SR-BI REGULATES PERIVASCULAR MACROPHAGES AND MODIFIES AMYLOID-RELATED PATHOLOGY AND CEREBRAL AMYLOID ANGIOPATHY IN AN AD MOUSE MODEL

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Scavenger receptor class B type I (SR-BI) is a High Density Lipoprotein (HDL) receptor that regulates cholesterol efflux from the peripheral tissues to the liver. SR-BI has been identified on astrocytes and vascular smooth muscle cells in Alzheimer’s disease (AD) brain and has been shown to mediate adhesion of microglia to fibrillar amyloid-β (Ab). Here we report that SR-BI mediates perivascular macrophage response and regulates Aβ related pathology and memory deficits in an Alzheimer mouse model. Reduction or deletion of SR-BI gene in heterozygous or homozygous deficient mice (SR-BI⁺/−, −/−) resulted in a significant increase in perivascular macrophages in the brain. SR-BI deletion had no effect on ApoE or ApoAI levels in the mouse brain. Our analysis revealed increased levels of SR-BI expression in the brains of huAPP (Swe Ind) transgenic mice (J20 line). To evaluate the role of SR-BI in AD pathogenesis, we inactivated one SR-BI allele in J20 transgenic mice. SR-BI reduction in J20/SR-BI⁺/− mice enhanced fibrillar amyloid deposition and cerebral amyloid angiopathy and also exacerbated learning and memory deficits compared to J20 littermates. Immunohistochemical analysis revealed localization of SR-BI on perivascular macrophages in tight association with Aβ deposits. Our data suggest that SR-BI reduction impairs the response of perivascular macrophages to Aβ and enhances the Aβ related phenotype and CAA in the J20 mice. These results reveal for the first time that SR-BI, a scavenger receptor primarily involved in HDL-cholesterol transport plays an essential role in AD and CAA.