High-Field MRI Detection of Magnevist Permeation Into Normal Mouse Brain Parenchymal and Ventricular Spaces

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INTRODUCTION The impedance of the blood-brain-barrier (BBB) to small molecule contrast agents (CAs) is well known, and useful for distinguishing cerebral pathology such as tumors, *via* relative CA-enhancement. However, it is known, from various small compounds that can be sensitively detected (radiotracers, etc), that these do cross the BBB, and evidence of standard small molecule MRI CA permeation in normal brain (~1-3% image intensity increases) has been observed at 3T (**1**) and 4T (**2**) More direct confirmation of these observations would have important implications both for MR-based molecular imaging, and for the potential for using (Dynamic-Contrast-Enhanced) DCE-MRI approaches. Determination of DCE-MRI parameters (K^{trans} measures the CA extravasation rate constant) in normal brain would enable detection of subtle perturbations from normal physiology. The detection sensitivity of MRI CAs has been predicted to increase with magnetic field strength due to tissue ^1H_2O T_1 increases, and the synergistic CA T_1 decrease.(**3**) We tested the hypothesis that permeation of standard monomeric Gd(III) chelate MRI CAs could be clearly detected in normal brain at ultra high field (8.5T). Our strategy to maximize CA entry into normal mouse brain parenchyma was to implement gradual i.v. $GdDTPA^{2-}$ (Magnevist) infusions sustained over long time periods.

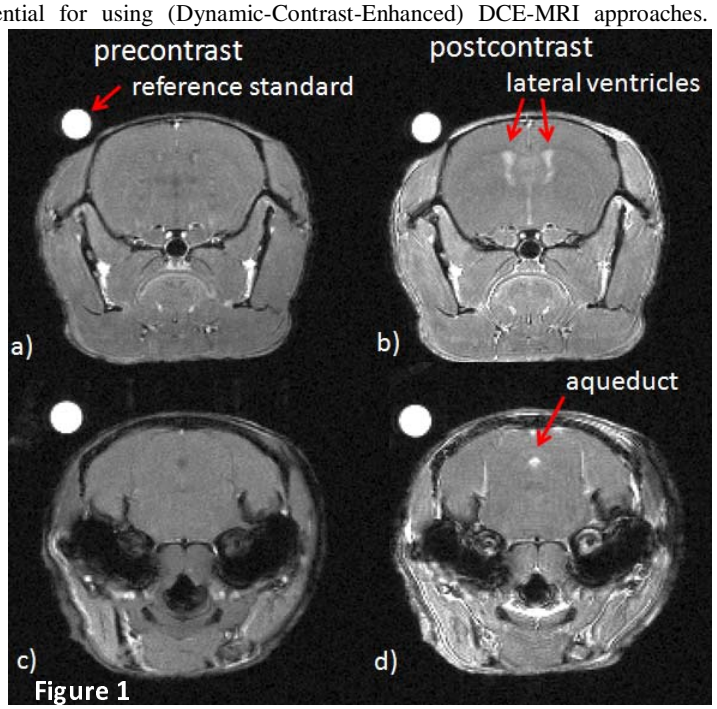

Figure 1

METHODS MR imaging was performed on a Bruker-Biospin 8.5T vertical wide-bore DRX-360 with an AVANCE console, a Paravision 3.0.2 software platform, and a Mini0.5 imaging system equipped with a 56 mm (ID) gradient set, and 20 mm birdcage resonator. Anesthesia and temperature were maintained with isoflurane and a thermostatted water blanket, respectively, while periodic saline infusions (i.p.) ensured proper hydration. Various (i.v) infusion rates (24-68 µL/hr-g) and times (1-2.5 hrs) of 8X diluted Magnevist were tested while multislice T_1-weighted images were continuously obtained (slice thickness 0.5 mm, (98 µm)^2 in-plane resolution).

RESULTS **Figure 1** compares pre- and post-contrast coronal-equivalent mouse head images, with **b)** and **d)** obtained after 2.5 hrs of (i.v.) infusion (8X-dilutedMagnevist, 35 µL/g-hr). **Figure 2** indicates the time-dependences of fractional intensity increases in various regions. As expected, large image (55%) intensity increases were observed in muscle tissue. Interestingly, marked intensity increases were observed in the ventricular system, 31% and 88% at the lateral ventricles and aqueduct, respectively. Importantly, substantial maximum fractional increases (11%) were also observed in nonventricular parenchymal brain. Of note is that interleaved single-slice T_1 images employing inflow saturation indicated that CA blood concentrations within major vessels had quickly reached a steady state during the infusion (not shown), paralleling the muscle tissue timecourse. The average maximum fractional increases (± SE) for various infusion protocols (n=4) are shown in **Table 1.**

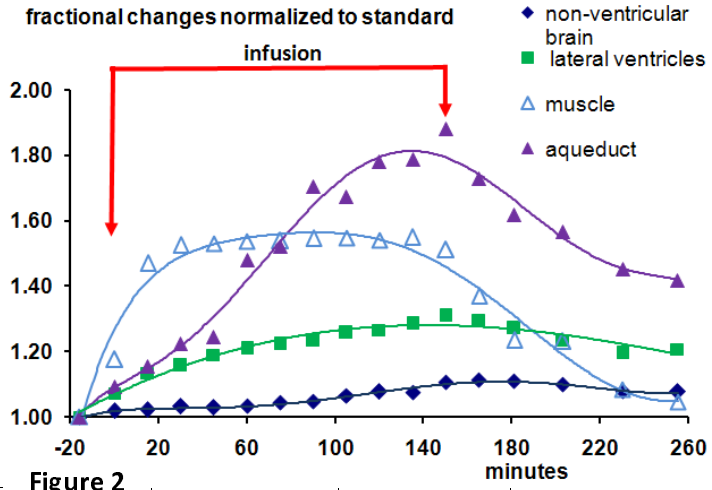

Figure 2

Non-ventricular brain	Lateral ventricle	aqueduct	muscle
1.086 (±0.009)	1.298 (±0.038)	1.707 (±0.105)	1.501 (±0.049)

DISCUSSION Two important observations emerge. First, substantial T_1-weighted image intensity increases at cerebral ventricular compartments were detected early during the sustained infusions. The rapid CA uptake into ventricular spaces suggests entry *via* the *choroid plexus*. To our knowledge this has not been previously reported, and may enable studies of CSF production and ventricular clearance. Second, the infusion protocols succeeded in inducing substantial image intensity increases [9(±1%)] in nonventricular brain parenchyma. This provides clear evidence that standard small molecule MRI CA permeation does occur and can be definitively observed with ultra high field MRI. Entry of CA into brain parenchyma could occur either *via* BBB crossing and/or CA transport from ventricular spaces. Comparison of various infusion protocols with increasing infusion rate or times suggested a diminishing ability to increase parenchymal CA uptake. This suggests net accumulation may be limited by slow entry combined with robust removal mechanisms.

CONCLUSIONS These data provide direct and convincing observation of standard small Gd(III) molecule MRI CA entry into normal brain ventricular and parenchymal spaces, consistent with the concept that high field MRI increases CA detection sensitivity. This potentially enables implementation of powerful new CA approaches in normal and diseased brain.

(**1**) Li, Kohama, Hobbs, Rooney, Jerosch-Herold, and Springer ; *PISMRM* **15**:1434 (2007). (**2**) Rooney, Telang, Springer, *PISMRM* **10**:1314 (2002). (**3**) Rooney, Johnson, Li, Cohen, Kim, Ugurbil, Springer, *MRM* **57**:308-318 (2007).