Myelin Mapping in Mouse Brain *in Vivo* Using Contrast-Enhanced Magnetization Transfer MRI

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Introduction

Myelin, which creates the typical glistening appearance of the white matter (WM), has a higher lipid content (> 40%) and a lower water content (about 40%) than the rest of the brain tissue (about 8% and 80%, respectively). While the protons of respective lipids yield T2 relaxation times that are too short to be directly detected by conventional MRI, the magnetization transfer (MT) MRI [1] has been proven useful for mapping myelin-rich WM. The MT method relies upon the indirect saturation of mobile water protons by off-resonance irradiation of highly immobilized protons bound to macromolecules. In general, the saturation of water protons by MT competes with the recovery of the longitudinal magnetization by T1 relaxation. Therefore, the administration of T1-shortening manganese ions (Mn^{2+}) (for a review see [2]) improves the contrast in MT MRI [3] because Mn^{2+} ions can be preferentially delivered to non-WM tissues. The hydrophilic Mn^{2+} ions are assumed to gain no access to the hydrophobic parts of the myelin, so that Mn^{2+} ions are less concentrated in myelin-rich WM and more concentrated in water-rich gray matter (GM). Extending this work, the idea here is to further improve the contrast by delivering Gd-DTPA preferentially to GM. While Mn^{2+} ions are assumed to mainly accumulate within the cells, Gd-DTPA is distributed over the extracellular space. Therefore these two hydrophilic paramagnetic substances are expected to efficiently complement each other in shortening the T1 of GM. The purpose of this study was to examine whether the intraventricular injection of Gd-DTPA improves the contrast between WM and GM in MT MRI of the central nervous system of living mice with and without manganese administration.

Methods

Animals. Fourteen mice (NMRI, 8—12 weeks, 30—46 g) were used. Five mice received a subcutaneous injection of manganese chloride (0.12 mmol/kg body weight) followed by an intraventricular injection of Gd-DTPA dissolved in physiological saline (5.0 μL, 100 mM, Magnevist®, Schering, Berlin, Germany) two days later. Another four mice received the intraventricular injection of Gd-DTPA only. The other five mice received the subcutaneous injection of manganese chloride only.
MRI. Before and after the injections, MRI measurements were carried out at 2.35 T using a MRBR 4.7/400 mm magnet (Magnex Scientific, Abingdon, UK). Radiofrequency (RF) excitation and signal reception were accomplished with use of a Helmholtz coil (inner diameter 100 mm) and an elliptical surface coil (inner diameter 20×14 mm), respectively. For MT-weighted MRI, an off-resonance RF irradiation with a frequency offset of 5 kHz and a mean amplitude of 200 Hz (flip angle 1045°) was incorporated into a spin-density weighted gradient-echo MRI (RF-spoiled 3D FLASH, TR/TE 30/7.6 ms, α 5°) at 117×156×156 μm resolution [4]. Magnetization-transfer ratio (MTR) was obtained from acquisitions with and without the off-resonance RF irradiation. T1 relaxation times of WM and GM were determined using a spin-echo multiple TR saturation recovery method. For evaluation of signal intensities, regions-of-interest were selected in WM (corpus callosum, external capsule, fimbria, ventral hippocampal commissure, cerebellar white matter), in GM (prelimbic cortex, thalamus, hippocampal formation), as well as in the cerebrospinal fluid (CSF).

Results and Discussion

As shown in **Fig. 1**, the delineation of WM with the use of MT contrast is considerably improved after the combined use of Mn and Gd-DTPA. This contrast enhancement can be explained by a number of quantitative evaluations summarized in **Table 1**. The combined use of Mn and Gd-DTPA increased the SNR by 26% in WM and 46% in GM, which resulted in a CNR improvement between WM and GM by 121%. The underlying T1 shortening due to the paramagnetic agents reduced the mean MTR by 31% and 56% in WM and GM, respectively. Accordingly, the T1 shortening enhanced the mean SNR in T1WI by 31% in WM and by 109% in GM. These findings can be explained by the drastic shortening of T1, which turned out to be much more pronounced in GM (– 62%) than in WM (– 39%). **Table 1** also shows that a single use of Mn or Gd-DTPA has the similar differential effect, i.e., more pronounced in GM than in WM. But each agent alone has a weaker T1-shortening effect than the combined use.

The T1 measurement also shows that Mn^{2+} administration alone does not effectively shorten the T1 of CSF. This is in line with our previous observations that CSF itself hardly shows signal enhancement after a systemic or after an intraventricular administration, even of a very high dose. Presumably, only after taken up into the cells and bound to intracellular substances, Mn^{2+} ions cause an effective T1 shortening and thus a clear MRI signal enhancement. In contrast to free Mn^{2+} ions, Gd-DTPA alone readily shortens the T1 of extracellular fluid in such a way that the signal intensity of CSF is greatly enhanced in T1W MRI following the intraventricular injection. Thus, intracellular Mn^{2+} and extracellular Gd-DTPA efficiently complement each other in shortening the T1 of brain tissue fluid.

In conclusion, an intraventricular Gd-DTPA administration enhances the WM/GM contrast in MT MRI, which can be complemented by a systemic administration of $MnCl_2$.

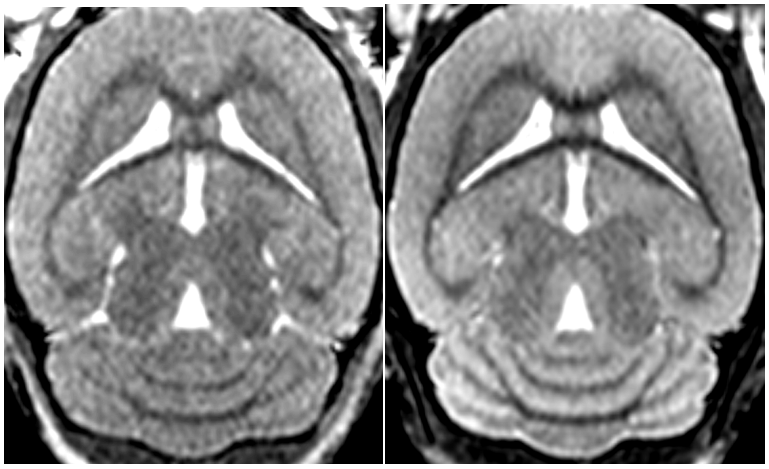

Fig.1 Magnetization-transfer weighted (see Methods) images of the brain (horizontal section) of a mouse (left) before and (right) after injections of $MnCl_2$ and Gd-DTPA.

Table 1. SNR, CNR and MTR in Magnetization-Transfer MRI, SNR in T1WI, and T1 Relaxation Times in Brain Tissue of Mice Before and After Contrast Agent Injection

		Control	+ Mn + Gd-DTPA	+ Mn	+ Gd-DTPA
SNR	**WM**	13.7 ± 0.9	17.2 ± 2.0 **(+26%)**	14.0 ± 1.3 (+2%)	14.8 ± 2.0 (+18%)
	GM	17.3 ± 1.0	25.3 ± 2.7 **(+46%)**	18.6 ± 1.8 (+8%)	22.7 ± 2.5 (+36%)
CNR (GM-WM)		3.7 ± 0.2	8.1 ± 0.9 **(+121%)**	4.7 ± 0.4 (+31%)	7.8 ± 0.6 (+92%)
MTR	**WM**	0.51 ± 0.01	0.35 ± 0.03 **(-31%)**	0.49 ± 0.04 (-5%)	0.39 ± 0.03 (-25%)
	GM	0.47 ± 0.01	0.20 ± 0.02 **(-56%)**	0.41 ± 0.02 (-12%)	0.24 ± 0.03 (-48%)
SNR (T1WI)	**WM**	14.0 ± 0.3	18.5 ± 0.8 **(+31%)**	15.7 ± 0.8 (+9%)	17.3 ± 0.7 (+23%)
	GM	12.4 ± 0.3	26.0 ± 1.1 **(+109%)**	16.0 ± 0.4 (+23%)	23.9 ± 2.0 (+81%)
T1 (ms)	**WM**	818 ± 66	503 ± 72 **(-39%)**	758 ± 107 (-10%)	581 ± 63 (-26%)
	GM	1294 ± 27	494 ± 37 **(-62%)**	919 ± 85 (-31%)	592 ± 73 (-55%)
	CSF	2751 ± 272	304 ± 72	2658 ± 109	299 ± 59

Values are given as mean ± SD; Values given in parentheses: % change from before the injection; CNR: contrast-to-noise ratio.

References

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