Manganese-enhanced MRI of Rat Brain Function under Forepaw Electric Stimulation: Comparison Between Accumulative Pain-evoked Activity and Activity-induced Manganese-dependent Contrast

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Introduction

Neuroimaging methods have been proposed to provide noninvasive approaches for neuroscience research. Functional MRI (fMRI) based on blood oxygenation level-dependent (BOLD) in brain research remains challenging, such as spatial resolution, motion suppression, complex paradigm and drug administration. Therefore, an alternative MRI approach is provided by manganese-enhanced MRI (meMRI), which has the potential to image neural activity by using manganese ion as a MR-detectable contrast agent [1-3]. Lauterbur first indicates the usefulness of paramagnetic ions for altering contrast [4]. During functional stimulation, such as electric stimulation of the rat forepaw, Mn^{2+} accumulates in the active areas of brain by entering active neural cells via voltage-gated Ca^{2+} channels, causing local signal increases in manganese-enhanced T1WI (meT1WI).

The purpose of this paper is to use the direct and effective meMRI in 3T MRI to map accumulative pain-evoked activity (APA) [1] and activity-induced manganese-dependent contrast (AIM) [2, 3] of electric stimulation of rat forepaw. In APA, the blood-brain barrier (BBB) is left intact whereas in AIM BBB is opened by high-osmotic solution. These two meMRI methods, APA and AIM, were used and compared in our study. We tested when the detectable signal of functional activity in rat brain could be measured using meT1WI after intraperitoneal administration of manganese chloride ($MnCl_2$) solution. In order to detect diluted concentration of Mn^{2+} in rat brain and to highlight the active area, contour plot of meT1WI and R1 map [5] were implemented. Our results indicated a clear relationship between Mn^{2+} enhancement and pain-evoked activity.

Materials and Methods

Adult Wistar rats were initially anesthetized with 2% isoflurane mixed O_2 gas and then were anesthetized with Urethane. $MnCl_2$ ($MnCl_2$-$4H_2O$, Osaka, Japan) was given by intraperitoneally injecting 2 ml of a 128 mM $MnCl_2$ solution. In the AIM study, to break the BBB, 20% mannitol solution was bolus-injected via the left carotid artery. Rat temperature was maintained at 37°C using warm water circulation after infusion. For electrical stimulation of the rat forepaw, two needles were inserted under the skin of the left forepaw and were connected to an electric stimulator (GRASS S44 stimulator, GRASS medical instruments, Mass., USA). Serial rectangular pulses of 2 mA current, 0.3 ms duration, and 3 Hz frequency were used. Stimulation was applied continuously until MRI acquisition. Rats were scanned with MRI before and 0.5~6 h, 12 h, and 24 h after experimental setup.

The data were acquired on a 3T MRI Biospec system (Bruker, Germany). A multislices multiechoes spin echo sequence was performed to obtain meT1WI. T1WI images were acquired with TR/TE = 500/10 ms, in-plane resolution of 187 μm, and slice thickness of 1.5 mm. R1 mapping images were acquired by the same sequence with 23 points sampled along the recovery with TR/TE = 300~6000/10 ms and with the same resolution.

Results and Discussions

In the study of optimum scan time that can probe the small functional signal after IP administration of $MnCl_2$ solution and electric stimulation of the rat left forepaw, adult Wistar rats 0.5~6 h, 12 h, and 24 h after $MnCl_2$ administration and electric stimulation and control were used. In the APA meMRI study (Fig. 2), consistent and robust responses were observed in anterior cingulated cortex (ACC) and motor area / cingulated cortex (CC) 12 h (Fig. 2a) as well as 24 h after $MnCl_2$ administration and electric stimulation, and 12 h was the best time to produce functional brain map. In order to highlight the stimulation specific activation region of rat brain, contour plot of meT1WI (Fig. 2b) and R1 map (Fig. 2c) were used. The threshold was set to maintain the same ventricle volume, nonspecific signal enhancement area, with control rat brain. The functional signal can be observed much clearly in ACC and motor area / CC region of 12 h after IP administration of $MnCl_2$ solution and electric stimulation than other time points.

The primary somatosensory (SI) cortex area cannot be observed in our APA study which can be detected in BOLD fMRI study [6] maybe because the cortex region is not near ventricle for easy uptake of Mn^{2+}. Therefore, the AIM approach (Fig. 3) was used. Mannitol solution was bolus-injected via the left carotid artery before $MnCl_2$ administration and electric stimulation to break the BBB. We can find consistent and robust responses in ACC, motor area / CC region, and right SI cortex area 0.5 h after $MnCl_2$ administration and electric stimulation of the rat left forepaw. The signal intensity of meT1WI in right SI cortex area increased significantly during 0.5~12 h (Fig. 3a). The contour plot of meT1WI (Fig. 3b) and R1 map (Fig. 3c) were also implemented and the clearer results were observed.

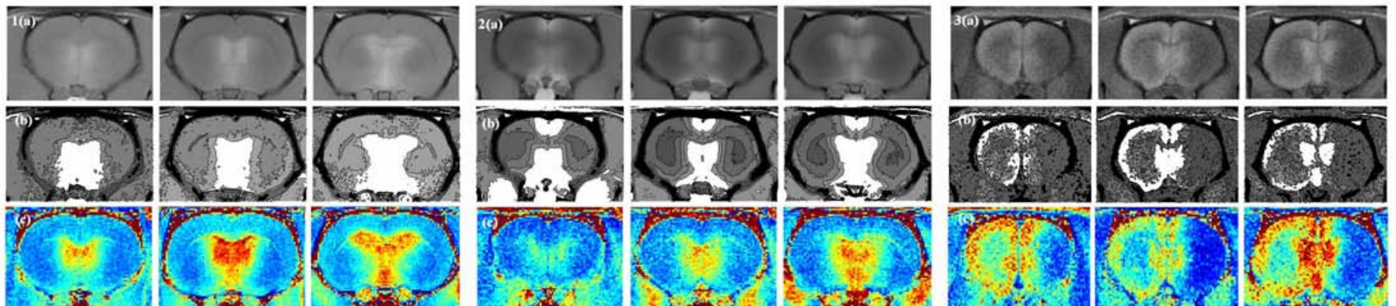

Fig. 1 meT1WI(a), contour plot image(b), and R1 map(c) of 12 h after $MnCl_2$ administration of rat brain (control group).

Fig. 2 Images of 12 h after $MnCl_2$ administration and electric stimulation of the rat left forepaw by using APA show accumulative pain-evoked activity in ACC and motor area / CC.

Fig. 3 Images of 12 h after $MnCl_2$ administration and electric stimulation of the rat left forepaw by using AIM show activity-induced manganese-dependent contrast in ACC, motor area / CC region, and right SI cortex area.

Conclusions

We have mapped the brain functional activation region of electric stimulation of rat forepaw using two meMRI methods non-destructively at 3T MR system. Our results indicated a clear relationship between Mn^{2+} enhancement and pain-evoked activity. It is likely that meMRI can also be used to map other sensory systems in rat, providing an important novel tool for mapping cortical development and plasticity in normal and surgically or genetically manipulated rat brain in the near future.

References

[1] X. Yu et al., Nature neuroscience 8, 961. 2005. [2] I. Aoki et al., MRM 48, 927. 2002. [3] E. C. Henning et al., MRM 53, 851. 2005
[4] P. C. Lauterbur, Nature 242, 190. 1973. [5] K. Chuang et al., ISMRM 1003. 2005. [6] W. Chen et al., Society for Neuroscience 189.2. 2005.