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Research report

The role of myocardin-related transcription factor-A in $A\beta_{25-35}$ induced neuron apoptosis and synapse injury

Ying Zhang [a,1], Hong-yan Pan [b,1], Xia-min Hu [a,*], Xiao-lu Cao [a], Jun Wang [a], Zhen-li Min [a], Shi-qiang Xu [a], Wan Xiao [a], Qiong Yuan [a], Na Li [a], Jing Cheng [a], Shu-qi Zhao [a], Xing Hong [a]

[a] Department of Pharmacology, Medical College of Wuhan University of Science and Technology, Wuhan 430080, PR China
[b] Tianyou Hospital Affiliated to Wuhan University of Science and Technology, Wuhan 430064, PR China

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ABSTRACT

Myocardin-related transcription factor-A (MRTF-A) highly expressed in brain has been demonstrated to promote neuronal survival via regulating the transcription of related target genes as a powerful co-activator of serum response factor (SRF). However, the role of MRTF-A in Alzheimer's disease (AD) is still unclear. Here, we showed that MRTF-A was significantly downregulated in cortex of the $A\beta_{25-35}$-induced AD rats, which played a key role in $A\beta_{25-35}$ induced cerebral neuronal degeneration in vitro. Bilateral intracerebroventricular injection of $A\beta_{25-35}$ caused significantly MRTF–A expression decline in cortex of rats, along with significant neuron apoptosis and plasticity damage. In vitro, transfection of MRTF-A into primary cultured cortical neurons prevented $A\beta_{25-35}$ induced neuronal apoptosis and synapses injury. And luciferase reporter assay determined that MRTF-A could bind to and enhance the transactivity of the Mcl-1 (Myeloid cell leukemia-1) and Arc (activity-regulated cytoskeletal-associated protein) promoters by activating the key CArG box element. These data demonstrated that the decreasing of endogenous MRTF-A expression might contribute to the development of AD, whereas the upregulation MRTF-A in neurons could effectively reduce $A\beta_{25-35}$ induced synapse injury and cell apoptosis. And the underlying mechanism might be partially due to MRTF-A-mediated the transcription and expression of Mcl-1 and Arc by triggering the CArG box.

1. Introduction

The prominent pathological hallmarks of Alzheimer's disease (AD) are extracellular amyloid β (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau (Selkoe, 1991). Especially, the abnormal metabolism and deposition of Aβ peptide in the brain are believed as a primary driving force in AD pathogenesis (Roberts et al. 2012). Synapse loss and neuronal apoptosis have been found as the common signs in the cortex and hippocampus of AD patients (Davies et al., 1987; Reix et al., 2007; Mormino et al., 2009). Actually, synaptic dysfunction and the impairment of intrinsic plasticity often occurred before the neuronal cell death in Aβ models of AD (Ford, Crossley et al. 2015). In addition, neuronal apoptosis induced by a variety of factors including oxidative stress, Aβ deposition and inflammatory processes (Cheng and Li, 2014) is currently regarded as a primary form of cell loss associated with AD (Yang et al., 2008).

In the nervous system, serum response factor (SRF) controls the activation of immediate early genes (IEGs), which have been demonstrated to be involved in synaptic activity, learning and memory, by binding DNA promoter at CArG box (CC (A/T) 6GG) (Knoll and Nordheim, 2009). Myocardin-related transcription factor A (MRTF-A), a powerful co-activator of SRF, is enriched in the forebrain, particularly in cerebral cortex (Alberti et al., 2005; Shiota et al., 2006). Kalita et al. (2012) found that the inhibition of MRTF-A decreased the neurite length and the formation of dendritic processes in cortical and hippocampal neurons, suggesting MRTF-A appeared to regulate plasticity-related structural changes in neurons. Our previous research (Cao et al., 2011) showed that over-expression of MRTF-A promoted neuronal survival against both hypoxia-trophic deprivation and hydrogen peroxide-induced apoptosis, which was mediated by enhancing the transcription and expression of target anti-apoptotic gene Mcl-1 (Myeloid cell leukemia-1) via triggering CArG box. Despite the fact that the role of MRTF-A in AD development is still unclear, however, it can be speculated that MRTF-A might be involved in $A\beta_{25-35}$ induced brain injury, and function as a neuroprotective factor in AD.

Abbreviations: MRTF-A, Myocardin-related transcription factor-A; SRF, serum response factor; Mcl-1, Myeloid cell leukemia-1; Arc, activity-regulated cytoskeletal-associated protein; IEGs, immediate early genes; F-actin, filamentous actin

* Corresponding author.
E-mail address: huxiamin@wust.edu.cn (X.-m. Hu).

[1] These authors contributed equally to this work and shared the first authorship.

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In the present study, we firstly showed the change of MRTF-A expression in an $A\beta_{25-35}$-induced AD rat model. Then, we investigated the effect of MRTF-A on $A\beta_{25-35}$-induced apoptosis and synapses injury in primary cultured cortical neurons and its underlying mechanism.

2. Results

2.1. MRTF-A is involved in $A\beta_{25-35}$ induced AD rats

Firstly, we adopted Morris water maze test to make sure the AD rats model was built successfully. As compared to control group, rats in the $A\beta_{25-35}$ group showed markedly higher latencies in finding the hidden platform from the second day ($p < 0.05$ or $p < 0.01$; Fig. 1A), and the time that the rats swam in the target quadrant was significantly shorter in the space exploration test ($p < 0.01$; Fig. 1B), suggesting $A\beta_{25-35}$ induced obvious spatial learning deficits in rats. Then, apoptotic cells and neurofilament expression in rat cortical and hippocampus were examined using the TUNEL assay and immunohistochemistry respectively. TUNEL-positive cells (apoptosis) in both hippocampus and cortex of rats injected with $A\beta_{25-35}$ were significantly increased compared with those of control rats (Fig. 1C, D). The level of neurofilament protein expression (brown) in cortex and hippocampus of $A\beta_{25-35}$-induced AD rats was decreased to 69% and 66% respectively, as compared to control group (Fig. 1E, F), and a few neurons were found scattered among the damaged cell layer in $A\beta_{25-35}$ group (Fig. 1E). The results showed that $A\beta_{25-35}$ has significantly induced neuron apoptosis as well as plasticity damage.

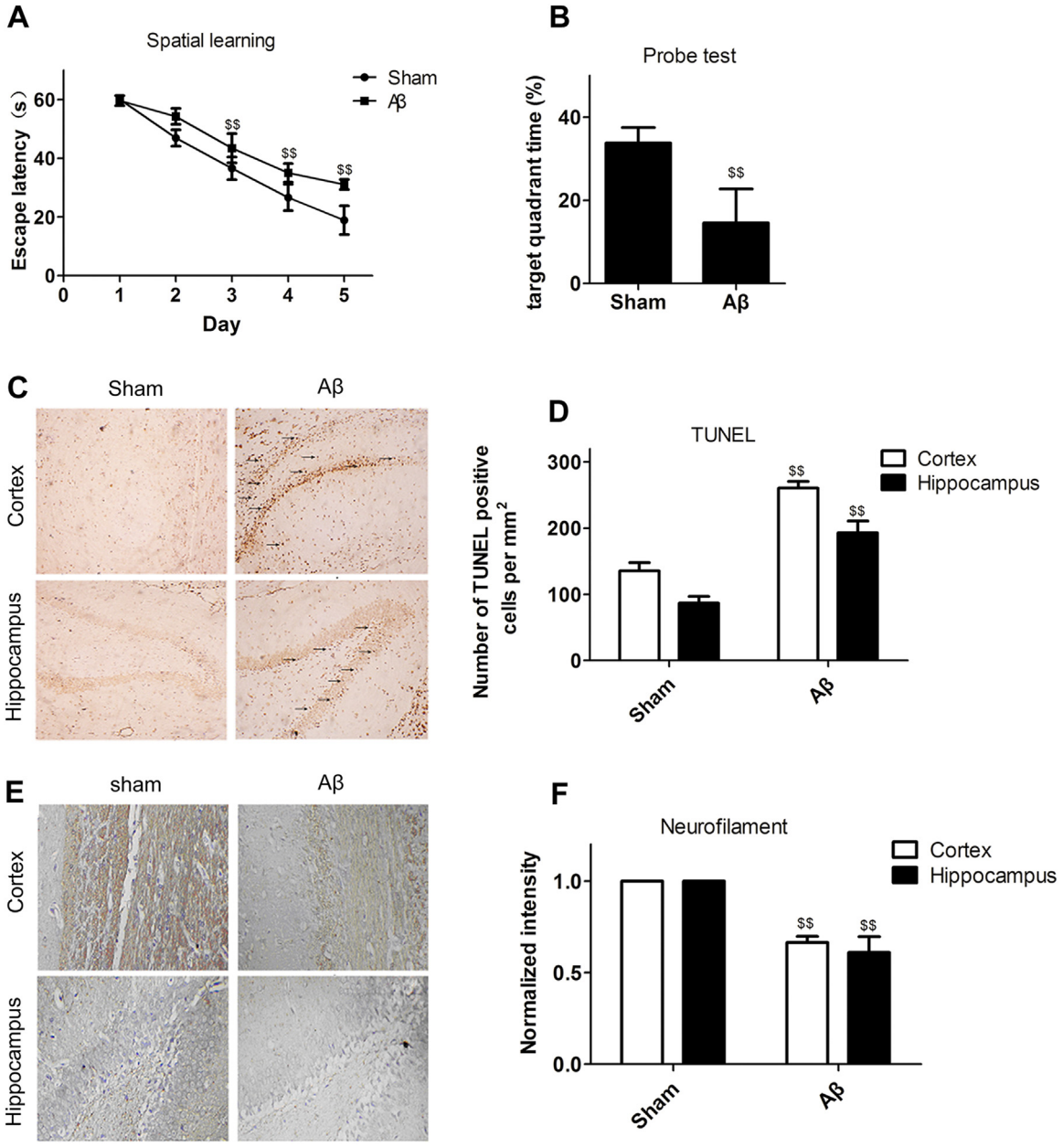

Fig. 1. $A\beta_{25-35}$ induced brain injury in rats. (A) Escape latency to find hidden platform for five days navigation test in Morris water maze a week after injection. (B) Percentage of time hovered in target quadrant in Morris water maze on the day after navigation test. (C) TUNEL detection of rat cortical and hippocampus apoptotic cells. TUNEL-positive cells are stained as brown particles. (D) Quantification of apoptosis positive cells. (E) Expression of neurofilament medium was determined by Immunohistochemistry. The neurofilament positive reaction cells (brown) in areas of hippocampus and cortex in control and Aβ group, nuclei was purple.(F) Quantification of the expression of neurofilament medium $^{\$}p < 0.05$, $^{\$\$}p < 0.01$, vs. sham group. c mag × 10, E mag × 40.