Discovery of probes that enhance expression of the neuroprotective protein Klotho

https://www.neurodegenerationresearch.eu/survey/discovery-of-probes-that-enhance-expression-of-the-neuroprotective-protein-klotho/

Principal Investigators

ABRAHAM, CARMELA R

Institution

BOSTON UNIVERSITY MEDICAL CAMPUS

Contact information of lead PI
Country

USA

Title of project or programme

Discovery of probes that enhance expression of the neuroprotective protein Klotho

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 784,913.76

Start date of award

15/09/2016

Total duration of award in years

1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease Related Dementias (ADRD)... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Basic Behavioral and Social Science... Behavioral and Social Science... Brain Disorders... Cerebrovascular... Dementia... Neurodegenerative... Neurosciences... Prevention... Translational Research... Vascular Cognitive Impairment/Dementia

Research Abstract
Abstract Cognitive functions such as learning and memory are of fundamental biological importance and diseases that affect these functions are among the most challenging biomedical problems of our time. Just like 50% of humans suffer from cognitive decline as they age, so do the rhesus monkeys. In a long term, large study of brain changes that occur with age in these monkeys, we have shown that normal brain aging is associated with a significant downregulation of Klotho expression. We reported that the levels of the Klotho protein in the brain decrease with age across species and, interestingly, others reported earlier that loss of Klotho accelerates the development of aging-like phenotypes, including cognitive deficits, whereas Klotho overexpression extends life span. Klotho is a type 1 transmembrane pleiotropic protein predominantly expressed in kidney and brain and shed by ADAM 10 and 17 into the blood and CSF, respectively (sKlotho). While the renal functions of Klotho are well known, its roles in the brain remain to be fully elucidated. In the brain, Klotho is mainly localized in the apical plasma membrane of epithelial cells of the choroid plexus and, to a lesser extent, hippocampal neurons. In search for Klotho’s function in the nervous system, we recently reported the following findings: 1) Pretreatment with sKlotho is able to protect primary hippocampal neurons from amyloid-? (A?) and glutamate toxicity. 2) sKlotho induces oligodendrocyte differentiation and remyelination. 3) In a high throughput screen, we identified small molecule compounds that increase Klotho expression. We now have lead compounds that, in vivo, elevate Klotho expression in mouse kidney and brain. 4) We recently demonstrated that increased Klotho levels are associated with enhanced cognitive functions in mice and humans and can prevent synaptic and cognitive impairments in a transgenic mouse model (hAPP mice from line J20) that simulates key aspects of Alzheimer’s disease (AD). We hypothesize that small molecules capable of elevating Klotho levels (“Klotho boosters”) can enhance neural functions and prevent and reverse the pathogenic effects of elevated A? levels in the brain. To begin to test these hypotheses we need to identify Klotho boosters that will fulfill all the necessary criteria to move forward towards preclinical studies. Therefore, we propose the following specific aims: Aim 1: Optimization and in vitro characterization of the lead series of Klotho enhancing compounds (boosters) to prepare potential probes with properties predictive of good pharmacokinetics (PK) and CNS exposure. Aim 2: In vivo characterization of lead compounds to select brain-penetrant chemical probes for in vivo efficacy studies. Aim 3: Preliminary target identification using an affinity ligand strategy Increasing levels of lifespan-extending factors such as Klotho can counteract cognitive dysfunction caused by aging or neurodegenerative disease and is of utmost interest to the fields of neuroscience, aging, and neurodegeneration. The proposed study will identify the best Klotho boosters to address this fundamental question and could identify a novel therapeutic strategy for the prevention and treatment of AD.

Lay Summary
Project Narrative Cognitive functions, such as learning and memory, are of fundamental biological importance, and diseases that affect these functions are among the most challenging

biomedical problems of our time. We recently demonstrated that elevating levels of the pleotropic protein Klotho enhances cognitive functions in mice and humans, and can prevent synaptic and cognitive impairments in a transgenic mouse model that simulates key aspects of Alzheimer’s disease. We hypothesize that small molecules capable of elevating Klotho levels (“Klotho boosters”) can prevent and reverse the pathogenic effects of elevated amyloid-? (A?) levels in the AD brain and therefore, in this proposal, we will begin to test these hypotheses by first identifying the best Klotho boosters for in vivo testing in wild type mice and for future testing in animal models of AD at the preclinical level.

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