

In vivo Detection of Glial Activity after Transient Forebrain Ischemia using Manganese-enhanced MRI

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Introduction

The cornu Ammonis 1 (CA1) neurons of the hippocampus are widely regarded as among the most vulnerable in the mammalian brain to ischemia [1][2]. Delayed hippocampal damage is observed 3 to 7 days after the insult in CA1 pyramidal neurons [2], suggesting that mechanisms that develop slowly after ischemia have an important role in ischemic neuronal demise. The four-vessel occlusion (4-VO) is famous as forebrain ischemia model that cause delayed neuronal cell death in the CA1 region of the rat hippocampus. Recently, the glial response to CNS injury is considered in the context of neuron-glial relationships. By supporting neuronal growth and metabolism, glial cells may determine the anatomical and function recovery after CNS injury. Manganese is good T₁ contrast agent for MRI. The manganese administration with intravenous injection can find unique contrast change that is dependent on the cell activity or cell density, it is known as Manganese-enhanced MRI (MEMRI). MEMRI is taken notice as useful molecular imaging technique for nervous system. We reported the possibility of detection of signal enhancement caused by the manganese accumulation using MEMRI in the gliosis area after temporary middle cerebral artery occlusion cerebral ischemia [3]. The purpose of this study is in vivo detection of glial function at the hippocampus after the 4-VO in the rodent.

Materials and Methods

Male Wistar rats (300.4 ± 15.6 g, n = 30) were divided into six groups consisting with 2 days, 3 days, and 10 days after 4-VO group and same time course of sham group. Twenty-four hours before the induction of ischemia, rats were anesthetized with pentobarbital sodium and the bilateral vertebral arteries were heat-cauterized at both vertebral arteries using a soldering iron. Both common carotid arteries were then gently isolated and a silicon tube placed around each vessel. The following day, both common carotid arteries were occluded with vascular clamps for 10 min under the 2.5 % isoflurane. T₁-weighted images and inversion recovery images were acquired at 2 days, 3 days and 10 days after the 4-VO using 4.7T MRI (Bruker, Germany) with the following parameters: {saturation recovery} spin-echo, repetition time (TR)/echo time (TE) = 400/12 ms, field of view (FOV) = 32 mm, and matrix size = 256 × 256, slice thickness = 1.0 mm, number of slices = 6 : {inversion recovery} TR/TE = 4000/10 ms, rare factor = 4, FOV = 32 mm, matrix size = 256 × 256, slice thickness = 1.2 mm, TI = 139, 300, 500, 800, 1000, 2000, 3000 ms. 50 mM MnCl₂ solution was infused via the tail vein before 24 hour scanning of the MRIs. Image processing was performed using MRVision (MRVisoin Co., MA).

Results and Discussion

Signal enhancement upon the manganese accumulation was observed in the CA1 region at 3 days and 10 days after 4-VO by the MEMRI (Fig. 1, 2). On the other hand, the cortex and dentate gyrus (DG) in sham group area were not shown the significant signal change. CA1 pyramidal neurons of 4-VO group was significant reduction 10 days after global ischemia. In addition the significant change was not observed in the sham group. A phenotypic alteration of astroglia, “astroglial activation”, is a common phenomenon observed on brain pathologies after the ischemia. The functional alteration of astroglia is important in tissue repair and cell death processes of the damaged CNS because of the many neurotrophic substances (Brain-derived neurotrophic factor ; BDNF, Glial cell-derived neurotrophic factor ; GDNF) are produced by the activated astroglia. In this study, MEMRI may reflect astrocytic activity in hippocampal and may suggest that the neuronal death occur the near future in CA1 area. MEMRI will detect glial activity which related with about of the neural death. In addition this study suggest that astrocytic change can precede neuronal death.

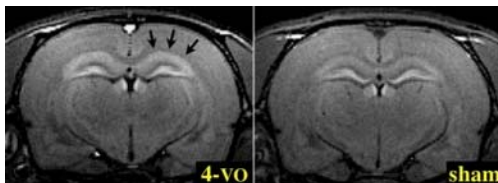


Fig. 1 : The typical MR images of MEMRI (3 days after the insult)

Signal enhancement was seen in the hippocampus region after the four-vessel occlusion.

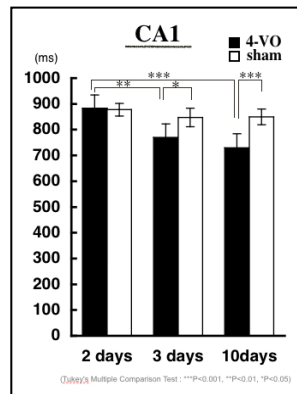


Fig. 2 : Comparison of T₁ value between global ischemia and sham group in MEMRI

Significant T₁ shortening was observed in CA1 area at 3 days and 10 days after the four-vessel occlusion.

References

- [1] Pulsinelli et al. Ann. Neurol 1982;11:491-498.
- [2] Kirino et al. Brain Res 1982;239:57-69.
- [3] Kawai et al. NeuroImage 2010;49:3122-31.