Mismatch between the manganese ion influx and decreased apparent diffusion coefficient of water in the focal ischemia

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Introduction
Activity-induced manganese dependent contrast (AIM) MRI is a new method of functional MRI using manganese ion contrast agent (1). Manganese ion (Mn2+) is handled in a manner similar to calcium ion (Ca2+) in many biological systems (2) and known to enter cells through ligand-gated or voltage-gated Ca2+ channels during nerve action potentials (3). Lin and Koretsky showed that the Mn2+ can be used as the contrast agent of nerve depolarization dependent (1). It is well known that severe cerebral ischemia leads to the depolarization of the nerve cell membrane. The depolarization causes Ca2+ influx into the nerve and gliacells due to open the voltage-gated Ca2+ channels. The purpose of this study is to detect the actual influx of Mn2+ in the focal ischemia, and to compare the area of Mn2+ influx with diffusion-weighted hyper-intensity area with decreased apparent diffusion coefficient (ADC).

Materials and Methods
Ten S.D. rats weighing about 300g were divided 2 groups: sham operated control (n = 5) and permanent middle cerebral artery occlusion (MCAO) model (n = 4). Rats were initially anesthetized with diethyl ether, orally intubated, and then ventilated with 1.2 % halothane in oxygen and nitrous oxide. Polyethylene catheters (PE-50) were placed in the femoral artery for blood pressure monitoring and blood gas sampling, and in the right external carotid artery for drug administration into the right common carotid artery. Rectal temperature was maintained at approximately 37°C by passing warm air and using warm pad. After animal surgery, a pentobarbital (50mg/kg) was injected intraperitoneally. To break the blood brain barrier (BBB), 25% D-mannitol solution (5 ml/kg) was injected via the right carotid artery using a syringe pump at the speed of 60 µmol/h (4.5 ml/h). The total volume of the infused MnCl2 solution was 0.3 ml (3 µmol). In the MCAO group, middle cerebral artery was permanently occluded using a suture at a few minutes after stopping the MnCl2 infusion. Total preparation time for animal was approximately 60 minutes.

MRI acquisition was performed on a 4.7 T horizontal spectrometer (CSI-H-1Omega, Bruker) with a shielded gradient coil 65 mm in diameter. A 30 mm homemade surface coil was used. The AIM MRI was performed using a T1-weighted image with the manganese contrast agent. The T1-weighted images were obtained using a SE sequence with the following parameters: TR/TE = 400 / 12 ms, matrix size = 256 x 256, field of view (FOV) = 28 mm, slice thickness (ST) = 1 mm, number of acquisitions (NA) = 8, number of slices = 8, and slice gap = 1mm. Acquisition time of the T1-weighted image was 13.7 minutes. The DWI were obtained using a SE with the following parameters: TR/TE = 5000 / 46 ms, matrix size = 128 x 128, FOV = 42 mm, ST = 2 mm, NA = 2, number of slices = 8, slice gap = 0 mm and b value = 0 and 1922 mm2/s. Acquisition time of the DWI was 10.6 minutes. The ADC map was calculated on the bases of the two b values using MRVISION software. All data were presented as the average ± one standard deviation.

Results and Discussion
The mean arterial blood pressures before and after pentobarbital administration were 100.7 ± 11.0 mmHg and 81.5 ± 15.3 mmHg, respectively. After mannitol injection, blood pressure changed by 14.8 ± 4.9 mmHg and returned to baseline immediately. Blood gases and pH were within normal physiological ranges. The ischemic region was detected within a few minutes after MCAO using the AIM MRI. This is the first report describing the detection of super-acute focal ischemia using the AIM MRI. Furthermore, the area of the hyper-intensity on AIM MRI was extremely small, compared with the area of decreased ADC. Considering that the severe cerebral ischemia leads to the depolarization of the nerve cell membrane, resulting in calcium influx, our finding may suggest that the AIM hyper-intensity showed the irreversible core of ischemic region. Thus, the mismatched area between manganese ion influx and decreased ADC of water in the focal ischemia may be consistent with the treatable region of reversible diffusion-weighted hyper-intensity after recirculation.

References

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