noise ratio. Relative signal enhancement can be over 80 - 100 % for glutamate administration, and over 50% for electrical stimulation at the forepaw on T_1-weighted MRI. A second major advantage of AIM is the fact that it does not depend on blood hemodynamics, and therefore does not rely on the cerebrovascular coupling to produce maps of increased cortical activity. Third, "positive" signal enhancement can be observed on conventional T_1-weighted MRI. Furthermore, AIM can produce both functional and anatomical images simultaneously. However, AIM-MRI experiments still have methodological issues to be solved, such as: (a) it is sensitive to background, resting or quiescent activity, which causes unexpected, unspecific signal enhancement; (b) it may elicit no response, depending on the anesthetic conditions and on animal physiology; (c) it is affected by a heterogeneous disruption of the blood brain barrier (BBB); and (d) it may present unknown signal enhancement in lateral hypothalamus (LH) without stimulation depending on dose of $MnCl_2$. The purpose of this study is to point these issues out and to present some examples of solutions for stable and reliable signal detection for AIM-MRI.

Materials and Methods

Seventeen male Sprague-Dawley (SD) rats (200-250g) were used. Rats were initially anesthetized with 4 % isoflurane and ventilated with 2.5%. Polyethylene catheters (PE-50) were placed in the femoral artery and vein to monitor blood pressure, sample blood gases and administer drugs. The right external carotid artery was also cannulated for drug administration. Rats were placed in a 4.7-T magnet (Biospec, Bruker) after the preparation. The experiment was performed according to previously described methods (1). Ten percent D-mannitol was slowly infused to prevent brain swelling due to BBB disruption. The BBB was disrupted using 25 % D-mannitol (6 ml/kg) injection after the first MRI scanning. For evaluation of the baseline signal enhancement and LH enhancement, $MnCl_2$ solution (12.5 or 25 mM, 0.3 ml) was administrated through the external carotid artery. After that, MRI was performed. This administration and MRI scanning was repeated 2 times without intentional stimulation. For the BBB homogeneity check, a $MnCl_2$ solution (25 or 50 mM, 0.3 ml) and glutamate (15 mg/ml, 0.3 ml) mixture were administrated through the external carotid artery, before obtaining another MRI. Blood $PaCO_2$, PaO_2, and pH were maintained throughout the experiments at normal physiological levels. T1-weighted coronal and sagittal images were acquired using a spin-echo sequence using 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, acquisition time for a set = 6.2 minutes. The BBB disruption was evaluated using a categorical scale consisting of 5 scores: excellent (opened homogeneously), good (opened homogeneously, but only partially), normal (opened homogeneously, except for some regions), poor (opened inhomogeneously), and close (mostly not opened).

Results and Discussion

Homogeneous BBB disruption

AIM-MRI was acquired after $MnCl_2$ and glutamate mixture administration. The BBB disruption was evaluated 90 minutes after mannitol administration: excellent (35.3 %, Fig 1A), good (23.5 %), normal (17.6 %), poor (17.6 %, Fig 1B), and closed (5.9 %). Although high concentrations of mannitol injected through the CCA can effectively disrupt the BBB, such disruption can be spatially inhomogeneous, as shown in Fig. 1B. The cause of such inhomogeneities is unknown, however, there are some factors such as injection rate, dose of mannitol, cannulation condition, distance from CCA, individual differences in vacular density or distribution, age, and tissue specific differences of BBB thickness or structure. Injection rate and dose should be selected to disrupt the BBB sufficiently and homogeneously. In addition, the BBB condition should be evaluated using $MnCl_2$ and glutamate mixture administration after functional or pharmacological AIM-MRI. Temporal occlusion of the CCA during mannitol injection is a certain method for homogeneous BBB disruption in which every operational step can be accomplished outside the magnet.

Signal enhancement in the LH without stimulation

Signal enhancement in the LH was 5.8% after 20 mg/kg and 52.9% after 40 mg/kg $MnCl_2$ administration (Fig. 2). It is suspected that the signal enhancement in the LH is $MnCl_2$ dose dependent. Signal enhancement of the LH without any stimulation under alpha-chloralose and urethane mixture, which could be observed in our studies, has already been reported (2). The LH is known as a nerve center for blood glucose control and feeding. Glucose administration with $MnCl_2$ enhanced the LH dramatically in AIM-MRI (data not shown). The hypothalamus is also known as a higher nerve center of autonomic nerves that integrate processes of autonomic nerve control between the spinal cord and the brainstem. The LH signal enhancement may reflect some responses of autonomic nerve due to reaction of $MnCl_2$ loading to the heart.

1) Aoki I, Naruse S, and Tanaka C. Manganese-Enhanced MRI of Brain Activity and Applications to Early Detection of Brain Ischemia. NMR in Biomed. 2004, in press.

2) Morita H, Ogino T, Seo Y, Fujiki N, Tanaka K, Takamata A, Nakamura S, Murakami M. Detection of hypothalamic activation by manganese ion contrasted T(1)-weighted magnetic resonance imaging in rats. Neurosci Lett. 2002 Jun 28;326(2):101-4.

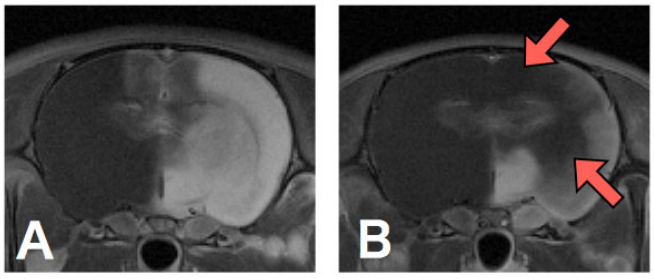

Figure 1. AIM MRI reflecting the BBB condition after $MnCl_2$ and glutamate injection. (A) BBB was disrupted homogeneously. (B) BBB of parietal cortex and a part of caudate-putamen were not disrupted in this case.

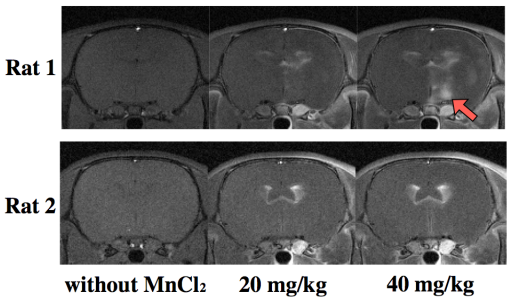

Figure 2. In rat 1, the hypothalamus was enhanced after injection of 40 mg/kg $MnCl_2$, but there was no significant enhancement at 20 mg/kg. In rat 2, the hypothalamus was enhanced neither after injection of 20 nor 40 mg/kg $MnCl_2$.