Functional MRI reveals strong hemodynamic impairment in arcAβ mice modeling vascular pathology of Alzheimer's Disease

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INTRODUCTION

Alzheimer's Disease (AD) is the most common neurodegenerative disease affecting ~10% of the population in the industrial world. Pathological hallmarks include intracellular accumulation of hyperphosphorylated protein τ in neurofibrillary tangles (NFT), accumulation of amyloid β (Aβ) peptides in amyloid plaques and Aβ deposits around vessels (cerebral amyloid angiopathy, CAA). Several genetically engineered mouse models for AD (cerebral amyloidosis) involving mutation of the amyloid precursor protein (APP) have been developed, which depending on the site of the mutation display different ratios of parenchymal plaques to vascular plaques. We used a physiological fMRI stimulation paradigm investigating vascular reactivity in arcAβ mice [1] (arctic/Swedish mutant) displaying mainly vascular plaques and compared them to APP23 mice (Swedish mutant) displaying comparable levels of vascular and parenchymal Aβ deposition [2].

METHODS

Animals: arcAβ mice (N=7) and their control littermates (N=5) (mean-age: 24.5month) were used for this study. Animals were anesthetized with Isofluoran, intubated and artificially ventilated during the MR experiment. Animals were placed on a water-heated cradle and all agents were injected via cannula into the tail vein. Experiments with the APP23 mice were done alike [3]. All animal experiments were performed in strict adherence to the Swiss law for Animal Protection.

fMRI protocol: Experiments were performed on a Pharmascan 47/16 (Bruker BioSpin GmbH, Karlsruhe, Germany). Scan parameters of the RARE sequence [4] were spatial resolution: 156x156x700 μm^3, temporal resolution: 40s, repetition time (TR): 2500ms, echo time (eff. TE): 80.2ms, field of view (FOV): 2x1.3cm^2, RARE factor: 32, matrix dimension: 128x128, slice thickness: 0.7mm, interslice distance: 1.2mm, number of averages: 4, number of slices: 5. fMRI measurement comprised 3 phases: 8 baseline images (S_{pre}) were acquired as reference for the determination of the relative cerebral blood volume (CBV_{rel}) changes. Thereafter scanning was interrupted and contrast agent (Endorem 55mg/kg) was injected as a bolus. After 15min to allow for contrast agent to reach steady state concentration, 7 postcontrast images (S(0)) were acquired. Manual injection of acetazolamide was followed by acquisition of 51 images (S(t)).

Stimulation paradigm: Acetazolamide, a carbon anhydrase inhibitor acts as a global vasodilator. Administration of 30mg/kg acetazolamide leads to an increase in cerebral blood volume. Data analysis was carried out using Biomap (Novartis, M. Rausch). Changes of CBV_{rel} in percentage of baseline values ($\Delta CBV_{\%}$) were computed on a pixel by pixel basis according to: $\Delta CBV_{\%}(t)=(\ln\{S(t)/S(0)\})/(\ln\{S(0)/S_{pre}\})*100$.

RESULTS

Following injection of acetazolamide in control littermates a distinct pattern of $\Delta CBV_{\%}$ of the order of 10-20% could be measured in various brain structures. Compared to the wildtype mice transgenic arcAβ animals showed significantly reduced $\Delta CBV_{\%}(t)$ values in response to acetazolamide stimulation in the primary sensory cortex (S1) (paired t-test, $N_{(wt)}=5$, $N_{(tg)}=7$, $p=0.045$). After drug administration CBV increased slower compared to controls. CBV changes leveled off at 5% of baseline values as compared to 15% in the age-matched wildtype animals (Figure1).

The reduction in the acetazolamide-induced CBV response was significantly larger in arcAβ mice as compared to APP23 mice [3] (paired t-test, $N_{(arcA\beta)}=7$, $N_{(APP23)}=6$, $p=0.007$) (Figure2).

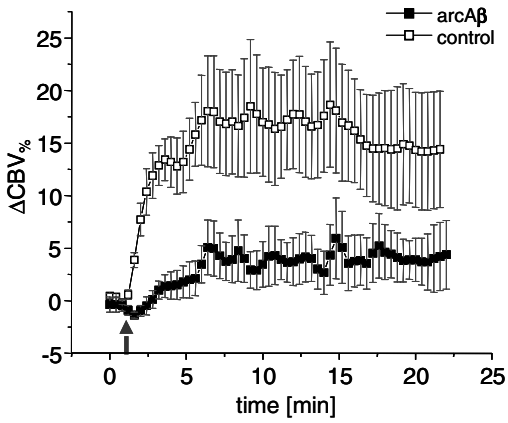

Figure1: $\Delta CBV_{\%}$ in primary sensory cortex as a function of time after injection of acetazolamide in arcAβ and control mice (values: mean±SEM).

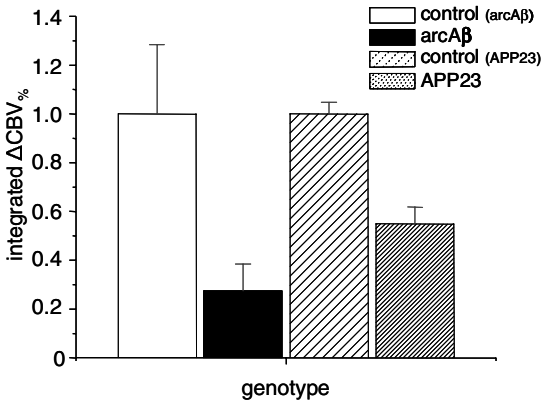

Figure2: Integrated $\Delta CBV_{\%}$ response of transgenic lines relative to the corresponding control littermate (integration 20min from time point of injection) in S1 (values: mean±SEM).

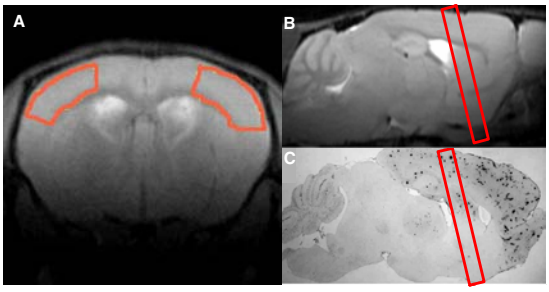

Figure3: A) Transverse section through brain of arcAβ mouse with ROI in S1 (red outline) overlayed on structural MRI slice (ROI:-0.82mm relative to Bregma). Slice position is indicated on sagittal image (B) and histological section stained for Aβ [1] (B).

CONCLUSIONS

CAA has been suggested to be associated with compromised vascular reactivity in the brain of affected animals as reflected by a reduced fMRI response to vasodilatory stimuli [3]. As shown by histology [1] arcAβ mice display preferential targeting of Aβ deposits to the vascular bed, in contrast to APP23 mice, with comparable parenchymal and vascular Aβ deposition at an age of 24 months. This translates into a significant reduction of the CBV response to acetazolamide in arcAβ as compared to APP23. This finding is in line with the hypothesis that CAA has a significant influence on the fMRI response, potentially also to CBV changes mediated through neuronal activity. The current study shows clearly that fMRI using vasodilatory stimuli such as acetazolamide allows probing the vascular pathologies present in the described animal models. In human studies vasoreactivity tests using acetazolamide are applied to discriminate vascular dementia from AD [5]. AD models displaying varying ratios of parenchymal versus vascular plaques could improve our basic knowledge of the origin of the compromised fMRI response in transgenic mouse models of AD.

REFERENCES

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ACKNOWLEDGEMENT

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