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 $MnCl_2$ 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 $MnCl_2$ 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^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^{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 $MnCl_2$ 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^{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 with relatively low GS contents (6), signal enhancement at Day 1 was apparently less pronounced compared to its surrounding subcortical structures (Fig. 1).

At Day 5, all brain structures remained significantly enhanced compared to pre-injection. As an extension to a previous study on systemic MEMRI of the cortex at Day 1 (10), the laminar architecture of the cortex could also be distinguished at Day 5 in this study, indicative of the slow efflux rate of Mn. At the same time, structures in Fig. 2b possessed further accumulation of Mn. It has been reported that CSF-brain uptake followed by redistribution through axonal transport is likely the major route of accumulation for systemic overexposures to Mn (2,3). While there are many parts of the neocortex innervating the caudate putamen, the nucleus accumbens and the caudate putamen also provide efferent fibers to the ventral pallidum and the globus pallidus (5). In addition, the amygdaloid complex and thalamus are reciprocally connected with multiple cortical sensory systems capable of conveying highly processed information from visual, auditory, tactile and gustatory cortices. Our results suggested the continuous redistribution of Mn through axonal transport in the late phase of systemic Mn administration 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 ΔR_1 comparisons in the normal, developmental, and pathological brains at different time points upon systemic Mn administration.

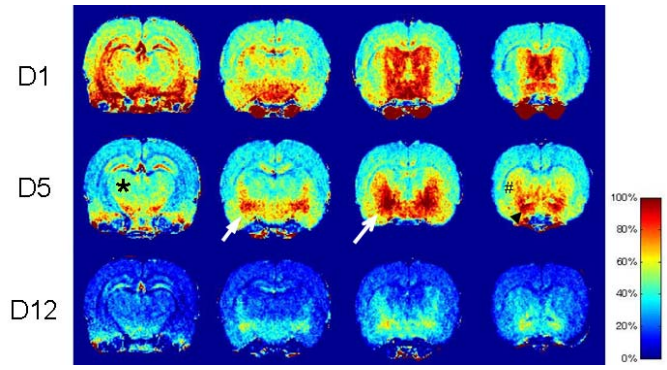

Fig. 1: Representative percentage maps of T1W signal increase relative to pre-injection at 1, 5 and 12 days after systemic Mn administration at Bregma = -3.72mm, -1.80mm, -0.60mm and 0.36mm (left to right). Note the apparent maximal signal enhancement ay Day 5 in the central amygdaloid nucleus (solid arrow), globus pallidus (open arrow), ventral pallidum (arrowhead), caudate putamen (#), and thalamus (*) when compared to other time points.

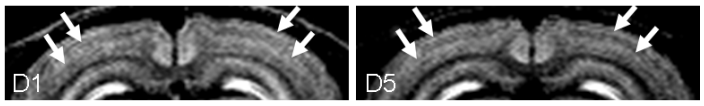

Fig. 3: Windowed T1WIs of the cortex at Bregma -4.80mm at 1 (left) and 5 days (right) after Mn^{2+} administration. Note the distinct cortical layers observable at both time points (arrows).

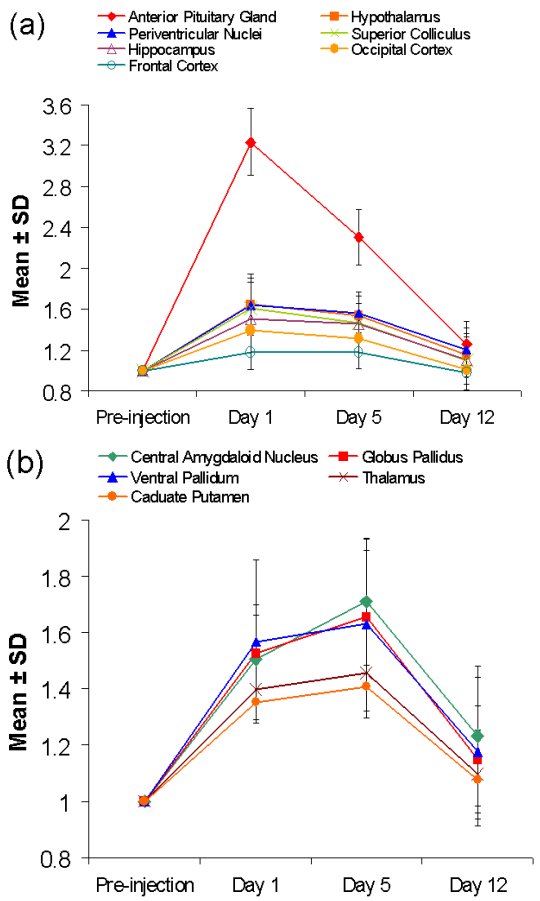

Fig. 2: Time profile of T1W signal increase at different brain components. Significant increase in T1W signal intensities was observed in all components measured at Day 1 and Day 5 after injection ($p<0.05$). Note the maximal enhancement at Day 1 in the brain components in Fig. 2a, compared to those with maximal enhancement at Day 5 in Fig. 2b.

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