Reduced Anisotropy in Hippocampal Subfields in a Mouse Model of AD

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Introduction

The transgenic mouse (Tg2576) overexpressing human APP_{695} with the "Swedish" mutation has shown potential as a model for Alzheimer's disease. The mouse develops age-dependent behavioral, biochemical and pathological changes resembling those in AD. Impaired performance in memory tests, increase in Aβ peptide and amyloid plaques were seen in mice 9 months or older, but not in younger mice [1]. To translate the potential of the mouse model into an early diagnostic tool for the human disease, knowledge of changes that occur in the brain prior to plaque development is essential. Toward realizing this goal, we have examined the early effects of mutant human APP overexpression on the microstructure of hippocampus, a central nervous system structure crucial for learning and memory, using diffusion MR imaging. Changes from normal cellular structures will be reflected in the magnitude and directionality of cellular water diffusion measured as Apparent Diffusion Coefficient (ADC) and anisotropy, respectively. Anisotropic water diffusion has been observed in the normal spinal cord and corpus callosum in vivo [2,3]. Reduced anisotropy has been associated with spinal cord injury in the rat [4], peripheral sciatic nerve damage in the frog [5], and spinal cord degeneration in the mouse [2].

Methods

Six-month old Tg2576 mice and age-matched wild-type controls were used (n=6). Anesthetized mice were perfused with PBS followed by 4% paraformaldehyde. Excised, perfusion-fixed brains were used for imaging. Multi-slice diffusion weighted images were acquired at 20°C on an Omega 9.4T imager using the following parameters: TR = 3.0s, TE = 45msec, Δ = 7msec, δ = 5msec, slice thickness = 1mm, in-plane resolution = 120 μm x 60 μm, number of slices = 8, number of averages = 8 per encoding step, and number of *b* values = 10, between 0 and 4000s/mm^2. ADC was measured along two perpendicular gradient directions (z and y). ADC in each image pixel was calculated from a plot of signal attenuation versus *b* value using software developed in-house. A measure of anisotropy which we termed "Anisotropy Index" was calculated from ADC values measured in the two perpendicular directions. Anisotropy Index (AI) = $[1-(D_y/D_z)]$ where *D* is the ADC in the direction indicated by the subscript. AI = 0 when D_z is equal to D_y such as when diffusion of water is isotropic. AI in selected hippocampal subfields was calculated by averaging all the pixels within that structure.

Results and Discussion

ADC was calculated from CA1, CA3 and dentate gyrus (DG) in the dorsal hippocampus, CA1 and dentate gyrus in the ventral hippocampus, as well as from corpus callosum (CC). The plots of signal attenuation versus *b* show good fit for mono-exponential diffusion behavior for water in the selected regions. Anisotropy indices calculated from measured ADC's are presented in Table I.

Table I. Anisotropy Index of Water Diffusion in Substructures of Hippocampus

	Dorsal Hippocampus			*Ventral Hippocampus*		
	CA1	*CA3*	*DG*	*CA1*	*DG*	*CC*
Wild-type	0.13	0.05	0.08	0.22	0.13	0.15
Transgenic	0.08	0.03	0.06	0.13	0.04	0.15

The magnitude of AI is a measure of the degree of anisotropic water diffusion and structural organization in the tissue. In wild-type mice, AI was higher in CA1 than in DG and CA3 regions of both dorsal and ventral hippocampus. Higher AI indicates greater ordering of cellular structures in the CA1 region. Individual fibers coalesce in the CA1 subfield to form the subiculum, a major structure for hippocampal output. AI was 38% smaller in the dorsal CA1 region of transgenic mice denoting enhanced isotropic water motion. Reduction in anisotropy of a similar magnitude was also detected in the CA1 region of ventral hippocampus in transgenic mice. Cellular changes responsible for altered anisotropy of water diffusion appear to be specific to hippocampal structures in the transgenic mouse. Corpus callosum, another highly ordered and myelinated structure, had the same AI in control and transgenic mice. The observed loss of directionality in water diffusion might be caused by demyelination of fibers, a process secondary to elevated Aβ in Tg2576 mice.

Tg2576 mice develop amyloid plaques only by 9 months [1]. Our results from 6 month old mice demonstrate that cellular changes do occur prior to plaque deposition in APP transgenic mice, and diffusion imaging is able to detect those changes. The early changes to cellular structure in CA1 that we have detected in Tg2576 mice parallel the functional decline of hippocampus that occurs prior to amyloid deposition in another APP transgenic mouse model of AD. Deficits in the basal synaptic transmission between hippocampal CA3 and CA1 cells and 30% lower neuronal density in CA1 were detected in 1-4 month old mice overexpressing FAD($717_{V->F}$) mutant human APP [6].

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