Evidence for cortical hypoperfusion by quantitative arterial spin labeling perfusion MRI in a mouse model of Alzheimer's disease

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Introduction: Alzheimer's disease (AD) is a devastating pathology characterized at the neuropathological level by cerebral accumulation of amyloid β (Aβ) deposits and neurofibrillary tangles. According to the amyloid hypothesis, amyloid and its derived products are the primary culprits in the disease and they initiate a cascade of events leading to the whole pathology. As a consequence, amyloid is the target for various therapeutic approaches that must be tested in animal models of the disease. In vivo biomarkers of the pathology are critical to follow these models and the effects of experimental drugs. Studies in AD patients showed that perfusion impairments can be detected non invasively by MR protocols based on spin labeling[1]. Such alterations might be related to the detrimental effects of amyloid on the vascular function[2]. In our study we evaluated perfusion modifications in APP/PS1 mouse models of AD by MRI. The mice were followed up in a longitudinal way and cerebral blood flow (CBF) was quantified in different brain regions in normo- and hypercapnia conditions by a pulsed arterial spin labeling technique.

Materials and Methods: APP/PS1 mice (Thy1 APP751 SL (Swedish mutation KM670/671NL, London mutation V717I introduced in human sequence APP751) x HMG PS1 M146L) modelling cerebral amyloid deposits and PS1, amyloid free, mice were studied in a longitudinal way at 54±1weeks ($n_{APP/PS1}$=9, n_{PS1}=10) and at 62.5±1weeks of age ($n_{APP/PS1}$=6, n_{PS1}=7). Images were recorded on a 4.7 Tesla Bruker Biospec system using a surface coil actively decoupled from the transmitting birdcage probe. Measures were performed in isoflurane-anesthetized animals under normo- and hypercapnia induced for 2 minutes by inhalation of 7% CO_2 balanced with O_2 and N_2. Perfusion measurements were performed using a FAIR Look-Locker gradient-echo method with adiabatic global or slice selective inversion pulses[3]. A series of 50 echoes were acquired under each condition (imaging parameters: TE/TR=1.59/150ms, α=12.5°, FOV: 20x20mm^2, slice thickness: 1.5mm, input matrix: 128x64; total acquisition time 32 min). Perfusion was evaluated from three regions of interest (ROI) localized in the parietal cortex, the thalamus and the hippocampus. In these ROIs, perfusion values were calculated from the saturation-corrected T1 values[3] as follows: $CBF/\lambda = [(T1^{global}/T1^{blood})*(1/T1^{selective}-1/T1^{global})]$ (where λ=0.9ml/g[4] and $T1^{blood}$=1.7ms) by using a program developed in an IDL environment (RSI, Boulder, CO). Statistical analyses were based on Mann Whitney's test and the statistical significance level was assigned for $p<0.05$.

Results: Under normocapnia, at both 54 and 62 weeks of age, APP/PS1 animals showed a significantly lower CBF in the parietal cortex than PS1 mice (fig. a). The difference between CBF in the parietal cortex of both groups was maintained under hypercapnia at 62 weeks of age and increased at 54 weeks of age (fig. a). In other evaluated brain regions, the CBF under normo- and hypercapnia was similar in both genotypes (fig b).

In 54 weeks old PS1 mice, hypercapnia condition led to a significant increase of the CBF in all evaluated brain regions (fig a, b). In the same mice, at 62 weeks, the hypercapnia-related CBF increase was observed only in the thalamus (fig. b) and hippocampus. On the other hand, in APP/PS1 mice, hypercapnia-related CBF increase was not observed in the cortex and was only significant in the thalamus of 54 weeks animals (fig. b) and hippocampus of 62 weeks animals.

Conclusion/Discussion: Our longitudinal study showed that under normo- and hypercapnia, the parietal cortex of APP/PS1 mice is less perfused than that of PS1 animals. In addition, under hypercapnia, almost all the evaluated brain regions from PS1 are more perfused than under normocapnia, which suggests an efficient vascular reactivity to the hypercapnia condition. Such modifications are more subtle in APP/PS1 mice and thus in addition to an already reduced CBF in the cortex, these mice might also present with an altered vascular reactivity. As perfusion can be measured non-invasively in both humans and transgenic mice, it should be useful as a translational marker to follow drug effects.

Reference: 1. Alsop et al., Ann.Neurol. 47(1): 93-100; 2000; **2.** Kalaria, Ann NY ac. Sci. 826:263-271; 1997; **3.** Kober et al., Magn Reson Med. 51:62-67; 2004; **4.** Sun et al. Magn Reson Med. 51:893-899; 2004.

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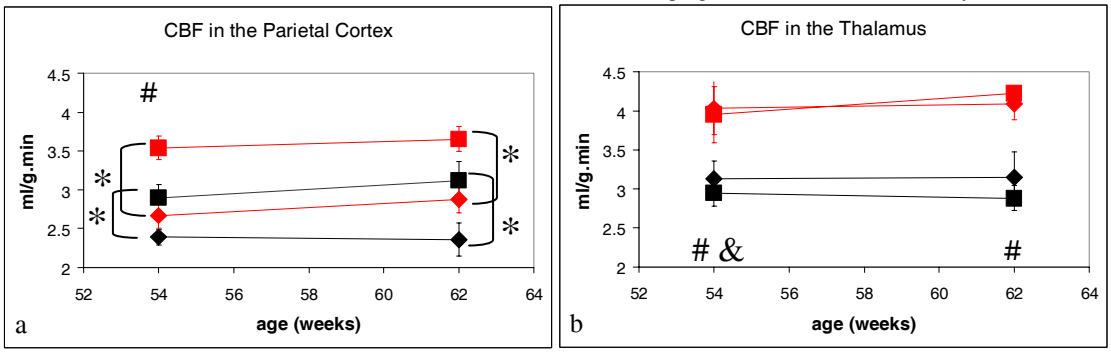

Figure: CBF values (mean±SEM) in the parietal cortex and in the thalamus of APP/PS1 and PS1 mice. *: significant difference in CBF between genotypes under the same condition. #, &: significant increase of the CBF under hypercapnia in PS1 and APP/PS1, respectively.