Therapeutic strategies targeting Alzheimer's disease-related molecules

August 5 2016

Therapeutic strategies targeting Alzheimer's disease (AD)-related molecule β-amyloid (Aβ), Tau protein and BACE enzyme have been recently explored. However, the therapeutic efficacy for a single target is not ideal. The clinical trials that clean Aβ from the brain in AD patients were largely unsuccessful. It is well known that the inflammatory response is one component of AD pathogenesis, leading to a series of irreversible pathological events. Epidemiological evidences show that long-term use of non-steroidal anti-inflammatory drugs has a sparing role in AD, but it failed to prevent the progression of symptoms in AD patients in randomized clinical trials. Possible reasons for the failure of anti-inflammatory drugs may be associated with: 1) the advanced state of disease or the dosing regimens of drugs; 2) most of the available anti-inflammatory drugs are not really "anti-inflammatory"; 3) these "anti-inflammatory" drugs only prevent the pro-inflammatory responses, but do not trigger the anti-inflammatory responses.

Fasudil, a selective Rho kinase (ROCK) inhibitor, may be a more appropriate therapeutic option in the treatment of patients with AD. Our previous studies provided many evidence that Fasudil inhibited the inflammatory response in both experimental autoimmune encephalomyelitis (EAE) and Parkinson's disease (PD) models through converting inflammatory M1 microglia/macrophage to anti-inflammatory M2 cells. The investigations from other groups also demonstrated therapeutic potential in EAE, PD and amyotrophic lateral sclerosis (ALS). It should be noted that the inhibition of inflammatory microglia is essential for the neuroprotective effects of ROK inhibitor

on MPTP-induced dopaminergic cell death. Based on these reasons, we designed the study to observe therapeutic potential of Fasudil, and explored possible mechanisms in APP/PS1 transgenic mice.

Our results show that administration of Fasudil improved learning and memory deficits in APP/PS1 Tg mice. The expression of Aβ1-42 in hippocampus and brain of mice was clearly observed in APP/PS1 Tg mice, while treatment of Fasudil reduced the expression of Aβ1-42 in hippocampus of APP/PS1 mice. Tau protein intracellular neurofibrillary tangles (NFTs) pathology is the major correlation between clinical symptoms and main feature in AD. Tau-induced animal models reproduce neuronal and glial Tau pathology, leading to the progressive cognitive and/or motor impairment and premature death. Our results demonstrated that the treatment of Fasudil decreased the number of p-Tau/Ser396-positive cells and expression of p-Tau/Ser396 protein in brain of APP/PS1 Tg mice. BACE is a β-site APP cleaving enzymes that is a major drug target for AD because of BACE-mediated cleavage of APP and decrease of Aβ. To investigate whether Fasudil intervention influences the levels of BACE, we observed the expression of BACE in the hippocampus and brain. The expression of BACE protein in brain of App/PS1+saline mice was elevated significantly compared with those of wild-type mice and were dramatically downregulated upon treatment with Fasudil for 8 weeks. PSD-95 is a synaptic protein regulating glutamate receptor anchoring, synaptic stability and certain types of memory that is regulated by Aβ. The treatment of Fasudil increased the expression of PSD-95 in App/PS1 mice. Taken together, Fasudil ameliorated learning and memory deficits, accompanied by reduced Aβ deposition, Tau phosphorylation, BACE expression, as well as increased PSD-95 expression in hippocampus.

It has become increasingly apparent that neuroinflammation plays an important role in the pathology of AD. Our results found that the treatment of Fasudil also inhibited TLR-2/4, MyD88, p-NF-κB/p65,

IL-1β, IL-6 and TNF-α, and induced IL-10 in App/PS1 mice.

AD is a complex aging-related disease caused by a variety of genetic and environmental factors. Currently therapeutic agents approved by the US Food and Drug Administration (FDA), including donepezil, rivastigmine, galantamine and memantine, are unable to prevent or reverse disease progression and are only modestly efficacious. A series of irreversible pathological events coexist in the pathogenesis of AD, including inflammatory response, toxic to neurons, oxidative stress, activated microglia and loss of Aβ clearance ability. The novel therapeutic strategy should target multiple aspects of AD, e.g., attenuates the Aβ burden and Tau phosphorylation, and/or converts beneficial microglia polarization. Fasudil exhibited a multitarget therapeutic effect in APP/PS1 transgenic mice by the reduction of Aβ deposition and Tau phosphorylation, the decrease of BACE and the increase of PSD-95, as well as inhibition of TLRS-NF-κB-MyD88 inflammatory axis. However, these results still need to be repeated and confirmed before clinical application.

More information: Yu, J.-Z.; et al. (2016). Multitarget therapeutic effect of Fasudil in APP/PS1transgenic mice, CNS Neurol. Disord. Drug Targets. DOI: 10.2174/1871527315666160711104719

Provided by Bentham Science Publishers

provided for information purposes only.