Pharmacological Activity-Induced Manganese Dependent Contrast (PhAIM) MRI - Detection of Neurotransmitter-Induced Neuronal Activity

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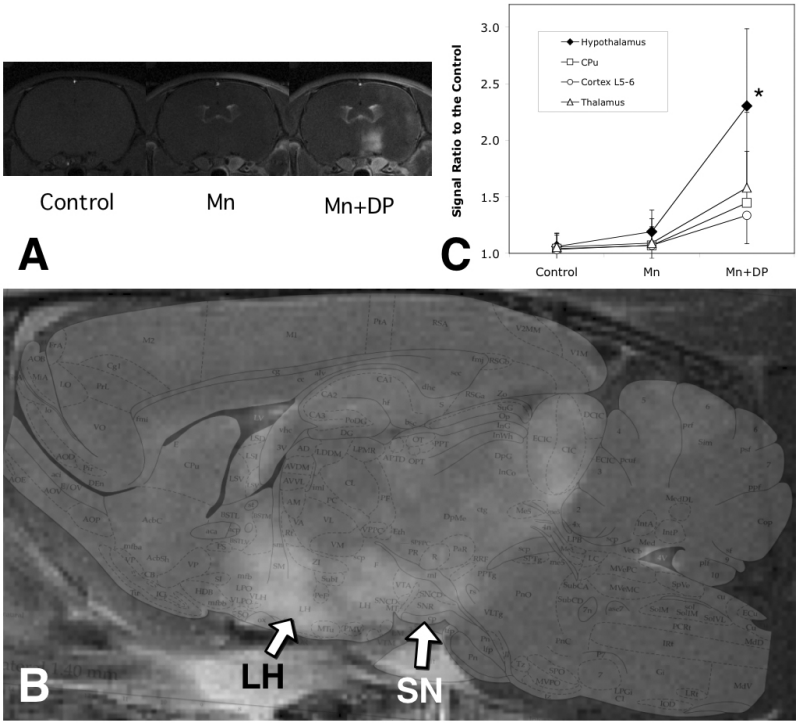
Introduction

Functional MRI techniques based on blood oxygenation level dependent (BOLD) contrast rely on changes in brain hemodynamics during increased neural activity. BOLD can be used to investigate regionally specific brain activity associated with the administration of CNS-active drugs, a technique referred to as pharmacological MRI (phMRI) (1). Recently, a new method for functional MRI, named Activity-Induced Manganese Dependent (AIM) MRI, was introduced as being independent of hemodynamic changes (2, 3). This early work showed that activation due to somatosensory stimulation and pharmacological stimulation with glutamate and amphetamine could be detected. The basis of AIM MRI is that manganese ion (Mn^{2+}) is an MRI contrast agent and handled in a manner similar to calcium ion (Ca^{2+}) in many biological systems. For example, it is known to enter cells through ligand-gated or voltage-gated Ca^{2+} channels during nerve action potentials. Therefore, we investigated whether AIM MRI would detect neurotransmitter induced brain activity in the rat. We named this new approach Pharmacological Activity-Induced Manganese Dependent MRI (phAIM MRI) with the goal of producing new neurotransmitter-sensitivity dependent contrast to enable MRI to map a neurotransmitter system, for example the dopaminergic pathway. In addition, we improve the AIM MRI method to avoid physiologic "baseline" brain activity using a dynamic method (4) as well as prevent brain swelling due to the rapid osmotic changing necessary to break the blood brain barrier (BBB) as required by AIM MRI.

Materials and Methods

Thirteen male Wistar rats (280-300 g) were used. Three groups of rats were used: the dopamine group (n = 6), the kainic acid group (n = 5), and the norepinephrine group (n = 2). Rats were initially anesthetized with 4.0 % isoflurane, and anesthesia was maintained with 1.5 - 2.0 % isoflurane mixed with a 1:2 O_2 / room air gas mixture. Rectal temperature was maintained at 37.5 ± 0.2 ºC using auto-controlled heating pad. Polyethylene catheters (PE-50) were placed in the left femoral artery and vein for drug administration, blood pressure monitoring and blood gas measurements, and in the right external carotid artery for drug administration into the right common carotid artery. Earplugs were placed in the external auditory canal. Pancuronium bromide (4 mg/kg) was injected IP for suppression of motion.



The experimental paradigm consisted of 5 steps as follows; 1) control T_1-weighted (T1W) MRI acquisition, 2) mannitol injection, 3) MRI acquisition after $MnCl_2$ and saline injection, 4) T1W MRI acquisition after $MnCl_2$ and dopamine injection, and 5) MRI acquisition after $MnCl_2$ and glutamate injection. At the first step, coronal and sagittal slices of T1W MRI were obtained 2 times as a control. After the control scan, glycerin solution (1g/kg, 100 mg/ml) was infused into the femoral vein at a rate of 10 ml/kg/hour to prevent brain swelling due to the rapid osmotic change caused by BBB opening with mannitol. The concentration of isoflurane was increased to 3.0 % to suppress brain activity. At the second step, 25% mannitol solution (1.0 ml/100g) at 37 ºC was injected at a rate of 1.8 ml/min into the carotid artery to break the BBB. At the third step, 1.0 ml/kg, 50 mM $MnCl_2$ solution (50 µmol/kg, Sigma) and 1.0 ml/kg saline was injected into the carotid artery at a rate of 1.2 ml/min, 10 minutes after mannitol injection. T1W MRI acquisition was started 5 minutes after $MnCl_2$ injection. At the fourth step, the same $MnCl_2$ solution and 1.0 ml/kg (10mM) dopamine solution mixture was injected into the carotid artery at a rate of 1.2 ml/min. At the fifth step, the same $MnCl_2$ solution and 10 ml/kg (10 mg/ml) glutamate solution mixture was injected into the carotid artery at a rate of 1.2 ml/min. Dopamine was replaced with kainic acid (5 mM, 2 ml/kg) or norepinephrine (0.2 mM, 2 ml/kg) to study these agents.

The MRI acquisitions were performed on a 4.7-T horizontal MRI (CSI-II-Omega, Bruker). A 30 mm Litz coil (Doty Scientific) was used Multi-slice T1W coronal and sagittal images were obtained for each step in the protocol using a spin-echo sequence with the following parameters: Pulse repetition time = 250 ms, echo time = 10 ms, matrix size = 256 × 256, field of view = 32 mm, slice thickness = 1.2 mm, number of acquisitions = 8, and acquisition time for one set = 8.5 minutes. All MRI data was normalized using the first control MRI. All statistical analyses were performed using StatView (SAS Institute). A probability value of less than 0.05 was considered significant for each analysis.

Results and Discussion

There were five major results in this study: 1) Neurotransmitter induced brain activity mapping was successfully performed with phAIM MRI using dopamine, kainic acid, and norepinephrine. 2) Dopamine induced signal enhancement was observed significantly in the hypothalamus, especially in the lateral hypothalamic area (LH), and substantia nigra (SN). 3) Norepinephrine induced signal enhancement was observed highest in the hypothalamus and less so throughout the hemisphere with the BBB. 4) Kainic acid induced signal enhancement was observed throughout the entire hemisphere. 5) The AIM MRI method was improved using pre-administration of glycerin solution to prevent brain swelling due to rapid BBB opening with mannitol and earplugs enabled avoidance of signal enhancement due to gradient noise. Figure A shows coronal T_1-weighted MRI for the dopamine administrated group. Signal was enhanced prominently in the hypothalamus in comparison with control without manganese administration (left) and manganese administration with saline (middle). There was a 230% increase in signal intensity in the hypothalamus after dopamine administration in comparison with the control (Fig. B). Figure C demonstrates a sagittal slice of phAIM MRI superimposed on a translucent brain map. SN and LH is known as a dominant core and transmitting pathway for dopaminergic neuron. These results indicate that phAIM MRI provides a new brain mapping tool reflecting pharmacological induced neural activity and should be applicable to many substances including many kind of neurotransmitters and toxic substances.

References

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