Cerebral perfusion, blood volume, vessel size, and vessel density in the B6.PS2APP mouse model for Alzheimer's disease

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Introduction

Hypoperfusion was detected with MRI in several cortical regions in patients with Alzheimer's disease (AD) (1) confirming this well established finding from PET studies. In this comprehensive preclinical MRI study, four neurovascular parameters were measured in an AD mouse model overexpressing mutated forms of APP and PS2 proteins, and in age-matched wild-type controls (C57Bl/6). Brain perfusion was assessed longitudinally from age 10 to 17 months in order to monitor its time course during disease progression. Cerebral blood volume (CBV), vessel size, and vessel density were assessed at age 17 months to further explore the functional and structural impairment of the neuro-vasculature.

Methods

Perfusion was measured in male double-transgenic (TG) B6.PS2APP mice (n=14) and wildtype (WT, n=13) male C57Bl/6 mice at age 10, 12, and 17 months using a 7 T Bruker Biospec. CBV, vessel size, and vessel density were measured in the same set of mice at age 17 months. Multi-slice MR data sets consisting of 13 axial planes (thickness 0.60 mm) with an in-plane resolution of 0.16 mm x 0.31 mm (matrix 128 x 64) were acquired. Absolute perfusion maps were quantified using continuous arterial spin labeling (CASL) images (RARE readout module; TR/TE=2.7 s/5.6 ms, RARE factor=32) and T_1 maps (IR–FLASH sequence) as described in (2). Changes in the relaxation rates ΔR_2 and ΔR_2^* were measured with a combined multi-gradient-echo-spin-echo sequence (TR =2.0 s, five gradient echoes with TE=3.3-20.2 ms, one spin echo with TE=47.8 ms) pre- and post-CA injection of Sinerem (Guerbet, France, dose 20 mg iron/kg) (3). Maps of CBV~ΔR_2, vessel density $N \approx Q^3 * 292$ s/mm^2 with $Q=\Delta R_2/(\Delta R_2^*)^{2/3}$ (4,5), and vessel size~$(\Delta R_2^*/\Delta R_2)^{3/2}$ (3) were computed. The MR parameter maps were co-registered automatically to a mouse brain template delineating several regions of interest (ROIs). The mean values were calculated for each ROI in individual animals. Normalized CBV and perfusion are indicated as percent difference from the mean in total brain in each individual.

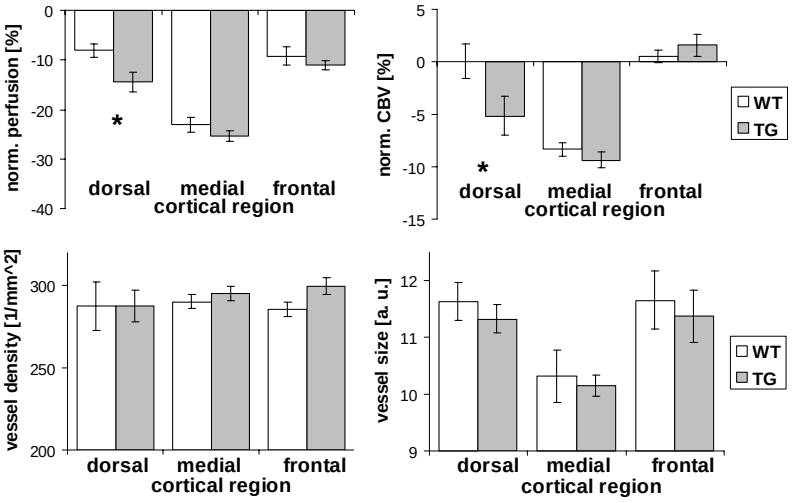

Fig.: Perfusion and CBV (normalized to total brain), vessel density and vessel size in the dorsal, medial and frontal cortical area of WT and TG mice at age 17 months. * p<0.05

Results

Significant differences in TG vs. WT were consistently observed for both perfusion and CBV in two regions: an increase in hippocampus and a decrease in the dorsal part of the cortex. Moreover, the perfusion measurements at age 10 and 12 months showed a significant increase in brainstem and significant decreases in the dorsal and medial cortices. These perfusion deficits persisted over the age of 10 to 17 months. Vessel density and vessel size showed no significant differences between the groups. A relevant correlation was found between perfusion and CBV (correlation coefficient 0.68/0.70 for WT/TG mice), but not between perfusion and vessel density or vessel size.

Discussion

We demonstrated vascular impairment in our TG mice with two independent MRI methods, i.e. perfusion and CBV measurements. Reduced perfusion was found in the amyloid-plaque-containing dorsal part of the cortex from age 10 to 17 months. This finding is supported by the reduced CBV in the same brain structure. The applied methodology to measure vessel density and size may not be sensitive enough to detect concomitant discrepancies in vascular geometry. In summary, our data indicate an impairment of the neuro-vasculature in the B6.PS2APP mouse model especially in the dorsal part of the cortex, which parallels the typical findings in AD patients.

References

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