MRI microscopy of Alzheimer plaques in APP751 transgenic mice: Effect of TE and spatial resolution on plaque detectability

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Synopsis

Amyloid plaques are the hallmark of Alzheimer disease (AD) but their identifications by non-invasive methods is difficult. Here we demonstrate for the first time, that Aβ plaques can be detected in APP751 transgenic (tg) mice without the need for contrast agents. In addition, we demonstrate that in-plane resolution of 50μm and slice thickness of 100μm are optimal for the detection of Aβ plaques in this tg strain. As expected, longer TE in the gradient echo sequence also increases the detectability of the Aβ plaques however, these images can be problematic due to their relatively low SNR.

Introduction

Alzheimer's disease (AD) is characterized by the formation of senile β-amyloid (Aβ) plaques. Indeed, in recent years, transgenic (tg) mice strains which develop typical Aβ depositions in the form of amyloid plaques have been engineered. Transgenic mice strains can serve as models for the development of diagnostic methods for AD and the evaluation of new drugs against AD. Detection of the Aβ plaques by non-invasive techniques, such as MRI would greatly improve the early diagnosis of AD. Specific contrast agents that specifically target amyloid depositions were recently developed.[1] However, due to of toxicity risks, efforts were devoted for the development of direct methods for imaging of amyloid plaques. Aβ plaques should appear as dark spots on T_2^* and T_2 weighted MRI images because of the relative high iron concentration in such Aβ plaques.[2, 3] In this study we attempted the visualization of plaque load in APP751 tg mice, a model of AD which not previously studied using MRI, and evaluated the effect of in-plane and slice resolutions as well as TE on the identification of plaques in these tg mice.

Methods

MRI experiments were performed using an 8.4 T spectrometer (Bruker, Germany) equipped with a micro5 gradient probe capable of producing pulse gradients of 190 Gcm^{-1} in each of the three dimensions. Formalin fixed brains of 15-month old APP751 tg mice expressing the double Swedish and London mutations were used in this study. Two dimensional T_2^*-weighted gradient echo images with a field of view (FOV) of (1.28 × 1.28) cm^2, were acquired with different in-plane resolutions. Gradient echo MRI images with 256 × 256 (2 h 51 min), 256 × 192 (2 h 8 min) and 256 × 128 (1h 25 min) digital resolution were collected and reconstructed to 256 × 256 images resulting in an in-plane resolution of 50μm. In addition, MR images with matrices of 128 × 128 (1 h 25 min), 128 × 96 (1 h 4 min) and 128 × 64 (43 min) were collected and reconstructed to 128 × 128 images with an in-plane resolution of 100μm. Ten continuous 100μm slices were collected using a TR of 1000ms and a TE of 25ms or 35ms. In addition, the effect of the slice thickness and TE on the ability to identify Aβ plaques was evaluated for the 256 × 128 (zero filled to 256 × 256) MR images.

Results

Figure 1 shows gradient echo MR images of a 15-month old tg mouse with two different in-plane resolutions acquired with two different echo times. The slices thickness was 100μm in all cases. All 4 images in Figure 1 contain dark spots that seem to represent amyloid plaques in the cortex and the hippocampus. Indeed relatively large dark spots attributed to Aβ plaques and seen in all images. However, some of the smallest dark spots that are clearly visible in the cortex at a resolution of 50μm are hardly detectable when the resolution was reduced to 100 μm. Figures 1A and 1C also show that decreasing the in-plane resolution to 100μm, which shortens the experiment time, requires increasing the TE to maintain the detection level of the Aβ plaques. After the estimation of the importance of the in-plane resolution on plaque detection, we tested the effect of the slice thickness. We found that reducing the slice thickness from 200μm to 100μm increased the detection level of the plaques. At a given spatial resolution, increasing the echo time (TE), while keeping all other parameters constant, resulted in better delimitation of many plaques (data not shown). However, increasing the TE reduces the SNR and may lead to incorect assignment of dark spots, due to a low SNR, as Aβ plaques.

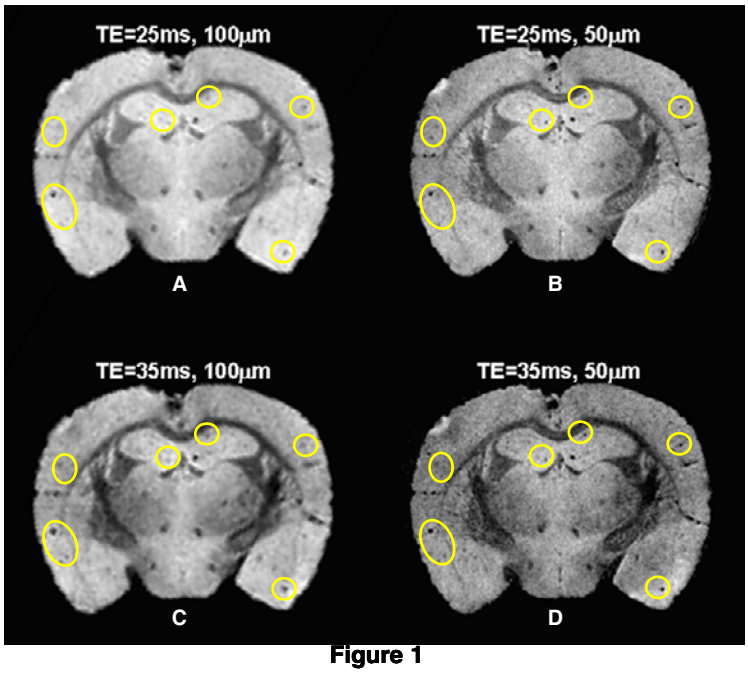

Figure 1

Discussion

In this study, we show for the first time that Aβ amyloid plaques can indeed be identified in APP751 tg mice by MRI without the aid of contrast agents. Because plaque sizes of tg mice are in the range of a few tens of micrometers to 100μm, 50μm in-plane resolution and a slice thickness of 100μm are optimal for their identification. In addition, as expected, we demonstrated that increasing TE from 15ms to 35ms in the gradient echo sequence increases the detection level of small Aβ plaques but should be analyzed with care.

References

[1] Poduslo, JF, Wengenack, TM, Curran, GL, Wisniewski, T, Sigurdsson, EM, Macura, SI, Borowski, BJ, and Jack, CR Jr. Neurobiology of disease, 2002; 11: 315-329.

[2] Jack CR Jr, Garwood M, Wengenack TM, Borowski B, Curran GL, Lin J, Adriany G, Gröhn OHJ, Grimm R, Poduslo JF. Magn Reson Med, 2004; 52: 1263-1271.

[3] Vanhoutte G, Dewachter I, Borghgraef P, Van Leuven F, Van der Linden A. Magn Reson Med, 2005; 53: 607-613.