Transportation of Mn^{2+} in the Brain of Rats with Exclusive Caudoputaminal Lesions after Transient Focal Cerebral Ischmeia

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Introduction Transient middle cerebral artery occlusion (MCAO) longer than 60 minutes can results in two types of lesions: exclusive caudoputaminal lesion (CP) and cortico-subcortical lesion (CP+), which develop and mature with different time courses, reflect different mechanisms of neurodegeneration, and results in different functional outcomes. Previous studies have shown that the CP lesions resulted from a 60-min transient MCAO had normal T_1 and T_2 relaxations times at two weeks after ischemia, and only led to minimal long-term sensorimoter deficits [1]. Histologically the CP lesion is associated with extensive selective neuronal loss and reactive gliosis, but the fiber tracts crossing the lesion remain largely intact, at least morphologically [2]. Several important questions remain: 1) whether or not the normal-appearing fiber tracts in the CP lesion are functionally impaired by ischemia? 2) whether the rapid recovery of sensorimoter functions in rat with CP lesion is associated with plastic reorganization of the relevant neuronal tracts such as the corticocortical and corticostriatal pathways? In attempting to address these questions, we measured the transportation and deposition of Mn^{2+} in the ipsilateral hemisphere of the rats having MCAO-induced CP lesions with manganese-enhanced magnetic resonance imaging (MEMRI).

Materials and Methods Twelve male Wistar rats were used: 7 control rats and 5 ischemic rats. The ischemic rats received transient suture-induced MCAO for either 60 minutes (n=2) or 90 minutes (n=3), and all had CP lesions (i.e., shown by T_2-weighted images (T_2WI) acquired at 1d post-ischemia). T_2WI were acquired on a Bruker Biospec 4.7 T/30 cm scanner at 1d and 6 weeks post-ischemia with FOV 3.5 cm×3.5 cm, matrix size 128×128, slice thickness 0.8 mm, TR 3 s and TE 20-120 ms. After imaging at 6 weeks, the rats received stereotaxic injection of 50 nl of 1 M $MnCl_2$ solution into the right (i.e., ischemic side) piriform cortex (PC, 3.2 mm anterior from bregma, 2.4 mm lateral from midline, and 7.4 mm ventral to skull surface). T_1-weighted images (T_1WI) were acquired 24 hrs later with the same geometric parameters as used in acquiring T_2WI, TR 300 ms and TE 13.5 ms. Relative T_1-weighted signal intensities of selected regions of interest (ROIs) were measured, normalized to that of the homolateral PC on the same imaging slice, and compared between the two groups with a Student's *t*-test.

Results The T_2WI acquired at 1d revealed that the ischemic rats had CP lesions, which largely resolved at 6 weeks after ischemia (Fig. 1). Compared to the control rats, the amount of Mn^{2+} (i.e., measured by relative Mn^{2+}-induced signal enhancement) transported from the PC to homolateral basal ganglia, sensorimotor cortex, thalamic nuclei and substantia nigra (SN) were significantly reduced in the ischemic rats (in the ipsilateral hemisphere to MCAO) (Fig. 2). The average enhanced area of SN, particularly that of substantia nigra pars reticulata (SNr), was significantly smaller in the ischemic rats (Fig. 1).

Discussion Previous results have demonstrated that the CP lesion resulted from MCAO is associated with selective neuronal loss, morphologically-intact fiber tracts and minimal consequent sensorimoter deficits. The results of this study show that, at 6 weeks after MCAO ischemia, the transportation of Mn^{2+} from the PC ipsilateral to ischemia to homolateral caudate putamen (CPu) and the brain regions connecting to the CPu via neuronal tracts, including globus pallidus, sensorimotor cortex, thalamic nuclei and SN, is impaired. Such impairment might either be the result of selective neuronal loss in the ipsilateral CPu (i.e., less neuronal Mn^{2+} uptake) or be due to functional deficits of neuronal tracts connecting CPu to the other nuclei implicated in motor control. The striatonigral terminals that form the synaptic contact with the nigroreticular neurons are primarily GABAergic [3], and the more prominently reduced signal enhancement of the SNr in the ipsilateral hemisphere may indicate that, in this MCAO ischemia model, the necrotic neurons in the ischemic striatum are mainly GABAergic neurons.

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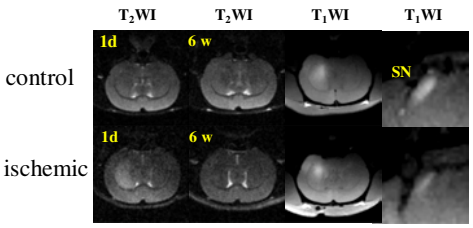

Figure 1. The left two columns show T_2-weighted images (T_2WI) of brain slices at the level of striatum acquired from a control rat and an ischemic rat at 1d and 6 weeks (6w) post-ischemia. Columns 3 and 4 show manganese enhanced T_1-weighted images (T_1WI) acquired at 6 weeks. Compared to control, signal enhancement of striatum and reticular pars of substantia nigra decreased significantly in the ischemic rats.

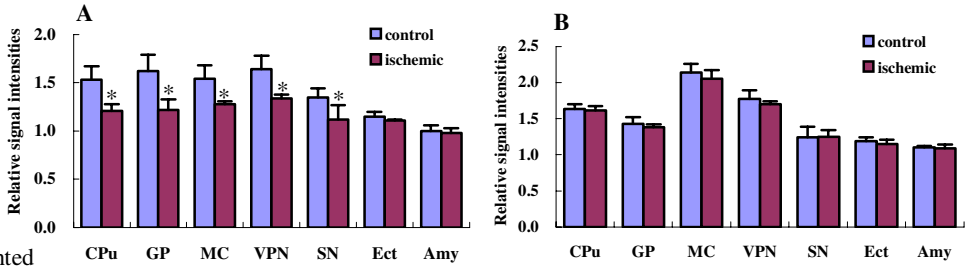

Figure 2. Relative T_1-weighted signal intensities of selected regions of interest (ROIs) in the hemispheres ipsilateral (also the ischemic side) (A) and contralateral (B) to manganese injection. All signal intensities were relative that of the homolateral piriform cortex on the same imaging slice. Compared to the control rats, the ischemic rats had significantly reduced relative signal intensities in the ipsilateral caudate putamen (CPu), globus pallidus (GP), sensorimotor cortex (MC), ventral posterior nucleus thalamus (VPN) and substantia nigra (SN). No statistically significant differences were found for the ipsilateral entorhinal cortex (Ect), amygdala (Amy), and all contralateral ROIs.

References: [1] H.J. Groenewegen, Neural Plast 10 (2003) 107-120. [2] S. Wegener, et al, J Cereb Blood Flow Metab 26 (2006) 38-47. [3] M. von Krosigk et al, Neuroscience 50 (2001) 531-549.