MR biomarkers of neurodegeneration in a transgenic mouse model of Alzheimer's disease

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Introduction

The histological abnormalities that characterize Alzheimer's disease (AD) are commonly divided into three major classes: amyloid plaques, neurofibrillary tangles and neurodegeneration (NDG). Much work has been done to image amyloid plaques in transgenic mouse models of AD (1,2) using the APP/PS1 mouse model. However, the APP/PS1 model was developed to study amyloid plaques and NDG changes are minimal in this model. Neurofibrillary tangles (aggregates of hyper phosphorylated tau protein) and NDG changes are prominent in human AD. NDG is thought to be mediated through aggregation of abnormal forms of the intracellular protein tau. It would, therefore, be useful to determine which MR techniques are sensitive to NDG in a transgenic mouse model specific for tau mediated neurodegeneration. The Tg4510 mouse model recapitulates NDG mediated through over expression of mutant human tau (3). In this work we compare the ability of various MR techniques (volume, $T_{1\rho}$, $T_{2\rho}$, ADC, FA) to detect the NDG in the Tg4510 mouse model compared to wild-type (WT) mice.

Methods

In vivo experiments were performed using a 9.4-T/31-cm horizontal bore magnet equipped with a Varian INOVA spectrometer. Four Tg4510 mice were imaged at 13 months of age and four WT mice were imaged at 12 months of age. Mice were anesthetized using 1.5% isoflurane and O_2/NO_2 and positioned in a custom-built device to immobilize the head during experiments. Body temperature was maintained at 37^0C by warm water circulation, and physiological monitoring for temperature and respiration was performed. All images were acquired using a quadrature surface coil (two loops, 10-mm diameter). The volume image was acquired with a 3D multi-asymmetric spin-echo pulse sequence (1) with resolution 120 µm x 120 µm x 400 µm. The apparent diffusion coefficient (ADC) and fractional anisotropy (FA) were measured with a 2D single slice diffusion-weighted spin-echo sequence with in-plane resolution of 80 µm x 80 µm, slice thickness of 1 mm and b-value equal to 800 s/mm^2. The rotating frame relaxation times, $T_{1\rho}$ and $T_{2\rho}$, were measured with a 2D single slice spin-echo sequence with in-plane resolution of 80 µm x 80 µm, slice thickness of 1 mm. Both relaxation constants were mapped by applying a train of 4 ms-long hyperbolic secant pulses. The length of the pulse train was 0, 4, 8, 12, and 16 pulses.

Results and Discussion

All MR techniques detected the expected differences between WT and Tg4510 mice as shown in Table 1. The hippocampal volumes were significantly reduced in the Tg4510 mice, indicating neuronal loss. The FA values in the corpus callosum were smaller in the Tg4510 mice than in WT mice, probably due to loss of axonal integrity. The ADC values were higher in the hippocampus of the Tg4510 mice than in WT mice indicating neuronal loss. The relaxation constants, $T_{1\rho}$ and $T_{2\rho}$, were both elevated in the hippocampus and corpus callosum of the Tg4510 mice. An increase in these relaxation constants is indicative of NDG due to a decrease in protein-water interaction (4). As expected, the $T_{1\rho}$ relaxation constant was more sensitive to this change than $T_{2\rho}$.

	Hippocampus		Corpus Callosum	
	WT	Tg4510	WT	Tg4510
Volume (mm^3)	28.9 ± 0.89	23.04 ± 1.34	--	--
FA	--	--	0.734 ± 0.011	0.631 ± 0.012
ADC (mm^2/s x10^{-3})	1.44 ± 0.01	1.66 ± 0.03	--	--
$T_{1\rho}$ (ms)	95.3 ± 0.8	105.0 ± 2.2	83.3 ± 0.4	89.8 ± 0.5
$T_{2\rho}$ (ms)	42.9 ± 0.1	46.6 ± 0.6	39.5 ± 0.2	41.5 ± 0.3

Table 1. Comparison of MR biomarkers in wild-type and Tg4510 mice.

These results show that NDG can be detected with various measurements in transgenic mice over expressing mutant human tau. These techniques are all in theory candidate biomarkers for human AD and could enhance diagnostic sensitivity and aid in early diagnosis of AD in humans.

References

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Acknowledgements

Supported by NIH P41 RR008079 and P30 NS057091, the Keck Foundation, and the Minnesota Partnership for Biotechnology and Medical Genomics.