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Degeneration of vascular architecture associated with disease pathology in the 5XFAD mouse model of Alzheimer's disease

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Abstract

Background: Beta-amyloid (Aβ) plaques have long been considered a defining hallmark of Alzheimer's disease (AD), though the pathogenic mechanism and therapeutic efficacy of targeting plaques remain unclear. Accumulating evidence suggests that cerebrovascular abnormalities are also associated with cognitive decline and neurodegeneration in AD patients. We examined the relationship between Aβ plaque deposition and vascular architecture in different brain regions in the 5xFAD mouse model of Alzheimer's disease.

Methods: Separate cohorts of male and female wild-type (WT) and 5xFAD mice (C57BL/6 background) were evaluated at different time points during the progression of AD pathogenesis. First, learning and memory were assessed using a contextual fear conditioning paradigm to evaluate cognitive function. Then, blood vessels were labeled using DyLight 594 tomato-lectin (tail-vein injection) and a TRITC-Dextran gelatin solution (cardiac perfusion); Aβ plaques were labeled ex-vivo with 6-OH-BTA-1 (an intervening derivative of Pittsburgh compound B). Confocal images of optically cleared (SeeDeepBrain method) sagittal sections (450 µm) were collected from four distinct regions (subiculum, dentate gyrus, cortex, and cerebellum) to analyze Aβ plaque deposition and vascular architecture.

Results: At 4 months old, 5xFAD and WT mice performed equally well in contextual fear conditioning, but by 8 months of age, 5xFAD mice exhibited lower freezing 24 hours after conditioning compared to their WT littermates. In 5xFAD mice, total Aβ plaque burden substantially increased from 4 to 8 months, but regions exhibited differential vulnerability, with the subiculum accumulating the most plaques while the cerebellum had none. Blood vessel health appeared to be more compromised in 8 compared to 4 month-old 5xFAD mice, while it remained largely unchanged with age in WT mice. Interestingly, the regions displaying the greatest Aβ plaque burden in 5xFAD mice also had the largest reduction in the intensity of intact vascular labeling.

Conclusions: These experiments demonstrate that by 8 months of age, 5xFAD mice on a C57BL/6 background exhibit significant learning and memory impairments, increased Aβ plaque burden, and deterioration of the cerebrovasculature. They further suggest that vascular degeneration may be related to regionally specific Aβ plaque deposition and that this is an important pathological feature of disease progression.