Comparison of Amyloid Plaque Characteristics in Transgenic Mouse Models of AD Using MR Microscopy

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Introduction

Although ^{11}C Pittsburgh Compound-B has been used successfully in labeling human amyloid plaques [1], PET imaging of amyloid deposits in APP transgenic mouse models of AD using this compound has not been successful [2]. Successful MR imaging of amyloid plaques in mice at 7T and 9.4T has been reported recently by several groups, a review of which can be found in [3]. We have employed MR microscopy at 14.1T to compare amyloid plaque characteristics in two APP transgenic mice, one expressing only an APP mutation and the other APP and presenilin-1 mutations. Our method, which does not involve the use of an external contrast agent, utilizes the high field strength imager and strong magnetic field gradients to achieve the high spatial resolution required to visualize plaques. We have found differences in plaque size, appearance and regional distribution between the two transgenic lines which differ in the severity and time course of plaque deposition.

Methods

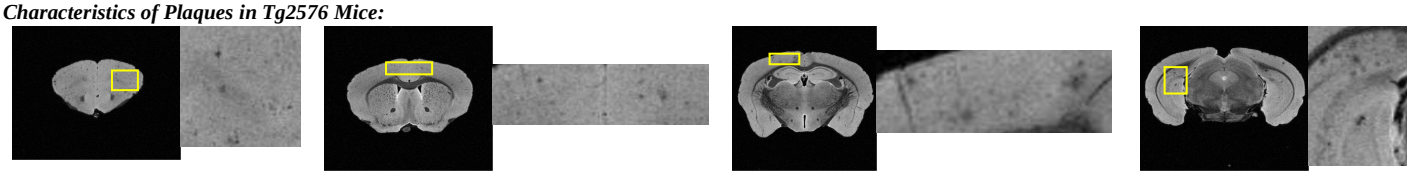
Transgenic Mice: Tg2576 mice overexpressing human APP695 with the "Swedish" mutation were purchased from Taconic. 5XFAD transgenic mice coexpressing a total of five FAD mutations [APP K670N/M671L (Swedish) + I716V (Florida) + V717I (London) and PS1 M146L + L286V] were generated in a collaborator's laboratory [4]. Amyloid deposition begins in the Tg2576 mouse brain at 14M and by 18M of age, a large number of plaques may be found. Plaques begin to appear in the 5XFAD mouse brain much earlier, at 2M, and levels off at 9M.

MR imaging: Brains fixed in 4% paraformaldehyde were used for imaging. During imaging, brains were immersed in Fomblin (a perfluorinated liquid) to prevent dehydration and reduce magnetic susceptibility gradients. All imaging experiments were performed on a Bruker Avance 14.1T imaging spectrometer fitted with a100G/cm gradient using a10 or 20mm resonator tuned to proton frequency (600MHz). 3D images were acquired using a fast spin-echo (RARE8) pulse sequence and the following imaging parameters: TR/TE*eff* 2500ms/40ms; pixel size 35µx35µx35µ.

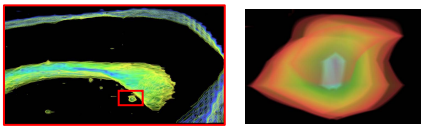
Results and Discussion

We carefully compared spin-echo and gradient-recalled echo images of the mouse brain at 14.1T and found that spin-echo images were superior for plaque contrast, and ability to detect small and large plaques. We also evaluated different echo times and pixel sizes before choosing the parameters listed in the Methods section for this study.

Characteristics of Plaques in Tg2576 Mice:



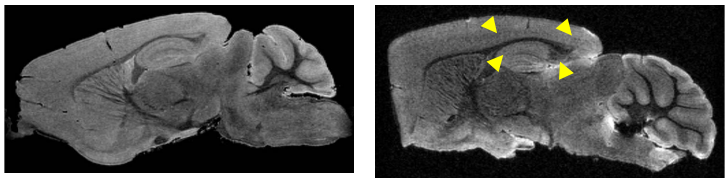
High resolution MR images of an 18M old Tg2576 mouse are shown in the figure above. The representative axial images are from a 3D RARE8 data set. Plaques appear as well-resolved, hypointense spots in these T2-weighted images. Selected regions containing a large number of plaques are marked on each slice with a yellow box, zoomed images of which are shown on the right. Occurrence of plaques, however, is not limited to the yellow boxes. Appearance of plaques in slices that include the frontal cortex (left panels), and dorsal and ventral hippocampus (right panels) reveal that amyloid plaques are present in the entire brain of the 18M old Tg2576 mouse. Furthermore, plaques appear in different sizes and varying contrasts. A large number of plaques measuree >50µ in cross section in this brain with the largest plaque measuring 200µ. Another notable feature of amyloid plaques in Tg2576 mice is that plaques are isolated from each other. Plaques with similar characteristics were found in all Tg2576 mouse brains at this age (n=4).



The high spatial resolution in our 3D images enabled in further processing of the data to view individual plaques in greater detail. The red box in the pseudo-color volume-rendered sagittal view of the brain on the left panel shows a large plaque (120µ in cross section) in the subiculum. Detailed, volume-rendered view of this large plaque is shown in the panel to the right. The plaque architecture represented by the different colors shows five layers of signal intensities with the lowest intensity (dark blue) in the middle and the highest intensity in the outer most rim (red). Appearance of a dark core in the middle and layers of increasing signal intensities on the periphery in this MR microimage resembles the reported ultrastructure of amyloid plaque in Tg2576 mice. Electron microscopy has revealed the presence of a dense core of amyloid fibrils in the center and dystrophic neurites and increased microglia in the periphery of both Tg2576 and human AD amyloid deposits [5].

Characteristics of Plaques in 5XFAD Mice:

Sagittal MR images of 5XFAD transgenic mouse brains are shown below. The image on the left panel is from a 2M old mouse in which there are few plaques . In contrast, the 9M old mouse brain (right panel) shows numerous plaques in the subiculum, hippocampus, and cortex (arrowheads). Plaque distribution in the 5XFAD mouse is limited to these structures and unlike the Tg2576 mouse, very few plaques were seen in other brain structures. Also, in contrast to the Tg2576 mouse, plaques in the 5XFAD mouse are more numerous, and much smaller in size (<50µ), but more uniform both in size and (hypo)intensity. Staining with antibodies for Aβ42 C terminus verify the characteristics observed in these MR images [4].



The observed differences in plaque characteristics between these two transgenic mice may be related to the differences in the time course of Aβ deposition and the severity of Aβ burden in these mice. Elevated Aβ42 levels are thought to drive the formation of insoluble fibrils that compose amyloid plaques. Aβ42 burden is greater in the 5XFAD mouse (140ng/g brain protein) compared to Tg2576 mouse (10ng/g); Aβ42 is produced faster and Aβ42/Aβ40 ratio is 25x higher in the 5XFAD mouse [J Neurosci. 26:10129 (2006)]. Transgene promoter specific expression may account for the different plaque distributions in the two transgenic lines. *(Supported by NIH Grant S10 RR13880)*

References

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