CEREBRAL BLOOD VOLUME AND METABOLISM, COGNITION AND NEUROPATHOLOGY IN APP/PS1 ALZHEIMER MICE AND APOE4 AND APOE KNOCKOUT MOUSE MODELS OF ATHEROSCLEROSIS

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Introduction: Vascular disorders such as atherosclerosis are important risk factors in the pathophysiology of Alzheimer’s disease (AD). Comparison between hemodynamical and neuropathological changes in transgenic animal models for AD and atherosclerosis is relevant for comprehensively ascertain the role of vascular impairment in AD progression.

Aims: In this study we examined cerebral macro- and microvascular blood volume in 12-month-old male C57BL6/J mice compared with a transgenic mouse model resembling familial AD (APPswe/PS1dE9) and two strains resembling vascular risk factors in sporadic AD by carrying human ApolipoproteinE4 (ApoE4) alleles, and ApoE knockout (-/-) mice. Behavior, spatial learning and memory, brain metabolite concentration, and neuropathology were compared.

Methods: Cerebral blood volume of macro- and microvasculature was determined at 12 months of age with a steady-state susceptibility contrast enhanced MRI and histogram analysis. Metabolites concentration in the hippocampus was determined with proton magnetic resonance spectroscopy (¹H MRS) at high field strength. Morris Water Maze (MWM), reverse MWM and Open Field test were used to assess spatial learning, memory and behavior. Brain tissue was analyzed immunohistochemically and biochemically for inflammatory markers and amyloid-β.

Results: We found decrease in the total and capillary blood volume in APP/PS1 mice, and more prominent defects in the macrovasculature of ApoE knockout animals. Dysfunctions in memory and behavior were found in all mouse strains studied. Brain metabolites concentration abnormalities were detected in both APP/PS1 and ApoE4 mice.

Conclusions: Metabolic abnormalities, neuronal degeneration, and cognitive impairment are possibly correlated with a common hypoperfusion status in APP/PS1, ApoE4 and ApoE knockout mice.