Prolonged and Homogenous Delivery of Gd Chelates to the Rat Brain with an Osmotic Pump

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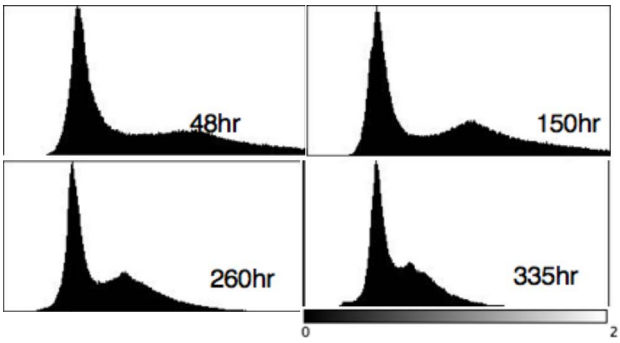
The purpose of this study is to demonstrate the very prolonged, chronic delivery of neutral & negatively charged Gd-chelates, in addition to the positively charged Mn^{2+} ion, directly to rat brain interstitium by direct infusion into CSF of the lateral ventricles using an osmostic pump. The main goal of this work is to develop a framework for delivering molecular imaging agents of interest, such as pH reporting agents, to the brain in a consistent & predictable manner. Previously, agents have been delivered over 5 hours while the rat is under anesthesia & secured in a stereotaxic frame. By using an osmotic pump, the rat is only under anesthesia for 1 to 2 hours required to surgically affix the brain cannula & the osmotic pump, but is otherwise awake (ie, not anesthetized) during the entire 72 hour period that the osmotic pump is operational (ie, pumping), except during MR imaging to measure the agent distribution in the brain. T_1 maps are acquired of the entire brain volume to monitor the relatively slow (characteristic time ~6 to 20 hours following the 5 hour infusion) agent distribution & washout time course. Previous studies utilizing the 5 hour infusion protocol delivered a 7.5 µmol dose of agent 1.5 µmol/hr by infusing 30µL of 250mM agent at 6 µL/hr. The 3 day infusion with the osmotic pump of the present study delivers a 50 µmol dose of agent at 0.69 µmol/hr by the osmotic pump driven infusion of 100 µL of 500 mM agent at 1 µL/hr for (approximately) 72 hours. It will be shown that while both the 5 hour & 3 day infusion protocols result in agent distribution throughout the brain parenchyma, the agent distribution time in the brain is on the order of 10 to 30 fold longer with the osmotic pump infusion protocol.

Methods. Experiments where performed on male Sprague-Dawley rats (450 to 550 gm). A 100 µL osmotic pump (Alzet) was loaded with 500 mM Prohance®. The rat was anesthetized & placed in a stereotaxic frame (Stoelting) to place the fused silica cannula (PlasticsOne) to the skull. The 5 mm cannula was placed at 1 mm caudal & 1.4 mm to the left laterally from bregma, placing the cannula tip in the left lateral ventricle. T_1 maps were obtained by inversion recovery gradient echo (Turboflash) MRI between 3 & 16hr after agent infusion using a 9.4T Varian system. Images were acquired at 9.4 T with 2 centric-ordered k-space segments, TE=2ms, TR=5ms, 128x128 matrix, 36x36 mm^2 FOV, 1 mm slice thickness, 5ms adiabatic full passage inversion pulse, 1ms Gaussian observation pulse, 16 inversion recovery delay times spaced logarithmically between 0.01 & 8 secs. T_1 maps were acquired in 2 to 5 minutes per slice. A full stack of 1 mm slices (~10) covering nearly the entire brain were acquired every hour. T_1 maps were converted to R_1 maps in order to calculate the spatial distribution of contrast agent in the brain with time. A 3D Turboflash sequence with TE=3ms & TR=30ms was also employed to obtain images with primarily T1 weighting & 200 micron isotropic resolution.

Results & Discussion. Figure 1 on the right shows whole brain histrograms of R1 values obtained from a large 3D volume containing the entire brain & the surrounding muscle tissue. The R1 values are shown between 0 & 2 sec^{-1}, as shown on the grey scale bar, which is also applicable to the R1 maps shown below The constant lorentzian shaped portion of the histogram on the left & approximate 0.5 sec^{-1} represents primarily the muscle R1's that are unaffected by the agent that is delivered specifically to the brain. The brain R1's are represented by the broad portion of the histogram on the right, which narrows & coalesces as agent becomes more homogenous & slowly washes out of the brain.



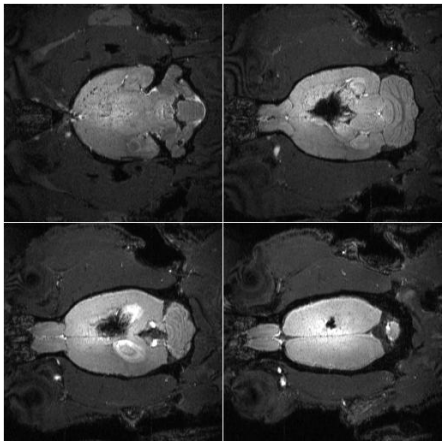


Figure 2 on the left shows the contrast obtained from different levels of the brain at 110 hours after implanting the 3 day osmotic pump loaded with Prohance. Normally, without any T1 agent present, the brain would be nearly indistinguishable from the surrounding muscle. on the R1 maps, which is clearly not the case for the maps shown. One feature that is evident with this implanted cannula is that the region surrounding the cannula tip in the left lateral ventricle experiences a region of signal wash out due to the high concentration of paramagnetic agent. On first approximation, it was expected that the agent would clear out of the brain completely with a time-constant of approximately 12 hours, as was observed consistently after infusing Prohance & other Gd-chelates over 5 hours. Instead, the agent appears to clear very slowly & is still apparent at significant levels for 100, 200, 300, & 400 hours after the pump stopped pumping. Clearly, the agent is getting sequestered in the brain parenchyma in some manner that was not apparent with the shorter 5 hour infusion protocol. These basic results with small molecules (ie, MW <1000 Da) of varying charge provide a framework for understanding & predicting the delivering molecular imaging agents to brain & may also improve our understanding of brain pharmacology.