Spatio-temporal patterns of manganese-enhancement in the sensorimotor network of rat brain after stroke

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Introduction

Stroke causes acute loss of sensorimotor function that usually recovers partially in time. Loss of function is related to injury to axons projecting to remote regions, whereas spontaneous functional recovery may be associated with plastic changes in the brain, e.g. neuroanatomical reorganization. Manganese-enhanced MRI (MEMRI) allows *in vivo* mapping of neuronal tracts after stroke [2], however the temporal pattern of manganese enhancement has not yet been characterized.

The aim of this study was to track changes in connectivity within the sensorimotor network in ischemic versus control rat brain, visualized by manganese enhanced MRI at different time points after manganese administration.

Methods

Transient focal cerebral ischemia was induced in male Wistar rats (240-300 g) (n=4) by 90 minutes occlusion of the right middle cerebral artery using the intraluminal suture technique [3]. Ten days after stroke induction, 0.2 µl 1M $MnCl_2$ solution was injected into the spared ipsilesional sensorimotor cortex (0.5 mm anterior and 2-3 mm lateral to bregma and at a depth of 0.5 mm). Similarly, $MnCl_2$ was injected in the right sensorimotor cortex of six control rats. MRI measurements were done on a 4.7 T horizontal bore spectrometer (Varian Instruments (Palo Alto, CA, USA)) at 3 days before and at 2, 4, 6 and 8 days after $MnCl_2$ injection. 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 = 0.25 x 0.25 x 1.2 mm) were acquired for anatomical details and delineation of the ischemic lesion. A saturation recovery, multi-slice T_1-weighted gradient-echo sequence with 7 repetition times (TR/TE = 55-3000/18 ms; acquisition matrix = 128 x 128; voxel resolution = 0.25 x 0.25 x 1.2 mm) was used to calculate T_1 maps at the different time points. T_1 shortening by manganese was determined in four ipsi- and contralateral regions of interest (ROI) within the sensorimotor network (sensorimotor cortex (SMCX), caudate putamen (CPu), thalamus (Th) and substantia nigra (SN)).

Results

In all rats, the cortico-striatal-nigral pathway was clearly visible on T_1 maps after $MnCl_2$ injection . Maximal T_1 shortening by manganese was observed at day 2 in all ROIs of the ipsilateral hemisphere, which gradually decreased thereafter for both control and ischemic rat brains. In ischemic rat brains, T_1 shortening was significantly reduced on day 2 and 4 after manganese injection in the ipsilateral substantia nigra as compared to control rat brains ($P<0.05$) (Fig 1). No significant differences in T_1 shortening between ischemic and control brains were found in the other ROIs.

Manganese-induced T_1 shortening was also found in all ROIs of the contralateral hemisphere of both ischemic and control brains. However, T_1 shortening in the contralateral ROIs was significantly greater in ischemic brains as compared to control brains ($P<0.05$) (Fig 2). In all ROIs, contralateral T_1 shortening was most pronounced on day 4 after $MnCl_2$ administration.

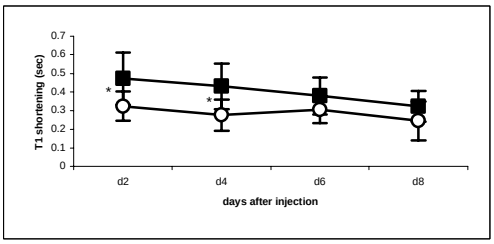

Fig 1. T_1 shortening (sec) in the ipsilateral substantia nigra (SN) of control (■) and ischemic (o) rat brains at 4 time points after $MnCl_2$ injection in the sensorimotor cortex . *P<0.05 vs controls.

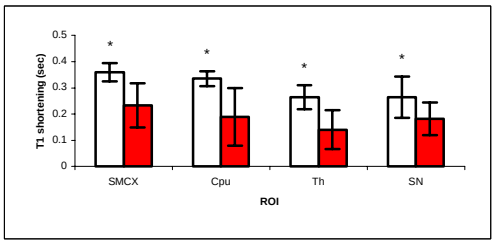

Fig 2. T_1 shortening (sec) in 4 different ROIs in the contralateral hemisphere of control (■) and ischemic ( ) rat brains at day 4 after $MnCl_2$ injection. *P<0.05 vs controls.

Discussion

Diminished manganese enhancement in the substantia nigra after stroke suggests that neuronal projections from the sensorimotor cortex to the substantia nigra are disturbed. However, this was not conspicuous after more than 4 days after manganese administration. Increased manganese-induced T_1 shortening in regions contralateral to the injection site points toward enhanced transhemispherical connectivity in ischemic rat brains. Our study also demonstrates that the pattern of manganese enhancement is time-dependent, suggesting different distribution mechanisms in stroke versus control brains. In conclusion, mapping neuronal connectivity using MEMRI provides unique *in vivo* information that may aid in elucidating mechanisms of functional loss and recovery after stroke.

References

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2. Longa EZ et al. *Stroke* 20: 84-91 (1989).