Detection of Reactive Gliosis using Manganese-enhanced MRI (MEMRI)

Y. Kawai[1], I. Aoki[2], N. Matsumoto[1], M. Umeda[3], T. Higuchi[1], J. Kershaw[2], A. C. Silva[4], and C. Tanaka[1]

[1]Neurosurgery, Meiji University of Oriental Medicine, Kyoto, Japan, [2]Molecular Imaging Center, National Institute of Radiological Sciences, Chiba, Japan, [3]Medical Informatics, Meiji University of Oriental Medicine, Kyoto, Japan, [4]Laboratory of Functional and Molecular Imaging, NINDS, NIH

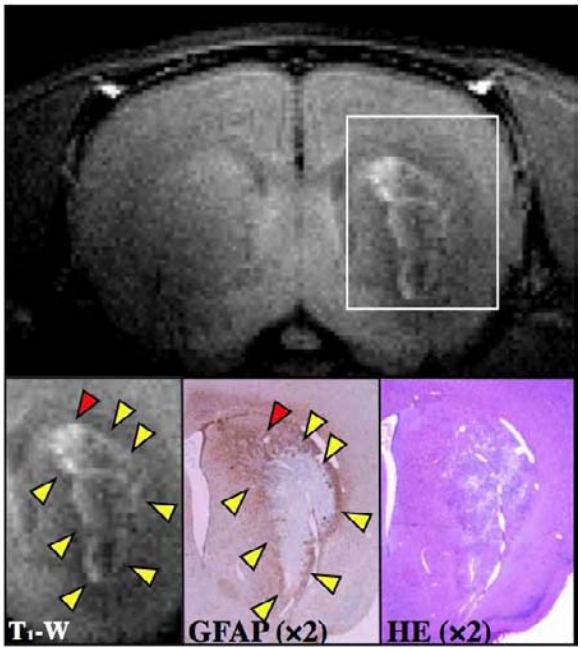
Introduction

Reactive gliosis is known as the hyperproliferation of astrocytes as a result of central nervous system (CNS) disturbances such as stroke and trauma. Recently, the protective role of reactive gliosis against inflammation was reported using a spinal-cord-injury model (Okada et al, Nat Med. 2006 Jul;12(7):829-34). On the other hand, gliosis obstructs the progress of nerve growth after CNS disturbance and therefore the regulation of the gliosis is an important theme for neuranagenic drug development. Therefore, in-vivo evaluation and visualization of reactive gliosis is needed for studies of CNS disturbance and neuranagenesis. Mn^{2+} has proven to be a useful MRI contrast agent for tracing neuronal pathways, for the enhancement of neuroarchitecture and for brain function. Previously, we reported that manganese-enhanced MRI (MEMRI) using systemic administration can enhance the neuroarchitecture of the brain 24-hours after administration (Aoki et al, Neuroimage. 2004 Jul;22(3):1046-59). The mechanism for manganese accumulation remains unclear, however is it hypothesized that reactive gliosis as a result of focal ischemia can accelerate manganese uptake and accumulation due to the hyperactivity or high density of glial cells. The purpose of this study was to investigate whether MEMRI can detect reactive gliosis after focal ischemia in-vivo.

Materials and Methods:

Male SD rats (250-260 g) were divided into three groups according to the number of days (1, 11, or 22; n = 5, 5, 5) after temporary middle cerebral artery occlusion (MCAO) they were administered manganese chloride solution. In addition, the same procedure was applied for three sham groups without MCAO (n = 3, 3, 3). Prior to manganese administration, T_1-, T_2-, and diffusion-weighted images (b = 1500 s/mm^2) were acquired using a 4.7T-MRI (Bruker, Germany). Thereafter, a $MnCl_2$ solution (50 mM, 75 mg/kg) was slowly infused via the tail vein (2 ml/h) and MRI measurements were performed again 24-hours after the administration. For three of the animals, MRI observations were periodically performed for 4 weeks after manganese administration.

Results and Discussion:



Ring- or crescent-shaped enhancement (Figure, yellow arrows) was observed in the peripheral region of the ischemic core 11 days after MCAO. This enhancement showed good agreement with the glial fibrillary acidic protein (GFAP) staining, strongly suggesting that MEMRI can detect reactive gliosis after stroke. A similar enhancement was also observed for the 22-day group and remained for 4 weeks after manganese administration even though the contralateral and unaffected tissues lost Mn-related enhancement. The highest signal intensity was observed between the lateral ventricle and ischemic region (red arrows). This phenomenon may support previous reports that reactive gliosis originated from ependyma of the ventricles and moved to the area that surrounds the affected site (Okada et al, Nat Med. 2006 Jul;12(7):829-34). Although the mechanism behind the manganese accumulation is still unclear, the following factors are suggested: 1) calcium channel activity of cells, 2) cell density, and 3) cytotoxic events such as apoptosis (calcium ion influx). In this model, the contribution of apoptosis is not dominant because the enhancement was still observed in the 22-day group after MCAO. In addition, the number of apoptotic cells was small in the ring-shaped region (yellow arrows), as confirmed by Tunel staining. Therefore, it is thought that calcium channel hyperactivity and/or high cell density due to gliosis were the dominant mechanisms behind the enhancement. In conclusion, this study clearly presented a good agreement between MEMRI and GFAP staining. MEMRI will provide useful information for neuranagenesis and stroke research in evaluating reactive gliosis in vivo.