In vivo Measurements of T1 Relaxation Times in Mouse Brain Associated with Different Modes of Systemic Administration of Manganese Chloride

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Introduction: There is increasing interest in the use of high field MRI and manganese enhanced MRI (MEMRI) to assess subtle changes in anatomical or functional information in murine models of disease (1). Although $MnCl_2$ has proven to be a potentially useful T1 contrast agent for MRI studies in animal models (2, 3), there has been no systematic assessment of the effect of the route of administration. Moreover, in addition to the fact that T1 varies with field strength, there is further evidence demonstrating that contrast enhancement can also vary with field strength (4, 5). Despite this, the T1 and T2 values of mouse brain at high-field strength (>9 T) and their changes after $MnCl_2$ administration have not been measured systematically in vivo. The aim of this study was to determine the T1 and T2 relaxation times and regional changes in T1 in murine brain after intravenous (IV), intraperitoneal (IP), or subcutaneous (SC) administration of $MnCl_2$. The results from this study will help to develop optimal protocols and new MRI sequences to maximize the application of $MnCl_2$ at high fields.

Materials and Methods: C57Bl/6 mice (12 – 15 weeks old, 20-25 g, Harlan, UK) were anaesthetized and baseline T1 and T2 measurements obtained prior to measurement of T1 after administration of $MnCl_2$ at 9.4T. $MnCl_2$ was administered systemically either by IV, IP, or SC routes. MRI measurements were performed by standard spin-echo multislice sequence. IV (N = 6), IP (N = 5), and SC (N = 6) injections were administered at doses of 5, 5 and 10ml/kg body weight, respectively. For IV and IP groups, T1 measurement was done at 15 min, 45 min, 24 h and 72 h post-$MnCl_2$ administration, while only 24 h and 72 h scans were performed for SC group. T1 and T2 maps for each MRI transverse slice were generated using commercial software (IDL, Research System Inc, Boulder, CA). The T1 and T2 values of white matter (WM) structures (corpus callosum [cc], internal capsule [ic], external capsule [ec] and anterior commisure [aca]), gray matter (GM) structures (cerebral cortex, thalamus, hypothalamus, lateral globus pallidus [LGP], caudate putamen [CPu], hippocampus, red nucleus [RMC], pontine reticular nucleus [PnO]), anterior (AP) and posterior pituitary (PP) gland and lateral ventricle (LV) were obtained by drawing regions of interest (ROI) on standard anatomic images (Fig 1) and then transferred to T1 or T2 map. ANOVA was used to compare the difference in T1 between different groups and different time point. A $P < 0.05$ was considered statistically significant.

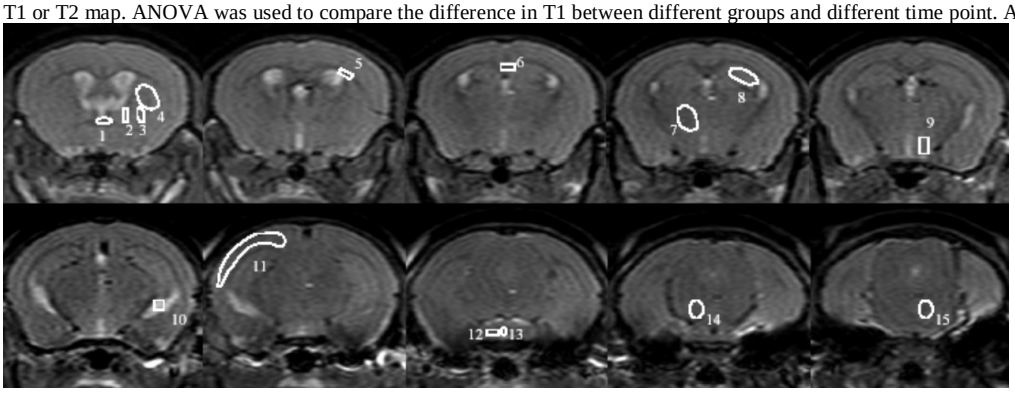

Fig 1. Proton-density images (TR/TE = 6000/18 msec, NEX = 1, matrix = 256 x 128) show the ROI locations from which T1 and T2 measurements were determined. 1 = aca, 2 = ic, 3 = LGP, 4 = CPu, 5 = ec, 6 = cc, 7 = thalamus, 8 = hippocampus, 9 = hypothalamus, 10 = LV, 11 = cortex, 12 = AP, 13 = PP, 14 = RMC, 15 = PnO

Results & Discussion

When compared with baseline values at lower-field, significant lengthening of the T1 values was shown at 9.4T, while no significant change was seen for T2 values (Table). Significant T1 shortening of the normal mouse brain was observed following IV (Fig 2), IP, and SC administration of $MnCl_2$, with IV and IP showing similar acute effects. Significant decreases in T1 values were seen for the pituitary gland and the ventricles 15 min after either IV or IP injection. GM showed greater uptake of the contrast agent than WM at 15 and 45 min after either IV or IP injections. GM structures, compared to WM counterparts, are mainly composed of cell bodies of neurons and also have higher microvessel density and may explain the greater manganese deposition in GM than in WM. These three routes caused no significant difference in the mean T1 times either at 24 ($P = 0.3$) or 72 hr ($P = 0.07$). However, higher-dose SC injection caused significantly lower T1 values at 72 hr ($P = 0.03$) than the lower IV and IP dose, while it did not achieve statistical difference at 24 hr after $MnCl_2$ administration ($P = 0.2$). Although both structures are within the blood-brain barrier (BBB), GM and WM revealed a steady decrease in T1 values at 24 and 72 hr after $MnCl_2$ injection regardless of the route of administration.

Anatomy	T1 times (N = 4)	T2 times (N = 4)
aca	1611.5 ± 152.8	36.0 ± 1.7
cc	1780.6 ± 133.2	35.4 ± 5.6
ec	1691.6 ± 146.6	32.2 ± 0.6
ic	1633.1 ± 151.7	31.7 ± 1.6
LGP	2037.2 ± 170.0	39.4 ± 1.4
CPu	2029.1 ± 168.9	39.1 ± 1.4
cortex	2132.7 ± 133.9	40.3 ± 0.5
hippocampus	2158.3 ± 127.0	43.6 ± 3.4
thalamus	1861.6 ± 123.3	36.4 ± 0.6
hypothalamus	1924.4 ± 151.8	37.2 ± 1.1
RMC	1904.7 ± 185.9	36.7 ± 1.7
PnO	1881.9 ± 169.8	38.2 ± 0.9
AP	1716.8 ± 208.5	32.0 ± 5.4
PP	1069.2 ± 142.1	30.4 ± 4.9
LV	4286.7 ± 1049.8	111.3 ± 10.7

Table

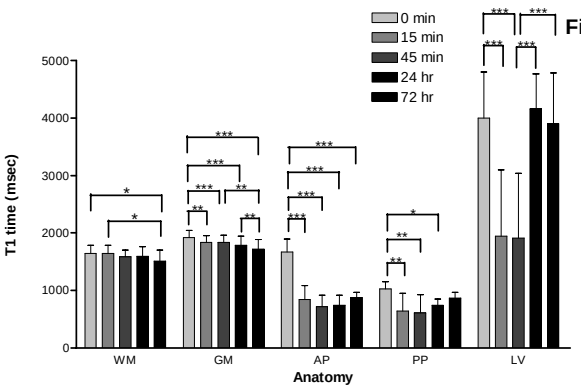

Fig 2 Changes in T1 relaxation times after IV administrations of $MnCl_2$. Results are given as the mean ± SD. * indicates $0.01 < P < 0.05$ (ANOVA with multiple comparison procedure), ** $0.001 < P < 0.01$ and *** $P < 0.001$.

Conclusion: Systemic administration of $MnCl_2$ by IV and IP routes induced similar time-course of T1 changes in different regions of the mouse brain. Acute effects (< 1h) of $MnCl_2$ administration were mainly influenced by either the presence or absence of BBB. Nevertheless, for some structures within BBB such as GM, IV and IP $MnCl_2$ are able to shorten their T1 values at acute stage, and all three routes can induce significant T1 shortening for both GM and WM at subacute stage (> 24h).

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