Is HSF1 the key in mediating Hsp90 inhibitor effect in AD?

https://neurodegenerationresearch.eu/survey/is-hsf1-the-key-in-mediating-hsp90-inhibitor-effect-in-ad/

Principal Investigators

LIAO, FRANCESCA-FANG

Institution

UNIVERSITY OF TENNESSEE HEALTH SCI CTR

Contact information of lead PI
Country

USA

Title of project or programme

Is HSF1 the key in mediating Hsp90 inhibitor effect in AD?

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,286,140.37

Start date of award

01/05/2015

Total duration of award in years

2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Dementia... Genetics... Neurodegenerative... Neurosciences

Research Abstract

? DESCRIPTION (provided by applicant): Induction of heat-shock proteins (HSPs), such as via

Hsp90 inhibition of heart shock protein 90 (Hsp90), is being investigated as a treatment option for neurodegenerative diseases such as Alzheimer's disease (AD). This is believed to be mediated primarily via activated heat-shock transcription factor/HSF1, a major eukaryotic stress-responsive factor that is expressed in most cell systems and protects cells from cell death. Recently, we administered a CNS-permeable Hsp90 inhibitor (NXD) in cultured neurons and mice, and found that this upregulated not only HSPs (iHSp70, Hsp40, Hsp27, etc.), but also several pre- and post-synaptic protein genes (e.g., synapsin, synaptophysin, PSD95, BDNF) at transcriptional levels. We found that this inhibitor completely rescued synapses from the detrimental effects of soluble Aß in C57BL/6 mice, preventing deterioration in hippocampus-dependent contextual fear conditioning. Notably, when a specific HSF1 inhibitor (KRIBB11) was co-administered with Aß and NXD to mouse brain, it completely abolished NXD's effect. Furthermore, chronic treatment of early symptomatic Tg2576 mice (9-12 MO) with systemic NXD completely rescued the spatial memory deficit, as determined by various maze tests, accompanied by increased iHsp70 as well as PSD95 and BDNF proteins in treated mice. Most interestingly, NXD treatment induced rapid and sustained HSF1 heat shock-like response, as evidenced by nuclear translocation (active state) and induced iHsp70 expression, which was most prominently expressed in the pyramidal neurons of hippocampal CA1, as compared to distal CA3 or neocortex. Together, our findings strongly suggest an important role of HSF1 in synaptic plasticity; to date, its neuronal functions remained largely unknown. We hypothesize that HSF1 is a key regulator of synaptic transcriptome, and regulates a large number of genes crucial and related to synaptic functions; NXD's protective effect on synapses is largely mediated via HSF1-dependent mechanisms. Since the NXD compound represents a good candidate for future development of new AD therapeutic strategies, we aim to investigate in-depth mechanisms underlying its protective effects, with special focus on HSF-1 dependent transcription. Accordingly, three specific aims are to test several hypotheses that 1) HSF1 plays a crucial role in AD and transcriptionally active HSF1 is required for Hsp90 inhibitor's effects in mice, 2) HSF1 can globally modulate the synaptic transcriptome related to synaptic plasticity (LCM/RNA-seq) of CA1/CA3 dendrites), and 3) chronically activated HSF1 works equivalently as Hsp90 inhibitor in rescuing AD mice. Successful outcomes from this study will likely validate HSF1 as a therapeutic target for synaptic and memory disorders.

Lay Summary

PUBLIC HEALTH RELEVANCE: We aim to validate the newly identified roles of druggable Hsp90 inhibitor in regulating synaptic functions in several acute and chronic mouse model of AD. Successful validation of its multiple beneficial effects may identify a potential therapeutic agent useful in preventing and treating AD.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

Database Tags:
N/A