COGNITIVE IMPAIRMENT IN A MOUSE MODEL OF HYPERTENSION: AN INNOVATIVE TOOL TO INVESTIGATE THE ETIOLOGY OF ALZHEIMER’S DISEASE

Ivana D’ANDREA1,2, Daniela CARNEVALE1, Shirley SHI DU YAN4, Igor BRANCHI2 and Giuseppe LEMBO1,3

1 Department of Anglo-Cardio-Neurology, IRCCS “Neuromed”, 86077 Pozzilli (IS), Italy
2 Section of Behavioural Neurosciences, Department of Cell Biology and Neuroscience, Istituto Superiore di Sanità, 00161 Rome, Italy
3 Department of Molecular Medicine, “Sapienza” University, 00161 Rome, Italy
4 Department of Pharmacology and Toxicology, Higuchi Biosciences Center, University of Kansas, Lawrence, KS 66047, USA

ivana.dandrea@neuromed.it

AIMS AND METHODS

In order to investigate the potential link among hypertension and AD, we focused on a particular model of hypertension, obtained by transverse aortic coarctation (TAC) and showing a significant hippocampal and cortical Aβ deposition within four weeks. Thus, we explored molecular markers and behavioral traits associated to AD in genetically modified mice for RAGE. In particular, the process of microglia activation and the expression of typical pro- and anti-inflammatory genes as well as learning and memory abilities in the Morris Water Maze test, were assess.

EXPERIMENTAL DESIGN

BEHAVIORAL ANALYSIS

Morris Water Maze
- Cerebral blood flow
- Microglia activation
- Expression of pro- and anti-inflammatory genes

BIBLIOGRAPHY


INTRODUCTION

Alzheimer’s disease (AD) is the most common form of dementia in the elderly. The pathological hallmark of the disease is characterized by the presence of senile plaques in form of extracellular β-amyloid (Aβ) deposition, accompanied by increases inflammatory responses and impairment in learning and memory abilities. For a long time, a clear association between AD and hypertension has been reported, although the pathological link underlies such association is still unknown. Experimental evidence provided by animal models has shown that RAGE receptor is involved in the transport of Aβ through the blood brain barrier, suggesting a role for this receptor in mediating the effects of neurovascular risk factors in the AD etiology.

RESEARCH DESIGN

A. Double-labeling of Iba-1 and CD68 shows increased CCR7 expression in TAC mice, associated with a lower count, both pro- and anti-inflammatory gene expression. Microglia reactive activated cells of TAC mice and Iba-1 staining at cortex level. Data are expressed as the fold changes in gene expression normalized to GAPDH and relative to sham mice and presented as the mean ± SD. * P < 0.05 and ** P < 0.01 vs sham.

B. Relative mRNA levels vs sham of RAGE, IL-1α, IL-1β, TNF-α, TGF-β and IL-10 in hippocampal and cortical tissue of TAC and sham mice. Data are expressed as the fold changes in gene expression normalized to GAPDH and relative to sham mice and presented as the mean ± SD. * P < 0.05 and ** P < 0.01 vs sham.

CONCLUSIONS

Overall, our findings point to a central role of hypertension-driven brain damage in the pathogenic mechanisms leading to amyloid pathology, confirming a role played by RAGE in the onset and progression of AD. Furthermore, the TAC model used here displays behavioral alterations having face validity with psychiatric symptoms of AD disease and thus appears as a valuable tool to explore the neural mechanisms underlying this pathology.

No potential conflict of interest