Distribution Characteristics of Intraventricularly Infused GdDTPA, GdDOTP, and GdDTPA-BMA in Rat Brain.

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Introduction. The successful presentation of MR contrast agents throughout the brain parenchyma would allow investigations of the physiological environment with high spatial and temporal resolution but is hampered by the presence of a blood brain barrier. The present study characterizes the distribution kinetics of charged and uncharged gadolinium contrast agents in the cerebrospinal and interstitial fluids of rat brain. Since the blood brain barrier precludes delivery by vascular routes, agents are infused directly into ventricular cerebrospinal fluid whereby useful quantities of agent occur throughout the brain parenchyma for up to 20 hours after infusion. We demonstrate a linear response in T_1-dependent signal changes over a 4-fold range of $GdDOTP^{5-}$ or $GdDTPA^{2-}$ infusate concentrations with maximum agent doses decreasing T_1 throughout the brain by up to an order of magnitude. Additionally, we compare the distribution characteristics of these negatively charged Gd-chelates to those of the uncharged amide analog of $GdDTPA^{2-}$, GdDTPA-BMA.

Materials and Methods. All experiments where performed on male Sprague-Dawley rats weighing between 390 and 420 gms. Isofluorane anesthesia was employed. A stereotaxic frame (Stoelting) was used to position a 26 Gauge infusion cannula to a depth of 3.4 mm from the dural surface at 1 mm posterior and 1.4 mm lateral from bregma. The contrast agents used in this study where prepared as solutions with concentrations ranging between 75 and 250 mM by diluting Magnevist® (Berlex) for the $GdDTPA^{2-}$, dilution of Omniscan® for the GdDTPA-BMA, or by making up fresh solutions of $GdDOTP^{5-}$ (in powder form from Macrocyclics) which were sterilized by pushing through a 0.02 µm syringe fllter. Images were acquired at 9.4 T with a Varian imaging spectrometer using a 3.2 cm surface coil. T_1 maps were obtained by inversion recovery gradient echo (Turboflash) MRI from a rat prior to, and at a range of times between 4 and 16 hours after infusing either GdDTPA-BMA, $GdDTPA^{2-}$, or $GdDOTP^{5-}$, respectively. Images were acquired in 2 centric-ordered k-space segments with TE=2 ms, TR=5 ms, 128x128 matrix, 3x3 cm FOV, 1 mm slice, 8 ms adiabatic full passage inversion pulse, 1 ms Gaussian 90º pulse, with inversion time delays of 0.01, 0.05, 0.2, 0.4, 0.7, 1, 1.4, 2, 3, 4, and 6 sec. Individual T_1 maps have a spatial resolution of 0.312 x 0.312 x 1 mm^3 and were acquired in 2 minutes per slice. The *in vivo* response of brain T_1 to contrast agent dose was measured for 75, 112, 187, and 250 mM GdDOTP solutions delivered in a 30 µL volume at a constant infusion rate of 6 µL/hr over 5 hours through the infusion cannula placed in the left lateral cerebroventricle (corresponding to GdDOTP doses of 2.25, 3.4, 5.6, and 7.5 µmol). Lighter grey-scale color of the brain corresponds to shorter T_1 values due to higher [Gd-chelate] in a region of interest (greyscale bar, Figure 1, calibrated from 0 to 5 seconds).

Results and Discussion. The primary goal of this study was to demonstrate the efficacy of consistently delivering Gd-chelate contrast agents of interest throughout the brain parenchyma by infusion to the CSF of the lateral ventricles. To this end, we demonstrate that it is possible to deliver Gd-chelates in a dose-dependent manner with a linear response in brain T_1. This is demonstrated for a four-fold range of GdDOTP doses in Figure 1. It is also clear that the agents undergo significantly different distribution kinetics as seen in Figure 2, where a significant difference in brain T_1 for GdDOTP, GdDTPA, and GdDTPA-BMA, respectively, is observed at each respective time-point after infusion. Still it is evident that the charge state of the Gd-chelate does not play a significant role in precluding agent exchange across the negatively charged ependymal membrane which demarcates cerebrospinal and brain extracellular fluid compartments. This is contrary to earlier studies suggesting that only uncharged agents such as GdDTPA-BMA can undergo significant exchange across the ependymal membrane [1,2]. These studies employed an acute injection of agents over several seconds in contrast to the prolonged several hour infusions in the present study. Additionally, our results point to the importance of infusing agents of interest into the headwaters of CSF flow in the lateral ventricles if one desires to deliver significant quantities of agent throughout the brain, in contrast to sites further down the stream of CSF flow such as the cisterna magna [3]. From linear fits to the T_1 time-courses in Figure 2, these Gd-chelates are cleared from the brain with rate constants of 0.03, 0.04, and 0.05 hr^{-1} for $GdDTPA^{2-}$, $GdDOTP^{5-}$, and GdDTPA-BMA, respectively. The $GdDTPA^{21}$ washout rate is similar to that reported by Quirk and coworkers [4]. For the maximum dose used, there were no apparent effects to the rats with GdDTPA or GdDTPA-BMA, but there was an acute effect to cardiac and pulmonary function leading to pulmonary edema and a markedly increased heart rate. These effects were only evident during and for 1 to 2 hours after the infusion and could be mitigated by specific pharmaceutical interventions.

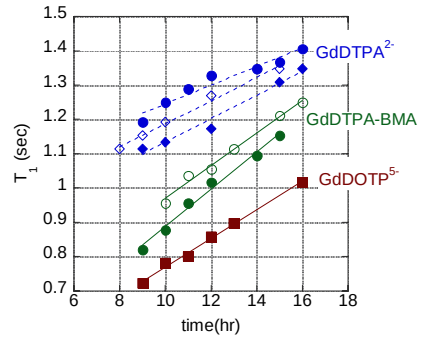

Figure 2. T_1 time-course from different rat brains infused with identical quantities of either $GdDTPA^{2-}$, $GdDOTP^{5-}$, or GdDTPA-BMA. The x-axis is hours after completion of the infusion surgery. The T_1 values were obtained from axial whole brain ROI's similar to those shown in Figure 1.

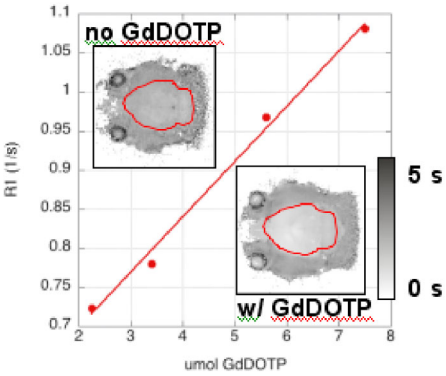

Figure 1. *In vivo* calibration plot showing the $GdDOTP^{5-}$ dose *vs.* T_1 response (R_1) for 30 µL volumes of different $GdDOTP_{5-}$ infusate solution concentrations infused to the left lateral ventricle of each respective rat at @ 6 µl/hr. T_1 values were obtained from the axial T_1 map ROI's.

In summary, these studies provide a method of measuring the exchange properties between cerebrospinal, extracellular, and intracellular fluid compartments [4]. Additionally, the ability to deliver different contrast agents to the brain in a consistent and predictable manner should allow use of functional agents having T1 relaxivities that are dependent on physiological parameters of interest such as pH, in addition to the requisite concentration dependence.

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