Micro-MR Angiography Using Gd-Loaded Micelles As Intravascular Contrast Agents In Mouse Models Amyloid Angiopathy

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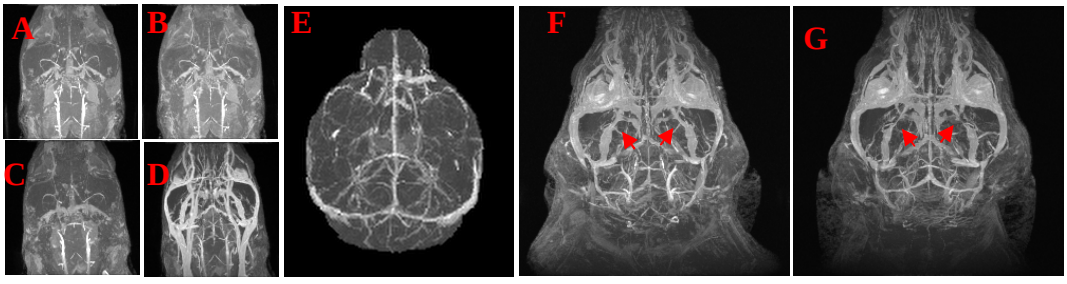
Introduction: Cerebral amyloid angiopathy (CAA) is a disease in which deposits of amyloid protein accumulate in the vessel walls ultimately leading to stroke, brain hemorrhage, or dementia. A large number of transgenic mice that develop vascular and parenchymal Aß plaques have been generated over the past decade to serve as animal models to study plaque deposition. A noninvasive method that accurately identifies vascular Aß plaques in these mouse models would be invaluable to better understand the correlation between the Aß deposits and the associated pathology. Furthermore, the same approach could be very useful for testing and monitoring new therapeutic strategies aimed at reducing amyloid burden. Our group and others have developed an *in vivo* mouse MRI approach that visualizes parenchymal Aβ plaques using magnetically labeled Aβ based peptides as targeted contrast agent (CA) **[1]**. Surprisingly, efficient parenchymal detection using gadolinium (Gd) was obtained when using susceptibility-weighted MRI **[2,3]**. When considering this same approach to target amyloid deposits in vessel walls, their visualization through dark enhancement can be confounded with normal and abnormal physiological events in the brain (hypoxia, brain hemorrhage, etc...). In this study, we propose the use of recently reported Gd-loaded micelles **[4]** as long living intravascular agents to achieve in vivo 3D micro-MR angiograms (µMRA) in mice. The steady state positive enhancement obtained from the construct and restricted to the vascular network is maintained long enough to achieve highly resolved µMRA data sets with 150-um and 100-um isotropic spatial resolution within 30- and 100-minute acquisition times, respectively.

Methods: Experiments were performed in both C57Black6 wild type mice (WT, N=7) and transgenic mice with double mutation APP/PS1 (Tg, N=5). Synthesis and characterization of physical properties of the Gd-loaded micelles were performed using the previously described protocol in which plasma half life (t½=1.4-hours) was assessed in C57Black6 wild type mice (N=3) **[4].** A modified 3D gradient-echo sequence was implemented which acquires a self-gating signal on the readout dephasing gradient within each TR **[5]**. The gating signal was used retrospectively for artifact free image reconstruction. All µMRI experiments were performed with a 7T Bruker Avance II console (Bruker Biospin, Ettlingen Germany). To monitor the effect of the micelles over a 2-hour period, a 3DGE sequence (TR=50ms, TE=4.07ms, FA=34°, BW=75Khz,) was acquired to provide a 150µm isotropic resolution within 30-minutes (Matrix size=128^3, FOV=19.2 mm, Nav=2). The protocol consisted of a pre-injection scan to acquire a contrast agent-free brain datasets followed by four consecutive post-femoral injection scans of either Gd-DTPA (WT, N=3) or Gd-loaded micelles (WT, N=3 / Tg, N=3) with a total experiment duration of less than 3-hours including the calibration step. A post-24h follow-up scan was also acquired to monitor the clearance of micelles. The isotropic voxels obtained facilitated the correction of misalignment between sessions and comparison between mouse brain datasets. Image analysis was assessed using the public domain program ImageJ (NIH Image, NIMH, NIH) and angiograms were obtained using maximum-intensity projection. For highly resolved datasets the same sequence (TR=50ms, TE=4.07ms, FA=34°, BW=75Khz,) was acquired in less than 87-minutes to obtain a 100µm isotropic resolution datasets (Matrix size=256^3, FOV=25.6 mm, Nav=2).

Results and Discussion:



All the image sets shown above are obtained using a anterior-posterior MIP. Figures A&B correspond to a WT mouse Pre and Post 2-hour Gd-DTPA injection (12.5mM, 250ul) demonstrating a complete clearance of the CA as expected from its well known plasma half life (t½=12-minutes). When injected with Gd-loaded micelles (D), the CA demonstrate superb and stable vascular details compared to pre injection (C) and throughout the 2 hours duration observed (data not shown) . This long living CA allows to obtain higher details as depicted in (E,F,G) with 100-um istropic resolution in less than 87-minutes acquisition time. The mouse examples in (F) and (G) were obtained from 2 Tg following micelle injection in which anastomosis on lateral vessels can be observed (red arrows).

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