

Hsp70 and donors of H₂S in aging-associated diseases and inflammation

Evgen'ev M.B., Garbuz D.G., Zatsepina O.G.

Engelhardt Institute of Molecular Biology, RAS, Moscow, Russia

Abstract: Heat shock protein 70, in humans is a key component of the machinery protecting the neuronal cells from various stress conditions whose production significantly declines in the course of aging. Alzheimer's disease (AD) is the most prevalent neurodegenerative pathology in the growing population of elderly humans and leads eventually to dementia and death. Despite tremendous efforts, no effective treatment for AD is currently available. Molecular chaperone Hsp70 plays protective role in various neurodegenerative disorders. Various data suggest that Hsp70 and other molecular chaperones function as a complex neuroprotective system, which fails in the brains of aged people and AD patients. In special experiments we demonstrated that rHsp70 effectively crosses the blood-brain barrier when administered intranasally. We also have shown that chronic administration of recombinant Hsp70 (rHsp70) decreased beta-amyloid level and preserved neuron density in two mouse models of Alzheimer disease. In both cases rHsp70 restored behavior and memory disturbed by Alzheimer disease and aging. We also explored the effect of rHsp70 on neurons morphology and survival in the cortex and the hippocampus of transgenic animals. The proportion of pathologic neurons decreased drastically in Hsp70-treated animals. Therefore, Hsp70 treatment of model mice protects neurons from deterioration and death in brain areas most affected in AD patients. Deep sequencing studies enabled to reveal candidate genes and signal pathways underlying beneficial effects of rHsp70 treatment. In our experiments we also demonstrated that intranasal administration of exogenous recombinant human Hsp70 can promote longevity in male but not female mice. The Hsp70 treatment normalized the synthesis of synaptophysin in aged mice and decreased accumulation of lipofuscin which represents the marker of aging and neurodegeneration processes. The treatment with rHsp70 performed by our group and colleagues from other Institutes demonstrated highly beneficial effects in several models of age-associated diseases including infarction and stroke.

Hydrogen sulfide (H₂S) represents another compound with strong anti-inflammatory properties able to modulate many biological processes, including ageing. Initially considered a hazardous toxic gas, it is now recognized that H₂S is produced endogenously and is a key mediator of processes that promote longevity and improve late-life health. In this reports, we will consider the key developments in our understanding of this gaseous signaling molecule in the context of health and disease, discuss potential mechanisms through which H₂S can influence processes central to ageing and highlight the emergence of novel H₂S and Hsp70-based therapeutics to treat age-associated diseases in humans.

Acknowledgements: This work was supported by grant from the Russian Science Foundation (project 17-74-300-30).