Decreased T_1 and T_2 in the brain of APP/PS2 mice, a model for Alzheimer's disease

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Introduction

A main neuropathological feature in Alzheimer's disease (AD) is the presence of amyloid-β plaques. Mouse models expressing the human gene for amyloid precursor protein (APP) develop amyloid-β plaques and can therefore be used to study the effects of amyloid plaque-lowering drugs. MR relaxation times have been proposed as potential non-invasive biomarkers for plaque depositions. Several papers report a T_2 decrease in AD mouse models compared to controls, e.g. in APP/PS1 mice (1), but there is only one paper describing a T_1 decrease in these mice (2). Our aim was to study T_1, T_2, and T_2^* in the double-transgenic APP/PS2 mouse model (3) and in age-matched controls and to correlate the findings with histology.

Methods

Male transgenic (TG) APP/PS2 mice (n=12) and wildtype (WT, n=15) male C57Bl/6 mice were used (age 12 months). The mice were anesthetized with isoflurane and scanned in a 7 T Bruker Biospec. T_1 maps were acquired with an inversion–recovery–snapshot–FLASH sequence (TR/TE=4.0 s/1.4 ms, 64×64 matrix, TI=0.10 s-1.15 s). T_2 maps were acquired with a multi spin echo sequence (TR/TE=2.0 s/10.0 ms-80 ms, 8 echoes, 128×64 matrix). T_2^* maps were acquired with a multi gradient echo sequence (TR/TE=2.0 s/3.5-21.8 ms, 6 echoes, 128×64 matrix). All image data sets consisted of 13 axial planes of 0.60 mm thickness and with FOV=20 mm x 20 mm. The maps were co-registered and warped automatically (by means of the open-source software SPM5) to a mouse brain template delineating several regions of interest (ROIs). The mean T_1, T_2, and T_2^* values were calculated for each ROI in each animal. An unpaired t-test was performed between WT and TG. For histology, sagittal cryo-sections (10 μm) were stained with a human anti-amyloid-β antibody and a fluorescence marker. The sections were digitized and plaque load was quantified in cortex and hippocampus as mean area of stained plaque divided by mean total area. The Pearson correlation coefficient was calculated between plaque load and T_1 or T_2 in cortex and hippocampus (T_1 and T_2 were averaged in total cortex for this correlation analysis).

Results

T_1 showed a significant decrease in TG vs. WT in the following brain regions: frontal cortex, thalamus, olfactory cortex, and somatosensory cortex (Fig. 1). T_2 showed a small, but significant decrease in brainstem, frontal cortex, thalamus, olfactory cortex, somatosensory cortex, perforant path, and cerebellum. Apart from brainstem and cerebellum, these are all regions that show plaque deposits. There were no significant differences for T_2^*. Immunohistochemistry confirmed the absence of plaques in WT animals (plaque load 0.0%) and the presence of plaques in TG animals in cortex (plaque load 4.3 ± 1.0%) and hippocampus (plaque load 2.9 ± 0.8%). Median plaque size was 210 μm^2 and 199 μm^2 in cortex and hippocampus, respectively. There was no correlation between T_1 or T_2 and histological plaque load in cortex and hippocampus.

Discussion

A small, but significant decrease in T_1 and T_2 was observed in plaque-containing areas. The absence of a correlation with histological plaque load suggests that T_1 or T_2 cannot be used as a quantitative measure for plaque load in this model. It was hypothesized that the decrease of relaxation times depends on the amount of endogenous iron that has accumulated in the plaques (4). Thus, plaques areas with very low iron content may not show a relaxation time change. It has to be investigated if iron content or other effects, e.g. tissue water content, are responsible for the T_1 and T_2 decrease in this model. A decrease in T_2^* has been detected in very small ROIs in APP mice aged 2 years compared to WT (5). In our study, it was not possible to detect differences in TG vs. WT in the mean T_2^* values which were averaged in relatively large ROIs.

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References

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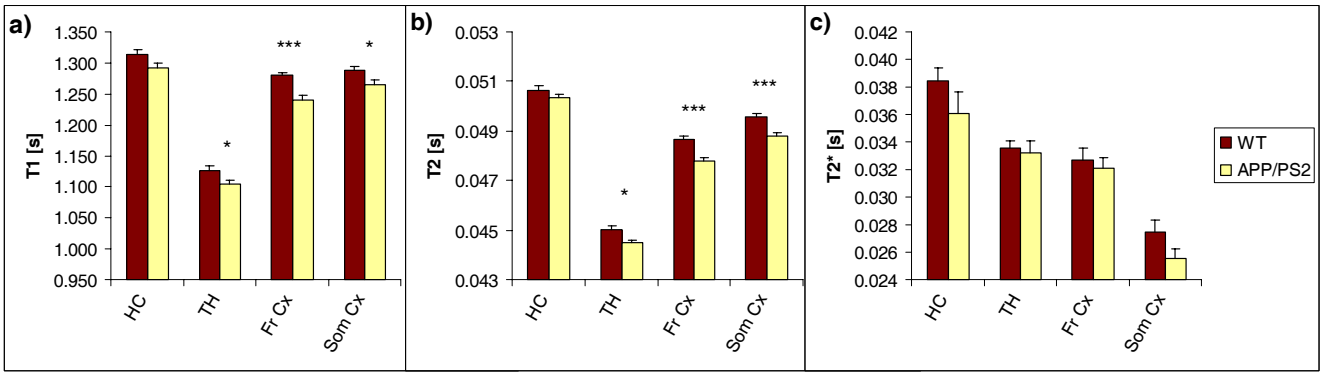

Fig.1: T_1 (a), T_2 (b), and T_2^* (c) in hippocampus (HC), thalamus (TH), frontal and somatosensory cortex (Fr Cx, Som Cx) in wildtype and APP/PS2 mice (mean ± SEM). A t-test showed sign. differences between the groups (*p<0.05, ***p<0.001).