Mapping cortical projections after stroke in rat brain with *in vivo* manganese-enhanced MRI

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Introduction

Loss of function after stroke may be the direct result of ischemic damage in specific functional fields in the brain, but may also be caused by injury to axonal projections while neuronal cell bodies are preserved. Manganese-enhanced MRI (MEMRI) has recently been applied as a tool for *in vivo* mapping of neuronal tracts.[1,2] Paramagnetic Mn^{2+}, a Ca^{2+} analogue, can be taken up by neurons and then transported transsynaptically. The aim of this study was to assess changes in neuronal projections originating from the sensorimotor cortex at the border of a focal cerebral ischemic lesion in rats, using MEMRI.

Methods

Transient focal cerebral ischemia was induced in adult male Wistar rats (300-400 g) (n = 4) by one hour occlusion of the right middle cerebral artery using the intraluminal suture technique as described by Longa et al.[3] At 2 days prior to MRI , 0.5 µl 1 M isotonic $MnCl_2$ solution was injected into the spared ipsilesional sensorimotor cortex, at 0.5 mm anterior and 2.5 mm lateral to bregma, and at a depth of 1.5 mm from the cortical surface. $MnCl_2$ was also injected at these coordinates in five control rats. MRI measurements were performed on a 4.7 T horizontal bore spectrometer (Varian Instruments (Palo Alto, CA, USA)). Multi-echo, multi-slice T_2-weighted images (TR/TE = 3000/17.5 ms; echo train length = 8; acquisition matrix = 128 x 128; voxel resolution = 0.35 x 0.35 x 1.2 mm) were acquired to localize the ischemic lesion at 2 days prior and 2 days after $MnCl_2$ injection. A multi-slice T_1-weighted spin-echo sequence (TR/TE = 400/19 ms; acquisition matrix = 256 x 256; voxel resolution = 0.35 x 0.35 x 1.2 mm) was used to identify manganese-enhanced brain regions at day 7 (n = 2) and 14 (n = 2) after ischemia induction, and in control rats (n = 5).

Results

At 2 days after $MnCl_2$ injection, clear signal enhancement was found in the healthy rat brains in following ipsilateral regions: the sensorimotor cortex (SMCX), the striatum, the thalamus (Th) and the substantia nigra (SN) (Fig. 1A). Increased signal intensity was also found in the contralateral cortex. In rats with a stroke, ischemic damage was characterized by hyperintensity on the T_2-weighted images. It was confirmed that the $MnCl_2$ injection site was at the border of the ischemic lesion. The pattern of manganese-induced contrast enhancement in ischemic rat brain was largely similar to that in controls. However, signal enhancement in the ipsilateral substantia nigra was significantly reduced as compared to control rat brain ($P < 0.05$) (Fig. 1B). Relative signal enhancement in this area as compared to contralateral was 32.2 ± 7.2% in controls and 10.7 ± 4.2% in ischemic rats.

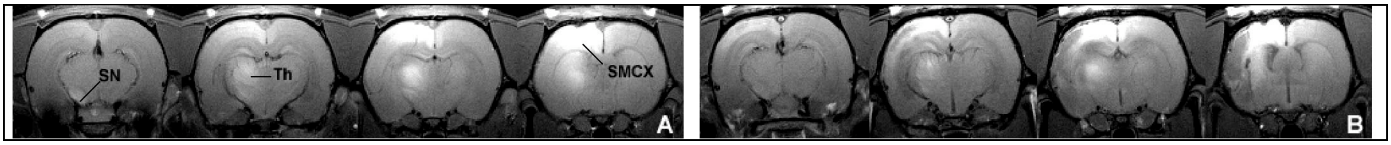

Fig. 1. Manganese-enhanced T_1-weighted images of adjacent coronal brain slices of a control rat (A) and of a rat 2 weeks after transient focal cerebral ischemia.

Discussion

The cortico-striato-nigral pathway of the sensorimotor network in rat brain was clearly visualized with MEMRI. In addition, in accordance with Allegrini and Wiessner [2], we detected transhemispheric connections. In ischemic rat brains, retrograde manganese labelling of the ipsilateral substantia nigra was significantly reduced. The loss of connections from intact brain to remote areas clearly plays a significant role in loss of specific functions after stroke. MEMRI therefore provides a unique tool for the *in vivo* assessment of the integrity of functional connectivity in injured brain.

References

1. Pautler RG, Silva AC, Koretsky AP. *Magn Reson Med* 40:740-748 (1998).
2. Allegrini PR, Wiessner C. *Proc Intl Soc Mag Reson Med* 11:498 (2003).
3. Longa EZ, Weinstein PR, Carlson S, Cummins R. *Stroke* 20:84-91 (1989).