HYPERTENSION-INDUCED B-AMYLOID DEPOSITION AND COGNITIVE IMPAIRMENT ARE MEDIATED THROUGH RAGE

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Introduction: Hypertension and Alzheimer's Disease (AD) have been associated but clear pathophysiological links are still missing. We have studied this association in a murine model of hypertension, showing typical “AD-like” traits, such as Ab deposition, neuroinflammation, brain hypoperfusion and most strikingly cognitive impairment.

Aims: Thus, aim of the present work was to investigate the molecular mechanisms involved in the induction of AD pathological changes observed in hypertensive mice. We focused on RAGE as the possible pathogenic mechanism, being the receptor that critically regulate Aβ transport at the BBB and that may be influenced by vascular challenges.

Methods: RAGE KO and WT mice were subjected to hypertension by performing transverse aortic coarctation (TAC), selectively imposing pressure overload impact to the cerebral circulation. Cognitive performance was evaluated by Morris Water Maze and brains were analyzed for Aβ deposition and neuroinflammatory markers.

Results: We found that WT mice early (8 hours) up-regulated RAGE after from TAC in cortex and hippocampus. Therefore we performed TAC in RAGE KO mice. We found that neuroinflammatory profile was strongly dampened, as evidenced by microglia activation and cytokine production. More interestingly, RAGE ablation rescued deficits in learning and memory tasks and shifted Aβ deposition from brain parenchyma into brain vessels in TAC hypertensive mice.

Conclusions: Overall our data demonstrate that RAGE activation is a crucial pathogenetic event in TAC-induced “AD-like” pathology, thus indicating that RAGE represents a potential therapeutical target in hypertensive patients at risk for AD.