Regional Difference in Mn Uptake and Retention in Mouse Brain

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Introduction

Mn has been used as a contrast agent for enhancing neuroanatomy in MRI [1,2]. Administration of $MnCl_2$ leads to signal enhancement in different brain regions due to difference in density, type, and activity of the cell. Mn-enhanced MRI for neuroanatomical studies are usually performed at 1 day after systemic Mn^{2+} administration as significant enhancement could be seen in specific brain regions [3]. But different brain regions could have different rates of Mn uptake and retention, and therefore scanning animals 1 day after Mn injection may not maximize the signal difference for visualization of different anatomical structures. In this study, we used changes in T1 relaxation rate (ΔR1) compared to the preinjection as an estimate of brain Mn concentration [4] to evaluate the difference in Mn uptake and retention in different brain regions.

Materials and methods

Animal study was approved by the local Institutional Animal Care and Use Committee. Total 8 female C57BL/6 wild-type mice were examined in this study. All animals were scanned before Mn injection (day 0) and at various time points following injection of 0.1 M MnCl2 intraperitoneally with dosage of 80mg/kg body weight at 0.25ml/hr infusion rate. Post-injection scans were performed at different sets of days on different animals to cater for wide range of study time points. 3 animals were scanned at 1, 4, 7, 10, 14, 21 and 28 days; 2 were scanned at 1, 7, 14, 21 and 28 days; 2 were scanned at 2 and 3 days; and the last animal was scanned on 1, 4, 7 and 10 days post-injection. Images were acquired on a 9.4T/31-cm magnet interfaced to a Varian console. T1 relaxation times were measured using a 2D Look-Locker sequence (TR = 10s, TE = 3 ms, flip angle = 20°, relaxation interval = 400 ms, sample points = 20, Voxel size = 0.11x0.11x0.50 mm^3) and T1 was calculated using a non-linear least-squares fitting algorithm and subsequent post-processing to compensate the effect of flip angle [5]. ROI selections were done manually in Dentate Gyrus (DG), Thalamus (TH), Olfactory Bulb (OB), Cerebellum (CB), Hypothalamus (HT) and Caudate Putamen (CPu) with the aid of Paxinos Mouse Brain Atlas [6] as shown in FIG 1. Changes in the R1 (1/T1) relaxation rates relative to the preinjection (i.e., $\Delta R1 = 1/T1_{DayN} - 1/T1_{day0}$) were calculated and plotted against time in FIG 2. The averaged ΔR1 values of the time course was fitted with a gamma variate function (eq. 1) using non-linear least square fitting (FIG 3). The time-to-peak (TTP), peak ΔR1 value and half life ($T_{1/2}$) were derived from the fitted function, while the Mn uptake rate was estimated by dividing the peak ΔR1 by TTP (Table 1).

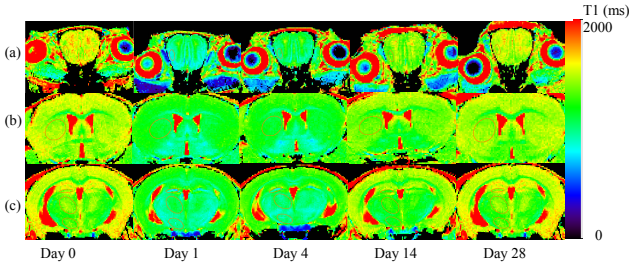

FIG. 1. Time series T1 maps from the same mouse at day 0, 1, 4, 7, 10, 14, 21 and 28 after Mn injection. Selected ROIs were shown in (a) CPu, (b) DG, TH and HT, (c) OB.

$$f(t) = \frac{t^{\alpha} e^{-t/\beta}}{\beta^{(\alpha+1)}\Gamma(\alpha+1)} \times \eta \cdots Eq(1)$$

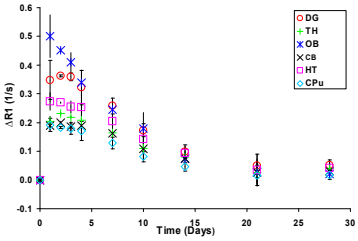

FIG. 2. Temporal changes in ΔR1 in different brain regions. Error bar represents standard deviation.

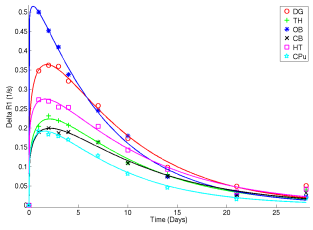

FIG. 3. Gamma variate fitting of temporal changes of ΔR1 for different regions

Table 1: Estimated values of TTP, Peak ΔR1, half-life ($T_{1/2}$) and uptake rate from gamma variate fitting

ROI	TT	Peak ΔR1	$T_{1/2}$	Uptake Rate
DG	1.8	0.36	9.9	0.20
TH	2.0	0.22	10.7	0.11
OB	0.6	0.51	6.6	0.90
CB	2.1	0.20	11.5	0.09
HT	1.6	0.27	10.6	0.17
CPu	1.6	0.19	8.9	0.12

Results and discussion

Large reductions in T1 relaxation times were observed throughout the brain on day 1 (FIG. 1). Temporal changes in ΔR1 shows Mn concentration reached peaks between day 1 to day 3 postinjection and regional differences in uptake rate and peak value can be clearly observed in FIG. 2. ΔR1 values were reported to correlate with the regional uptake and bioelimination of cerebral Mn [3,4] and therefore ΔR1 time courses could be regarded as the relative concentration-time curves of Mn^{2+} contrast media. Since the ΔR1 time course has a rather quick rise to the peak followed by an exponential type of decay which is very similar to the indicator dilution time course following injection of contrast agents, we approximated it by a gamma variate model [7]. It could be seen from FIG. 3 that the gamma variate model fits nicely to ΔR1 time courses of most brain regions. Brain regions with slower time-to-peak, like the Thalamus, can be modeled better because day 2 and 3 fall in the uptake phase, where as, more samples between day 0 and 1 will be required for more accurate estimation of regions with much faster uptake like the olfactory bulb. Unlike generally assumed peaking at day 1, there are considerable regional differences in time-to-peak, peak value and half-life (Table 1). Taking both the peak value and TTP into account, the OB has fastest uptake, followed by DG, HT, and with CB the slowest. The estimated half-life also varied around 7 to 12 days, which is similar to that estimated in the rat brain [4]. Further studies will include imaging at earlier time points for better estimation of uptake rate. Application of this estimation method in animal models with modified transport mechanism will facilitate the study of specific transporters involved in transport of Mn and other divalent metals. This technique will also guide the selection of best timing for maximizing contrasts in neuroanatomical studies.

References:

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