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

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INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia in the elderly. The pathological hallmarks of the disease are 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.

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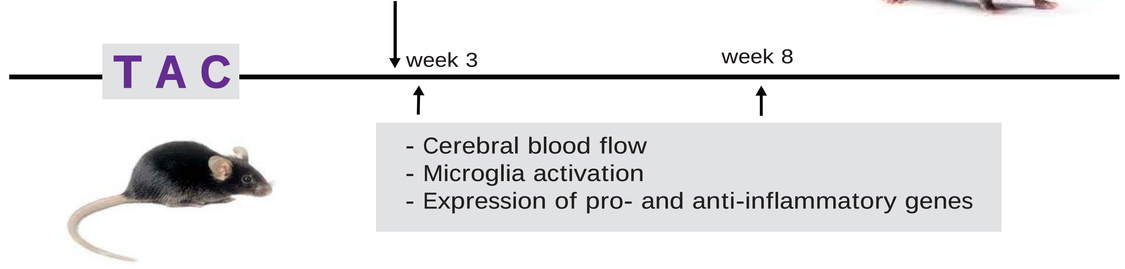
AIMS AND METHODS

In order to investigate the potential link among hypertension and AD, we focused on a particular model of hypertention, obtained by tranverse 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

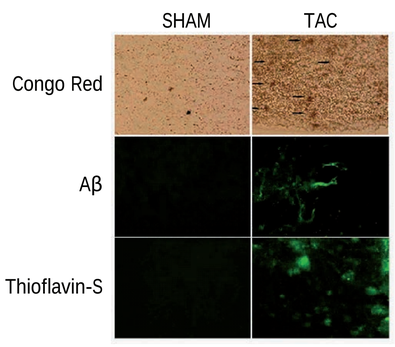


ROLE OF HYPERTENSION IN THE AD ETIOLOGY

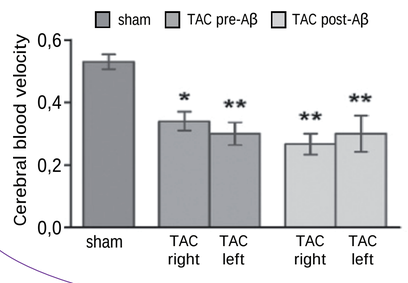
AMYLOID DEPOSITION IN THE BRAIN

TAC-induced hypertension determines amyloid deposition in brain parenchyma and around blood vassels as evidenced by Congo red, anti-Aβ and Thioflavin-S.

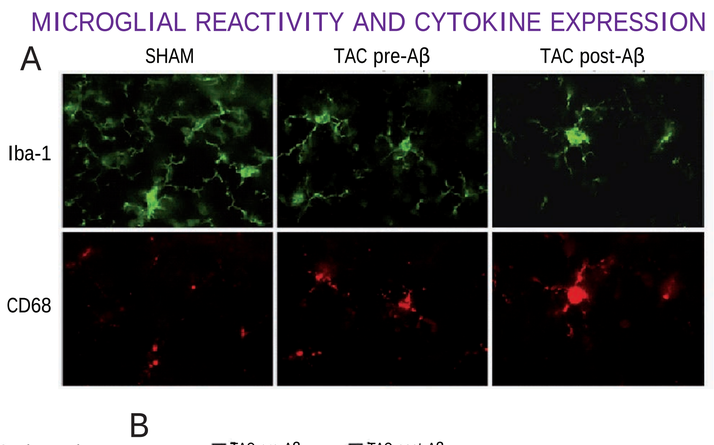
Cerebral blood velocity was significantly reduced in both hemispheres in TAC pre-Aβ and TAC post-Aβ mice (n = 5 for each group). *p = 0.05 and **p = 0.01 vs sham.



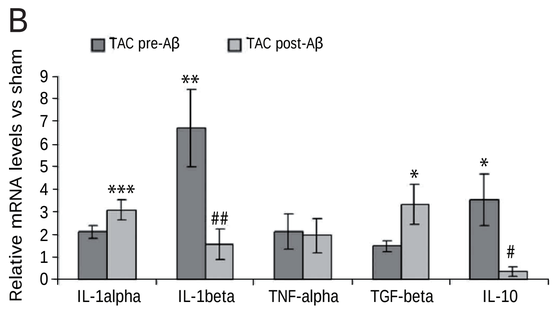
CEREBRAL BLOOD VELOCITY



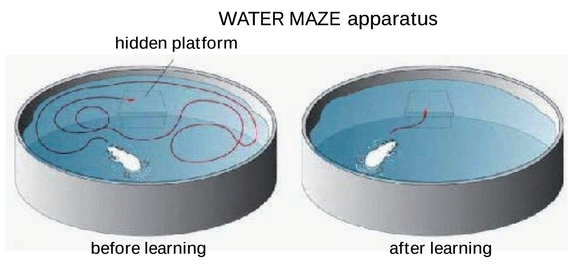
MICROGLIAL REACTIVITY AND CYTOKINE EXPRESSION

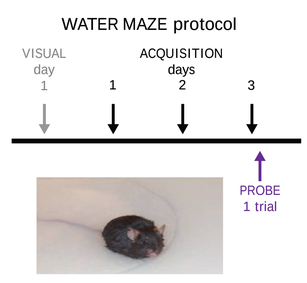


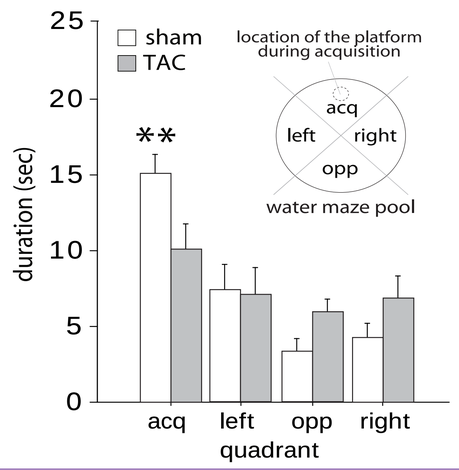
(A) Double-labeling of Iba-1 and CD68 shows increased CD68 expression in TAC mice, colocalized with Iba-1 staining, both pre- and post-Aβ deposition. Hippocampus representative images of n = 4 for each group are presented. (B) Hippocampal mRNA levels of IL-1alpha, IL-1beta, TNF-alpha, TGF-alpha and IL-10. Data are expressed as the fold changes in gene expression normalized to HPRT and relative to sham mice and represented as scatter plot. *p = 0.05, **p = 0.01 and ***p = 0.001 vs sham; #p = 0.05 and ##p = 0.01 vs TAC pre-Aβ .



MORRIS WATER MAZE TASK







TAC procedure impaired learning and memory abilities in the Morris water maze, a hippocampus dependent task. TAC micespent significantly less time than sham mice in the quadrant where the platform was located, indicating a reduced memory of the position of the platform during the acquisition. Data are means ± S.E.M. (n =10 for each experimental group). Comparisons were made using one-way analysis of variance (ANOVA).
**p< 0.01vs each other quadrant.

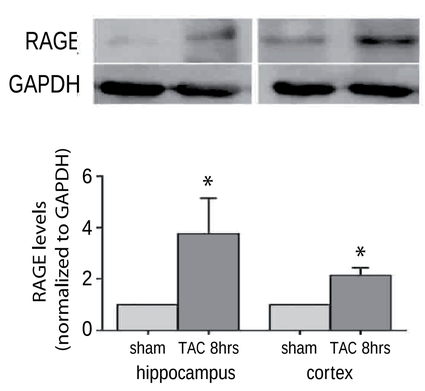
REGE ABLATION PREVENTS BRAIN AMYLOID DEPOSITION AND COGNITIVE IMPAIRMENT

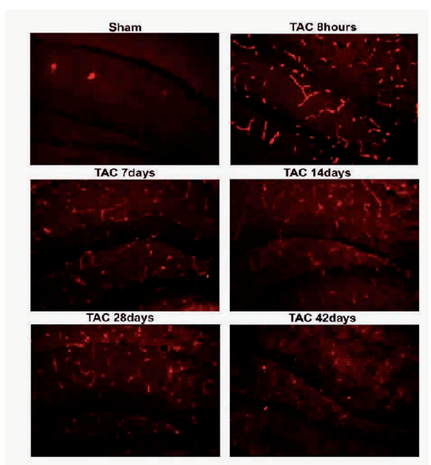
Hypertension early up-regulates RAGE expression in hippocampus and cortex and sustains it over time.

RAGE ablation (RO mice) prevents development of hypertension-induced alterations. Indeed, microglia activation and cytokine increased were showed only in RAGE WT genotype, and not in KO mice. (*p = 0.05 vs sham).

Likewise, Rage KO mice recovered in cognitive abilities in Morris Water Maze test, displaying the same behavioral profile showed by sham mice. (** p < 0.01 vs each other quadrant).

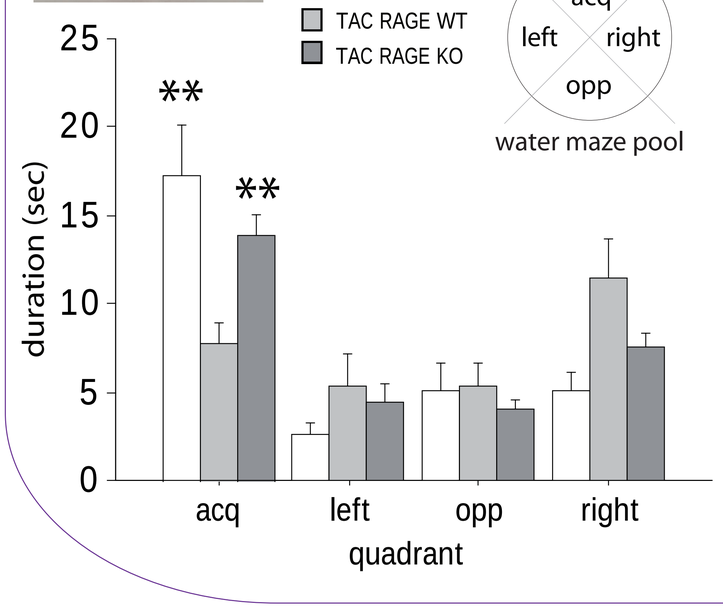
RAGE EXPRESSION IN TAC MICE





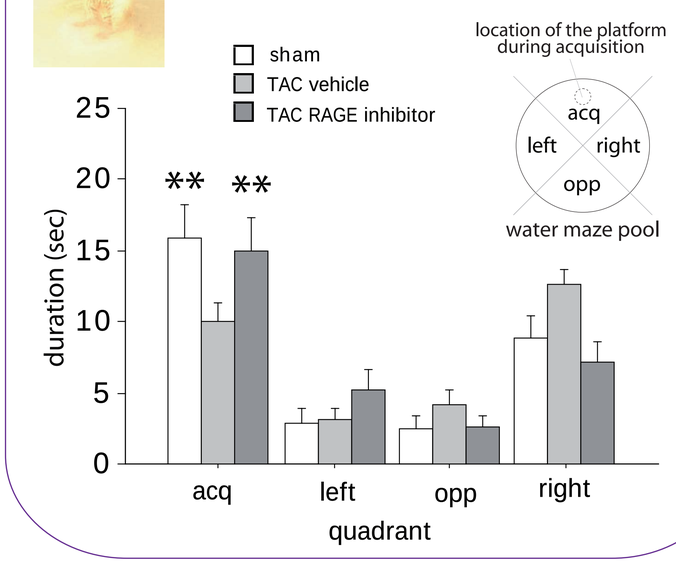
MICROGLIAL REACTIVITY AND CYTOKINE EXPRESSION

MORRIS WATER MAZE



TREATMENT WITH RAGE INHIBITOR

TAC-induced cognitive impairment showed in Morris Water Maze test, were prevented by treatment with RAGE inhibitor. (** p< 0.01 vs each other quadrant)



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