Infiltration contrast agent in tissue increases the MRI detectability of amyloid plaques in rabbit AD model

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Introduction: The amyloid hypothesis, which has been intensively studied, emphasizes abnormal deposits of beta-amyloid (Aβ) protein as an upstream causative factor of Alzheimer's disease (AD). Extracellular amyloid deposits constitute the main target for new diagnostics and therapeutics. We recently reported that rabbits fed a long-term low-level cholesterol (CH) diet develop a specific type of extracellular Aβ plaque in their brains. These iron associated plaques are detectable on clinical field-strength MRI, although with some difficulty (2). In this study, we evaluate an MR protocol based on infiltration of gadolinium contrast agent into brain samples (1). Our goal is to determine if this method could improve the detectability of amyloid plaques in the rabbit model using clinical field-strength MRI.

Methods: Rabbits were fed either a CH-enriched (n=4) or normal chow diet (n=4) for 24 months. Excised brains were soaked in a 1:100 mixture of 0.5 mmol/mL Magnevist and 10% buffered formalin. MRI studies were performed on a 3T scanner with a 40mm diameter surface coil for signal acquisition. Half brains were scanned before, 4 and 24 hours after Magnevist treatment. T1, T2 and T2* relaxation times were measured using inversion recovery fast spin-echo sequence, multi-slice fast spin-echo sequence and multi gradient echo sequence respectively. High-resolution MR images (100 x100x 200 µm3) were acquired using 3D FIESTA and 3D FSPGR sequences. After imaging, brains were cut and Aβ-42 immunostaining and Prussian blue iron staining were performed on brain sections.

Results: Magnevist treatment significant reduced T1, T2 and T2* relaxation times and improved the image signal-to-noise ratio (SNR) and contrast (Figure 1) .In 3D FSPGR images, the SNR of the whole brain increased 76% and the CNR between gray matter and white matter increased 45% after 24 hours contrast agent treatment. High-resolution MR images from the CH-fed rabbit revealed distinct hypointense spots throughout the brains, which were not seen in the control animals. The contrast and visibility of these spots improved significantly (42% increase in CNR) and some spots were only visible after immersion in the contrast agents (Figure 1). These hypointense spots were primarily located in the hippocampus and adjacent cortex, striatum and thalamic regions and correlated to clusters of iron-rich amyloid plaques in matched histological sections (Figure 2).

Conclusion: We have demonstrated that infiltration contrast agent into brain tissue increases the *ex vivo* MRI detactability of amyloid plaques in the rabbit AD model. These results point to the possibility of using intrathecal injection of contrast agent for *in vivo* imaging amyloid plaques using clinical-strength MRI.

References: 1. Dhenain M. et al. (2006) MRM, 55: 687-693; 2. Ronald J.A. et al. (2009) Brain, 132: 1346–1354

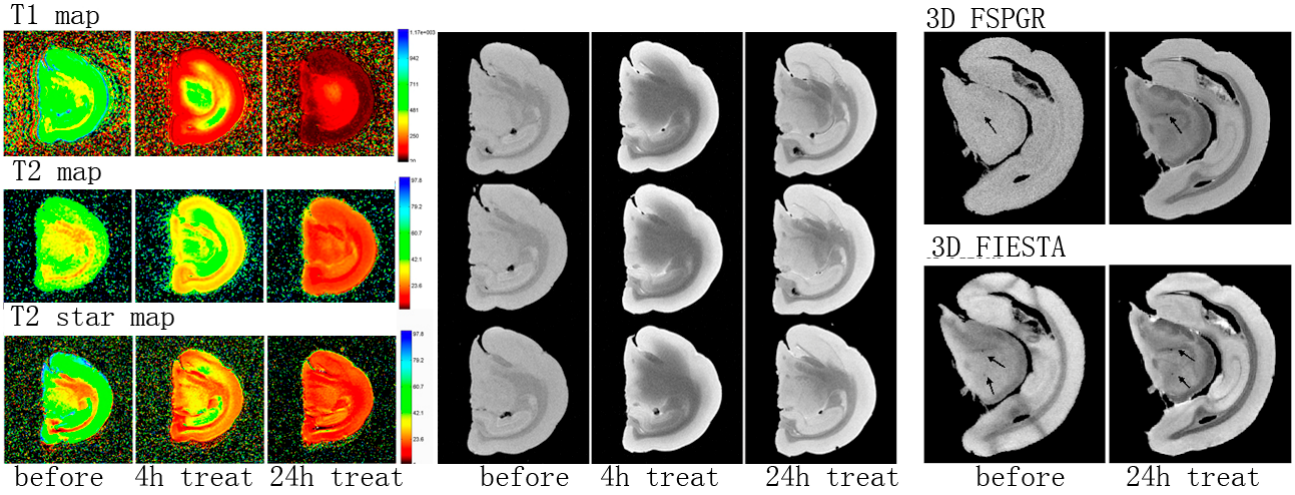

Figure 1. T1, T2 and T2* maps show Magnevist treatment reduces T1, T2 and T2* relaxation times (left). 3D FSPGR image show Magnevist treatment improves the signal and noise ratio and image contrast.(middle). Magnevist treatment increases the contrast of the hypointense spots on both 3D SPGR and 3D FIESTA images in CH-fed rabbit (right).

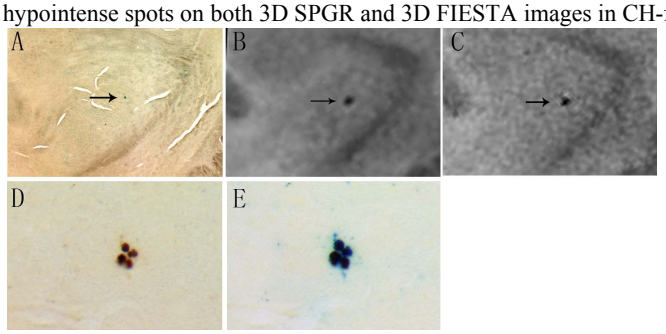

Figure 2. Histology of beta amyloid and iron staining shows the typical iron-rich plaque (A, arrow). Corresponding 3D FSPGR (B) and 3D FIESTA (C) image with the identified locations of the histology confirmed plaques superimposed. High magnification of beta amyloid staining revealed that amyloid plaques were found typically as clusters (D). Subsequent Prussian blue iron staining revealed that plaques were rich in iron (E).