Late Manganese-enhanced MRI of Rat Cortical and Subcortical Structures

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INTRODUCTION: Manganese (Mn) has been increasingly used as a positive MR contrast agent to study both structures and functions in the central nervous system (CNS). Several studies indicated that the brain tissues were mainly enhanced maximally in T1WI at 1 day after systemic administration of MnCl\textsubscript{2} in rodents (1,2). However, the specific cellular fate of Mn following overexposure is not yet fully understood (3,4). In this study, Mn-enhanced MRI (MEMRI) was performed at later time points to better understand the mechanisms related to the uptake, distribution and action of Mn in rat brain tissues before its global clearance from the brain.

MATERIALS AND METHODS: Sprague-Dawley rats (250-300 g, N=6) were prepared and injected intraperitoneally with MnCl\textsubscript{2} solution at 45mg/kg and 100mM. MEMRI was performed before, and at 1, 5 and 12 days after injection. All MRI measurements were acquired utilizing a 7 T Bruker scanner under inhaled isoflurane anaesthesia. 2D T1-weighted RARE sequence was acquired with FOV = 3.2 x 3.2 cm\textsuperscript{2}, matrix resolution = 256 x 256, slice thickness = 1 mm, number of slices = 10, TR/TE = 400/7.5 ms, RARE factor = 4 and NEX = 16. The mean signal intensities (SI) of the ROIs at 12 brain components were measured using ImageJ v1.40g with reference to the rat brain atlas, and were normalized to the pre-injection time point to evaluate the rate of signal increase after Mn\textsuperscript{2+} administration. Signal changes of the same brain component were compared using two-tailed paired t-tests. Results were considered significant when p<0.05.

RESULTS: Systemic MnCl\textsubscript{2} injection resulted in an increase in T1W SI in all brain components measured at Day 1 and Day 5 compared to pre-injection (p<0.05) (Figs. 1-2). In the components in Fig. 2a, signal enhancement was found to maximize at Day 1. However, in the central amygdaloid nucleus, globus pallidus and ventral pallidum, a higher signal increase was observed at Day 5 than the other 3 time points (p<0.05) (Fig. 2b). The caudate putamen and thalamus were also apparently enhanced maximally at Day 5 compared to Day 1 (p<0.15). Distinct cortical layers were observable at both Day 1 and Day 5 (Fig. 3), but were not apparent before or at Day 12 after Mn administration. SI in all brain structures decreased from Day 5 to Day 12 (p<0.05).

DISCUSSIONS AND CONCLUSIONS: Transport of Mn from plasma into CNS parenchyma takes place across both the cerebrospinal fluid (CSF) and the cerebral capillaries (5). While Mn can diffuse and enter excitable cells via voltage-gated Ca\textsuperscript{2+} channels (1,2), structures with SI maximization at Day 1 in the current study possess high contents of glutamine synthetase (GS)(6), which may reflect high glutamatergic activities (7). Since GS is 30% saturated with Mn only (5), the metalloproteins in these structures may uptake more Mn diffused after systemic Mn administration (4,8,9); whereas in the striatum before global clearance of Mn from the brain at Day 12. These may help understand the dynamic properties of the Mn uptake and distribution in the neuronal pathways, and may provide a basis for more controllable design of intrinsic AR\textsuperscript{2+}, comparisons in the normal, developmental, and pathological brains at different time points upon systemic Mn administration.