Phenotyping the APP/PS2 mouse model for Alzheimer's disease: cerebral perfusion, blood volume, and vessel density

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Introduction

Recent studies indicate that neurovascular dysfunction is an important factor in the development of Alzheimer's disease (AD) (1). Hypoperfusion was detected with MRI in several cortical regions in AD patients (2). For studying the pathogenesis of AD and for drug development it is important to assess a potential impairment of brain vasculature in animal models. In this comprehensive MRI study, three neurovascular parameters were measured in an AD mouse model (APP/PS2 mice (3)) and in age-matched wild-type controls (C57Bl/6): brain perfusion using arterial spin labeling (ASL), cerebral blood volume (CBV) and vessel density (using an iron oxide-based intravascular contrast agent (CA)).

Methods

Male double-transgenic (TG) APP/PS2 mice (n=14) and wildtype (WT, n=16) male C57Bl/6 mice were used (age 12 months). The mice were anesthetized with isoflurane and scanned in a 7 T Bruker Biospec. Using a tail vein catheter, Sinerem (Guerbet, France) was injected intravenously (dose 20 mg iron/kg). Total scan time per mouse was 50-60 min. The multi-slice MR data sets consisted 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). Absolute perfusion maps were quantified using continuous arterial spin labeling (CASL) images (acquired with a RARE readout module; TR/TE=2.7 s/5.6 ms, RARE factor=32) and T_1 maps (acquired with an inversion–recovery–snapshot–FLASH sequence) as described in (4). Maps of the change in relaxation rate ΔR_2 and CBV maps were calculated from the pre- and post-CA injection spin echo images (TR/TE=2.0 s/10.0 ms) (5). ΔR_2^* maps were calculated from pre- and post-CA injection multi gradient echo images (TR/TE=2.0 s/3.5-21.8 ms, 6 echoes). Maps of the index $Q=\Delta R_2/(\Delta R_2^*)^{2/3}$ (6) and of the vessel density $N \approx Q^3 * 292$ s/mm^2 were computed (modified from (7)). The MR parameter maps were co-registered automatically (by means of the open-source software SPM5) to a mouse brain template delineating several region of interest (ROIs). The mean values for the parameters were calculated for each ROI in individual animals. CBV and perfusion values were normalized to the average values in total brain and are shown as difference in % from the total brain values.
Immunohistochemistry was performed in sagittal sections (10 μm) to determine plaque load (stained with anti-amyloid-β antibody) and vessel density in the frontal cortex (endothelial cells stained with anti-CD31 antibody).

Results and Discussion

A significantly decreased perfusion in TG vs. WT was detected in thalamus, hippocampus, and entorhinal cortex (Fig. 1). These regions contain amyloid plaques, as has been shown by histology. A significant decrease in CBV in TG vs. WT was observed in the thalamus. Similar CBV values were reported in a study using 4-month-old APP mice (5). A significant difference in vessel density was observed only in one region (increased in TG in the perforant path). Histological analysis did not show a significant difference in vessel density between TG and WT in frontal cortex in accordance with the MRI findings. To our knowledge, neither ASL nor vessel density MRI have been performed in AD mouse models. Our values for the vessel density index Q are in good agreement with literature values in rat brain (6). Wu et al. (7) reported higher values for Q and vessel density in 4-month-old WT mouse brain.
In conclusion, our data indicate an impairment of the brain vasculature in APP/PS2 mice. The most striking difference between TG and WT was observed by perfusion measurements.

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References

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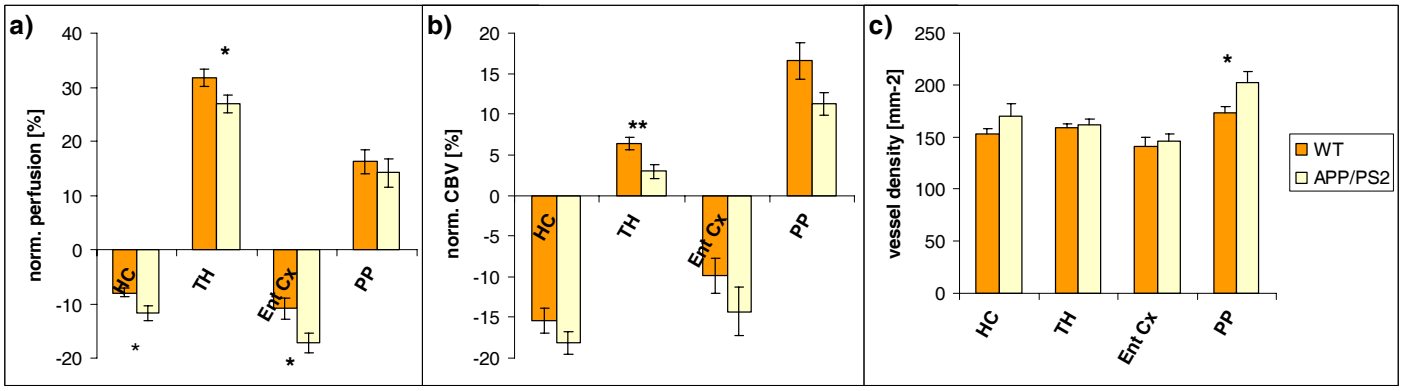

Fig. 1: Normalized perfusion (a), normalized CBV (b), and vessel density (c) in hippocampus (HC), thalamus (TH), entorhinal cortex (Ent Cx), and perforant path (PP) in wildtype and APP/PS2 mice (mean ± SEM). A t-test showed significant differences between the groups (*p<0.05, **p<0.01).